Clinical Aspects of Type 3 Long-QT Syndrome

An International Multicenter Study

BACKGROUND: Risk stratification in patients with type 3 long-QT syndrome (LQT3) by clinical and genetic characteristics and effectiveness of β-blocker therapy has not been studied previously in a large LQT3 population.

METHODS: The study population included 406 LQT3 patients with 51 sodium channel mutations; 391 patients were known to be event free during the first year of life and were the focus of our study. Clinical, electrocardiographic, and genetic parameters were acquired for patients from 7 participating LQT3 registries. Cox regression analysis was used to evaluate the independent contribution of clinical, genetic, and therapeutic factors to the first occurrence of time-dependent cardiac events (CEs) from age 1 to 41 years.

RESULTS: Of the 391 patients, 118 (41 males, 77 females) patients (30%) experienced at least 1 CE (syncope, aborted cardiac arrest, or long-QT syndrome–related sudden death), and 24 (20%) suffered from LQT3-related aborted cardiac arrest/sudden death. The risk of a first CE was directly related to the degree of QTc prolongation. Cox regression analysis revealed that time-dependent β-blocker therapy was associated with an 83% reduction in CEs in females (P=0.015) but not in males (who had many fewer events), with a significant sex × β-blocker interaction (P=0.04). Each 10-ms increase in QTc duration up to 500 ms was associated with a 19% increase in CEs. Prior syncope doubled the risk for life-threatening events (P<0.02).

CONCLUSIONS: Prolonged QTc and syncope predispose patients with LQT3 to life-threatening CEs. However, β-blocker therapy reduces this risk in females; efficacy in males could not be determined conclusively because of the low number of events.

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Sources of Funding, see page 880

Key Words: arrhythmia, cardiac ■ death, sudden, cardiac ■ genetic testing ■ long-QT syndrome ■ risk assessment ■ SCN5A protein, human

Clinical Perspective

What Is New?

- Long-QT syndrome type 3 (LQT3) is caused by gain-of-function mutations in the *SCN5A*-encoded Nav1.5 sodium channel. The phenotype differs from the more common potassium channel–mediated forms, among other characteristics, by a more lethal course. Risk stratification in LQT3 is not well defined, and the effectiveness of β-blocker therapy has not been studied in a large LQT3 cohort.
- In a study of almost 400 LQT3 patients (1 to 40 years of age), it was demonstrated that the risk of a cardiac event was directly related to the degree of QTc prolongation. In addition, the presence of syncope doubled the risk for future life-threatening events. β-Blocker therapy significantly reduced the cardiac event rate in females, but in males this effect could not be determined conclusively because of the low number of events.

What Are the Clinical Implications?

- The clinical implications of this study are that LQT3 patients can be stratified as to their risk of life-threatening cardiac events based on clinical and genetic characteristics. A high-risk subpopulation of LQT3 patients with QTc ≥500 ms and a history of syncope can be identified, and this population may require adjunctive therapy.
- β-Blocker therapy significantly reduced the risk for cardiac events.

Several large studies have described the clinical course of patients with long-QT syndrome (LQTS).[1,2] Initially regarded as 1 disease entity, it has become increasingly clear that the underlying genetic substrate, now subdividing LQTS into at least 16 genotypes, impacts many aspects of the disease phenotype including prognosis and therapy.[3] Approximately two-thirds of all LQTS patients host loss-of-function mutations in 1 of 2 potassium channel genes, *KCNQ1* (LQT1) or *KCNH2* (LQT2).[4,5] β-Blocker therapy or other antiadrenergic measures are effective in the majority of these patients.[4–8]

Type 3 long-QT syndrome (LQT3) is caused by gain-of-function mutations in the *SCN5A*-encoded Nav1.5 sodium channel involving a pathological increase in late sodium current, a pathological increase in the window current (as one of the mechanisms of the late sodium inward current), or both. LQT3 comprises ≈5% to 10% of patients with LQTS. The phenotype differs from the more common potassium channel–mediated forms in various aspects. Cardiac events in LQT3 frequently occur at rest or with inactivity and are less likely to be triggered by adrenergic stress or emotions.[7] In comparison with patients with LQT1 and LQT2, patients with LQT3 have more marked resting bradycardia, and the first cardiac event is more likely to be lethal and seems to occur later in childhood, during or after puberty.[9,10] On the basis of these data, and in contrast with the well-established efficacy of β-blockers in LQT1 and LQT2, there is anxiety and fear that β-blockers may not be effective in LQT3[6,7] and might, in fact, be proarrhythmic.[11] This concern has translated into a relatively high use of prophylactic implantable cardioverter defibrillators (ICDs) in LQT3 patients, even among those who are asymptomatic.[12,13] Patients with defective Nav1.5 channels may also manifest other arrhythmia phenotypes (Brugada syndrome, progressive cardiac conduction disease, atrial arrhythmias, and sinus node disease), and patients with LQT3 frequently present with associated characteristics including discrete conduction disturbances, bradycardia, atrial arrhythmias, or right precordial ST elevation.[14] Indeed, even patients with the prototypical LQT3 mutation, p.K1505_Q1507del (ΔKPQ), have notably longer cardiac conduction intervals than do patients with either LQT1 or LQT2.[15]

The present study involves the largest multicenter LQT3 cohort described to date and is designed to identify the risk and therapeutic factors associated with cardiac events in patients with *SCN5A*-mediated LQT3. The risk factors evaluated include clinical features (age, sex, and electrocardiographic measurements), the mutation type, and topological location of the mutation in Nav1.5. The therapeutic effects of β-blocker therapy, other medications, and ICDs on outcome were also evaluated.

METHODS

Study Population

The study population comprised 406 patients with LQT3 (90 LQT3 probands and their 316 LQT3-positive family members). The patients were enrolled from 7 centers including the US Rochester, NY/Cleveland portion of the International LQTS Registry (n=186), the Dutch (Amsterdam) LQTS Registry (n=75), the Italian (Pavia) LQTS Registry (n=48), the Israeli LQTS Registry (n=30), the Japanese (National Cardiovascular Center) LQTS Registry (n=29), the Mayo Clinic LQTS Registry (n=28), and the Denmark LQTS Registry (n=10). In all centers, institutional review board approval was obtained for this type of study. Not included in the study population were 14 patients with evidence of mutations involving ≥2 LQTS genes, and 2 patients with multiple *SCN5A* mutations. In addition, patients/families with clear evidence of an *SCN5A*-mediated hybrid/overlapping phenotype (ie, conduction disease or right precordial ST elevation, the so-called overlap syndromes as, for example, the large Dutch *SCN5A*-1795insD family[16]) were not included in this study. All patients or their guardians provided informed consent for the genetic and clinical studies.

Phenotype Characterization

Routine clinical and electrocardiographic parameters were acquired at the time of enrollment in each of the registries. To minimize the influence of coronary disease on cardiac

events, follow-up was censored at age 41 years. Measured parameters on the first recorded ECG included PR, QRS, QT, and R-R intervals in milliseconds, with QT corrected for heart rate by the Bazett formula (QTc). The QTc was expressed in its continuous form and categorized into 3 appropriate risk levels as subsequently described. Clinical data were collected on prospectively designed forms with information on demographic characteristics, personal and family medical history, electrocardiographic findings, therapy, and end points during long-term follow-up. As in the 2 previous studies in LQT1 and LQT2 subtypes by our group,[4,5] data on patients with the LQT3 genotype were merged electronically into a common database.

Genotype Characterization

The *SCN5A* mutations were identified using standard genetic tests performed in either a molecular-genetic research laboratory in a participating center or in one of the commercially available LQTS genetic-testing laboratories. Thiry-two patients died of unexplained sudden cardiac death (SCD) and had not been genotyped. We assumed that the *SCN5A* mutation, which was established as LQT3-associated in their respective families, was also present in these 32 patients.

Genetic alterations of the amino acid sequence were characterized by location in the Nav1.5 channel protein (subdivided into N terminus; transmembrane-spanning domains DI, DII, DIII, and DIV; their respective interdomain linkers [IDL]; C terminus; and the type of mutation [missense, frameshift, and in-frame deletions]). The different regions of the *SCN5A*-encoded Nav1.5 channel were defined as the coding sequence involving amino acid (aa) residues from N terminus (aa1–126), DI (aa127–415), IDL I–II (aa416–711), DII (aa712–939), IDL II–III (aa940–1200), DIII (aa1201–1470), IDL III–IV (aa1471–1523), DIV (aa1524–1772), and C terminus (aa1773–2016). The genetic mutations are presented in online-only Data Supplement Table I by coding effect, location, and frequency.

Statistical Analysis

The primary end point was the time from age 1 year until the first cardiac event (syncope, aborted cardiac arrest [ACA], or LQT3-related SCD), censored at loss to follow-up, or age 41 years, whichever occurred first. The restricted, more severe secondary end point was ACA or LQT3-related SCD, whichever occurred first. All long-term analyses were conditional on cardiac event–free survival to age 1 year to curtail any potential influence of cardiac events in the first year of life on the model for the remaining 39 years. Accordingly, 391 of 406 patients (96%) with LQT3 were eligible for long-term analyses.

Clinical characteristics were described using means and standard deviations for continuous variables or proportions and counts for categorical variables. Kaplan-Meier curves were used to estimate distributions of censored time-to-event outcomes, with inference based on the log rank test. A total of 35 of 391 (8.9%) in the study population >1 year of age did not have a recorded ECG; 25 of the 35 patients without an ECG died. Missing QTc values were imputed based on sex and mutation, using regression imputation. There were 5 prevalent mutations (N1325S, K1505_Q1507del, I1768V, E1784K, and D1790G), whereas the other rare mutations (<5% prevalence each, together constituting <41% of all patients) were pooled to form a sixth mutation group. Each of the 6 mutation groups was stratified by sex, resulting in a total of 12 sex-mutation subgroups. Missing QTc values were imputed as the mean of the nonmissing QTc values among patients in the corresponding sex-mutation subgroup.

The Cox model[17] was used to evaluate the independent contribution of clinical, therapeutic, and genetic factors to the risk of the first occurrence of time-dependent cardiac events from age 1 year through age 40 years. Cox models were stratified by sex to relax the assumption of proportional hazards by allowing sex-specific nonparametric baseline hazard functions for males and females. The effect of β-blocker therapy was modeled using a time-dependent indicator for being on versus off β-blockers at each point in time, allowing for the fact that patients may start and stop β-blockers at different ages. Interacting time-dependent β-blocker status with sex allowed estimation of sex-specific hazard ratios for β-blockers, and a test of equality of the effect of β-blockers for males versus females, as well.

The effect of syncope on the risk of ACA or death was similarly modeled using a time-dependent indicator for having had at least 1 syncopal event. There was insufficient evidence that risk differed for those whose first syncopal event occurred on versus off β-blockers, although the power to test this was limited.

Effects of the 5 most common mutations (each 5% to 18% prevalent) were modeled by comparing each with the pooled set of all infrequent mutations (<5% prevalent each, but totaling 41% of all patients), and then further pooling the 3 nonsignificantly different common mutations (I1768V, K1505_Q1507del, and N1325S) with the infrequent mutations to estimate the hazard ratios for E1784K and D1790G relative to all others.

Effects of QTc and birthdate were modeled using continuous piecewise linear splines to account for their significantly nonlinear effects that could not be well modeled using discrete groups. In particular, the log hazard increased linearly for QTc up to 500 ms but then leveled off. For Kaplan-Meier curve estimation, QTc was categorized into 3 groups: <450 ms, 450 to 490 ms, and ≥500ms. The log hazard was constant until 1955 but then increased linearly with birth date after 1955.

Proportional hazards assumptions were tested by interacting predictors with follow-up time, with stratification used to extend the model to remedy violations. All 2-way interactions between pairs of predictors in the model were considered for inclusion, one at a time. Frailties (nonsignificant) and robust group jackknife inference (yielding generally smaller not larger standard errors) for family membership were considered but were found unnecessary after adjusting for mutation. SAS version 9.3 (SAS Institute Inc) was used for all analyses, and a 2-sided significance level of 0.05 was used for hypothesis testing. See comments in the online-only Data Supplement Appendix regarding relevant interpretation of multivariate Cox model analyses and associated predicted survival analyses for males and females hypothesized to be always on and always off β-blockers.

RESULTS

First Year of Life

The LQT3 study population involved 406 patients. Twelve patients were symptomatic in the first year of their lives: 7 had unexplained syncope thought to be related to LQT3, 6

Circulation. 2016;134:872–882. DOI: 10.1161/CIRCULATIONAHA.116.021823

had ACA (4 of them died in the first year of life while receiving what was thought to be appropriate LQTS therapy), and 1 had documented torsades de pointes (published case[18]). It is generally appreciated that LQTS patients who are symptomatic in the first year of their lives have a poor prognosis,[19,20] and, for this reason, we excluded these patients in subsequent analyses that begin at age 1 year. Three patients had no follow-up after 1 year of age, so they were also excluded from the long-term follow-up study. See online-only Data Supplement Table II for clinical and genetic details on these 15 patients.

Study Population Beginning at Age 1 Year (n=391)

Baseline Characteristics

The clinical characteristics of the 391 remaining LQT3 patients are summarized in Table 1. Baseline patient characteristics, electrocardiographic parameters, and genetic variables were similar in the 3 geographic sources of the patients. The use of β-blockers was less frequent in Japan ($P<0.01$), but other modalities of treatment were similar by geographic region. For the 82 LQT3 probands and their 309 mutation-positive family members, 51 distinct LQT3-associated mutations were identified including 47 missense mutations in 322 patients (82%) and 4 deletion/insertion/frameshift mutations in 69 patients (18%). Overall, 275 patients (70%) had mutations located in either the transmembrane-spanning domains or the interdomain linkers, 115 patients (29%) had mutations located in the C terminus, and only 1 patient had a mutation located in the N-terminus region.

Clinical Outcome: Univariate Analyses (Unadjusted)

One hundred eighteen (41 males, 77 females) patients (30%) experienced at least 1 suspected LQT3-triggered cardiac event of syncope, ACA, or SCD by age 40 years. The cumulative probabilities of a first cardiac event for syncope, ACA, or SCD; for ACA or SCD; and for SCD as the first event as a function of age for the 391 patients are presented in Figure 1, with cumulative event rates of 38%, 20%, and 14%, respectively. The risk of a first cardiac event was related directly to the degree of QTc prolongation, at least between the ages of 16 and 26 years (Figure 2). Females had a higher probability of a first cardiac event than did males, especially in the 30- to 40-year age range (Figure 3). The duration of the QRS interval was not associated with an increased probability of cardiac events (data not shown). Removing patients with imputed data, including the 25 individuals who died without known QTc, did not essentially change the obtained results (data not shown).

Various therapies were used in the treatment of these LQT3 patients. Sixty-nine patients (17.6%) received an ICD during follow-up. Unfortunately, we have only limited documentation about the indication for ICD implantation or the frequency of interrogation-recorded ICD therapy for ventricular tachyarrhythmic events. No patient who had received an ICD died during a median follow-up of 36 months. One-hundred eleven patients (28.3%) were started on β-blockers, and because of the time-dependent use of β-blockers, ie, when they were on and off of β-blockers, and the influence of various risk factors influencing β-blocker efficacy, the appropriate effectiveness of β-blockers can be evaluated only in multivariate analyses. The efficacy of other therapies (flecainide, mexiletine, ranolazine, and left cardiac sympathetic denervation) could not be judged because of the relatively small number of patients so treated (in addition to lack of data) and few events.

Clinical Outcome: Multivariate Analyses

Findings from the multivariate Cox regression analyses for the end point of syncope, ACA, or SCD, whichever came first, are presented in Table 2. Contrary to the speculated proarrhythmic risk of β-blocker therapy in LQT3, time-dependent β-blocker use was associated with a reduction in cardiac events of 83% in females, whereas in males a nonsignificant 6% decrease was observed (Table 2). Hence, there appeared to be a significant sex × β-blocker interaction ($P<0.04$). Each 10-ms increase in QTc duration up to 500 ms was associated with a 19% increase in the risk for cardiac events, and patients born after 1955 had a 5% annual increase in the risk for cardiac events. There is no apparent increase in risk for QT when >500 ms. It appears that this is attributable, at least in part, to the difference between the adjusted versus unadjusted effects of QTc. In our multivariable Cox models, there is insufficient evidence that risk increases with QTc beyond ≈500 ms (see Methods for the multivariable Cox model approach). Two mutations, E1784K and D1790G, were relatively benign, with hazard ratios for cardiac events significantly <1.0.

When the end point was restricted to ACA or SCD (Table 3), time-dependent syncope doubled the risk for the more malignant cardiac events ($P=0.02$), whereas the other risk variable effects were similar to those presented in Table 2. β-Blockers reduced the risk of ACA/SCD by 80% among females ($P=0.03$) and by 49% among males (not significant).

The numbers of patients with cardiac events by time-dependent β-blocker status are provided in online-only Data Supplement Table III, and the numbers of patients with cardiac events while on β-blocker therapy are provided in Table 4. All together, during a median follow-up of >7 years, 5 patients developed life-threatening arrhythmias on β-blocker therapy (3 died). Figure 4A and

ORIGINAL RESEARCH ARTICLE

Table 1. Clinical Characteristics of 391 LQT3 Patients, Event-Free at Age 1 Year

Characteristics	USA	Europe	Japan	Missing	Total
No. of patients	208	155	28	–	391
Male, n (%)	85 (41)	72 (46)	17 (61)	–	174 (45)
Proband, n (%)	37 (18)	34 (22)	11 (39)	–	82 (21)
Age at ECG, y	26±19	31±20	25±19	33	28±20
ECG, mean±SD					
RR, ms	865±240	896±206	946±213	33	884±225
PR, ms	159±36	162±28	165±30	84	161±33
QRS, ms	83±13	104±112	87±16	35	92±73
QTp, ms	353±78	362±70	387±81	36	359±75
QT, ms	442±87	443±84	473±89	35	445±86
QTc, ms	479±50	471±63	487±62	35	476±57
QTc males, ms	487±52	475±60	487±69	9	482±57
QTc females, ms	473±48	466±67	486±51	26	471±56
Treatment, n (%)					
β-Blockers	77 (38)	31 (21)	3 (11)	8	111 (29)
LCSD	1 (0)	5 (3)	0 (0)	3	6 (2)
Pacemaker	13 (6)	6 (4)	0 (0)	3	19 (5)
ICD	49 (24)	16 (10)	4 (14)	–	69 (18)
Location, n (%)					
N Terminus	1 (0)	0 (0)	0 (0)	–	1 (0)
Transmembrane	77 (37)	77 (50)	15 (54)	–	169 (43)
C Terminus	59 (28)	44 (28)	12 (43)	–	115 (29)
Intra	71 (34)	34 (22)	1 (4)	–	106 (27)
Mutation type, n (%)					
Missense	153 (74)	147 (95)	22 (79)	–	322 (82)
Deletions	55 (26)	8 (5)	6 (21)	–	69 (18)
E1784K	47 (23)	10 (6)	12 (43)	–	69 (18)
D1790G	0 (0)	29 (19)	0 (0)	–	29 (7)
First cardiac event					
Syncope	51 (25)	28 (18)	7 (25)	–	86 (22)
ACA	4 (2)	3 (2)	0 (0)	–	7 (2)
Sudden cardiac death	19 (9)	6 (4)	0 (0)	–	25 (6)
Ever cardiac events					
Syncope	51 (25)	28 (18)	7 (25)	1	86 (22)
ACA	8 (4)	8 (5)	6 (21)	–	22 (6)
Sudden cardiac death	27 (13)	11 (7)	2 (7)	1	40 (10)
Appropriate shock	4 (2)	0 (0)	1 (4)	1	5 (1)

Information on the use of mexiletine and flecainide was not uniformly collected in Europe and Japan. ACA indicates aborted cardiac arrest; ICD, internal cardiac defibrillator; LCSD, left cardiac sympathetic denervation; LQT3, type 3 long-QT syndrome; and QTp, QT peak interval.

4B shows Cox model–based predicted distributions of the age at first ACA or SCD, conditional on event-free survival to age 1 year, by β-blocker status and sex for asymptomatic patients (no prior syncope) born in 1971 (median) with a QTc of 470 ms (median risk, Figure 4A) and a QTc of 500 ms (high risk, Figure 4B) and neither

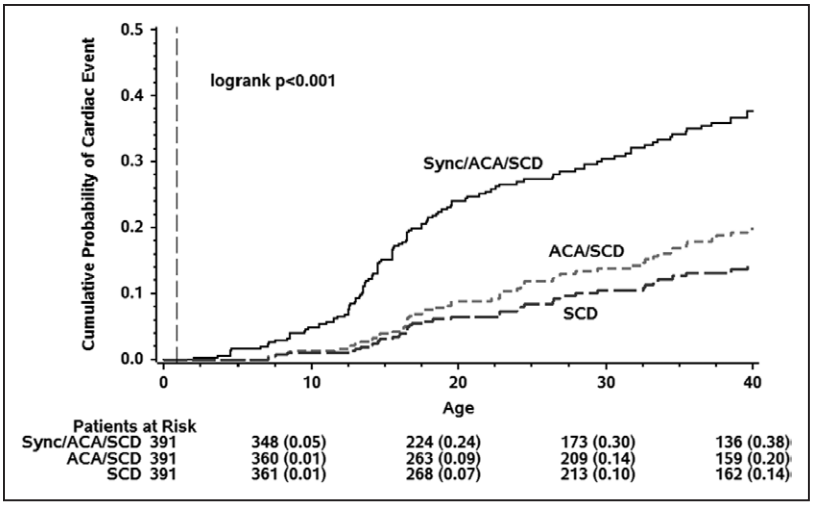

Figure 1. Kaplan-Meier cumulative probability of first LQT3-triggered cardiac event for combinations of syncope, ACA, and SCD, conditional on event-free survival to age 1 year.
ACA indicates aborted cardiac arrest; LQT3, type 3 long-QT syndrome; and SCD, sudden cardiac death.

lower-risk mutation (not E1784K or D1790G). As is shown, β-blockers appear clearly effective in females. In males, the number of cardiac events is much lower, precluding the ability to detect a further attenuation of risk by β-blocker therapy. However, a proarrhythmic signal is absent. Again, the importance of baseline QTc is evident.

Because one may argue that pacemaker/ICD therapy may protect against the possible detrimental effects of β-blockers, we ran additional analyses where we censored patients at the time of pacemaker or ICD implantation and found similar results for β-blocker efficacy among those without a pacemaker or ICD: hazard ratio=0.22 (*P*=0.035) and 0.25 (*P*=0.059) for females, and hazard ratio=1.03 (*P*=0.94) and 0.60 (*P*=0.52) for males.

DISCUSSION

We studied 391 LQT3 patients, asymptomatic during the first year of life and found that the degree of QT prolongation and history of syncope were the major risk factors for an LQT3-related cardiac event including ACA or SCD. The risk for a first event increased rapidly during adolescence and continued to increase in both sexes, although more slowly, during the adult years. β-Blocker therapy significantly reduced the risk for cardiac events in treated individuals, in particular, in females.

Clinical Risk Factors

In the present study, we confirmed the age-dependent occurrence of cardiac events; with the exception of a few events in very young infants ≤1 year of age; these 12 patients were excluded in the long-term follow-up analyses. The number of individuals who experienced a sentinel cardiac event increased rapidly between age 10 and age 20 years; by the age of 40 years, almost 40% of patients had experienced a first cardiac event. Among those experiencing a LQT3-related cardiac event, ≈50% were ACA or SCD (Figure 1). As in other LQTS subtypes,[4,5] probands were at higher risk than were family members (not shown), probably reflecting a referral bias on the basis

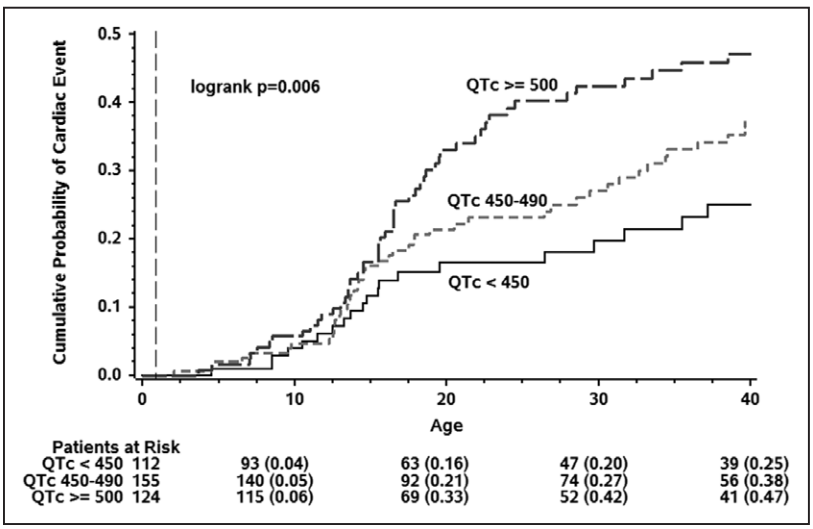

Figure 2. Kaplan-Meier cumulative probability of cardiac events (syncope/aborted cardiac arrest/LQT3-related sudden cardiac death, whichever comes first) for 3 QTc ranges, conditional on event-free survival to age 1 year.
LQT3 indicates type 3 long-QT syndrome.

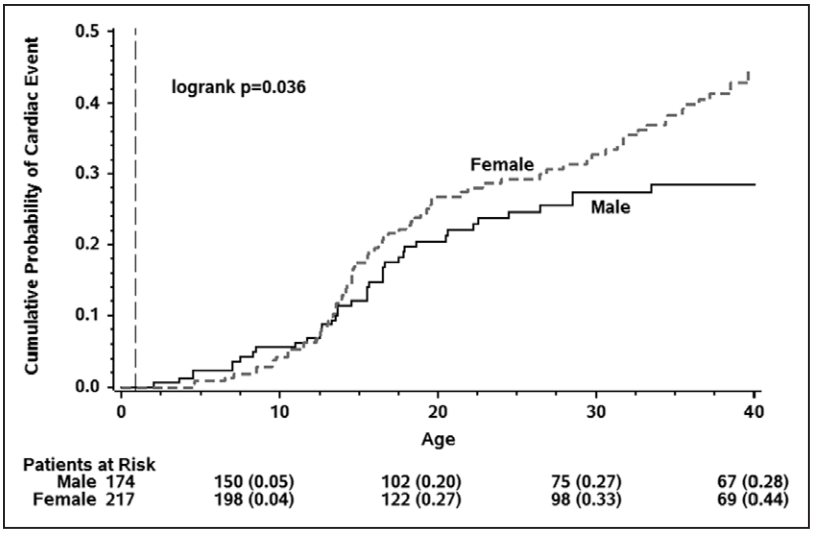

Figure 3. Kaplan-Meier cumulative probability of cardiac events (syncope/aborted cardiac arrest/LQT3-related sudden cardiac death, whichever comes first) for females and males, conditional on event-free survival to age 1 year.
LQT3 indicates type 3 long-QT syndrome.

of earlier or more severe first symptoms than in affected family members and also the fact that the probands' QTc values were greater than the QTc values of the affected family members because the length of the QTc was an independent predictor of cardiac events (Figure 2). Females had a greater risk than did males, especially in the older age group (Figure 3). However, unlike in LQT1 and LQT2, where the risk in males occurs predominantly before puberty, the risk of an LQT3-triggered event in males shifts to postpuberty and continues throughout adulthood. Unfortunately, no 24-hour Holter monitoring data were available for analysis, nor were data available on the circumstances leading to cardiac events.

Mutation Type and Mutation Location

Mutation type and mutation location did not have a significant effect on outcome, although patients with some particular mutations (E1784K and D1790G; Tables 2 and 3) had a rather benign clinical course.

Therapy for LQT3

β-Blocker therapy reduces the risk for cardiac events in patients with LQT1 by >95% and in patients with LQT2 by 70% to 80%.[4,5] In contrast, the early genotype-phenotype studies showed no demonstrable β-blocker efficacy for LQT3.[6,7] Subsequent cellular in vitro studies raised concerns regarding the possible proarrhythmic effect of β-blockers for LQT3,[11] which got translated prematurely to the bedside with an unproven view that β-blockers might be contraindicated in LQT3. For the past decade, this notion has resulted in a fairly high rate of prophylactic ICD therapy in LQT3.[12,13] The theoretical arguments, based on just a few cases, suggested that β-blockers should not be used in LQT3, especially in patients with longer QT intervals at low heart rates with associated events during sleep or rest.[7] Atrioventricular block,[21] bradycardia,[22] sinus pauses,[23] and sinus arrest were thought to be possible mechanisms of death in LQT3.[23,24]

Our large study provides evidence that β-blocker therapy is not proarrhythmic. In contrast, a clear and significant protective effect for cardiac events was

Table 2. Multivariate Cox Model Analyses for Risk of Cardiac Events: First Cardiac Event (Syncope, ACA, or LQT3-Related SCD)

Parameter	*P* Value	Hazard Ratio	95% Confidence Interval	
			LCL	UCL
β-Blockers among females*	0.014	0.17	0.04	0.70
β-Blockers among males*	0.895	0.94	0.40	2.21
E1784K mutation	< 0.001	0.35	0.19	0.62
D1790G mutation	0.007	0.32	0.14	0.73
QTc per 10 ms (up to 500 ms)	<0.0001	1.18	1.11	1.26
Year of birth (>1955)	<0.0001	1.05	1.04	1.07

End point = cardiac event (118 CE: 25 SCD + 7 ACA + 86 syncope). ACA indicates aborted cardiac arrest; CE, cardiac event; LCL, lower confidence limit; LQT3, type 3 long-QT syndrome; SCD, sudden cardiac death; and UCL, upper confidence limit.
*Test for β-blockers × sex interaction: β-blockers for males versus females, *P*=0.039.

Table 3. Multivariate Cox Model Analyses for Risk of Cardiac Events: First ACA or LQT3-Related SCD

Parameter	*P* Value	Hazard Ratio	95% Confidence Interval	
			LCL	UCL
Syncope	0.023	2.03	1.10	3.72
β-Blockers among females*	0.032	0.20	0.05	0.87
β-Blockers among males*	0.308	0.51	0.14	1.88
E1784K mutation	0.001	0.09	0.02	0.37
D1790G mutation	0.049	0.30	0.09	0.99
QTc per 10 ms (up to 500 ms)	<0.001	1.33	1.19	1.48
Year of birth (after 1955)	<0.001	1.06	1.03	1.09

End point = ACA/SCD (56 ACA/SCD: 34 SCD + 22 ACA). ACA indicates aborted cardiac arrest; LCL, lower confidence limit; LQT3, type 3 long-QT syndrome; SCD, sudden cardiac death; and UCL, upper confidence limit.

*Test for β-blockers × sex interaction: β-blockers for males vs females, P=0.353.

demonstrated. The effect was clear in females; in males, their lower event rate precluded a demonstration of efficacy. However, a detrimental effect of β-blocker therapy in males with LQT3 is absent (Tables 2 and 3; see online-only Data Supplement comment for additional information regarding Figure 4A and 4B). Only 3 patients (3%) died on β-blocker therapy during a median follow-up of >7 years (Table 4).

The absolute risk of dying of LQT3-related arrhythmias (in individuals asymptomatic until age 1 year) is <15% by the age of 40 years (Figure 1). QTc and the presence of symptoms are strong modifiers of this risk (Tables 2 and 3), and it is likely that high-risk patients with prior syncope or ACA or QTc in the 500-ms range may require adjunctive therapy, such as left cardiac sympathetic denervation,[25–27] ICD,[12,13,28] or LQT3-directed pharmacotherapy with medications such as mexiletine, flecainide, and more specific late sodium current blockers, including ranolazine and some experimental drugs.[29–34] However, the present study cannot address precisely when these therapies should be used. Treatment in high-risk patients requires clinical judgment with balance of the disease risk versus the risk/benefit related to the selected therapy in each patient based on age, sex, QTc duration, and prior symptoms, as well as tolerance and clinical response to β-blocker therapy.

Study Limitations

Although this is the largest study for this third most common subtype (LQT3) of LQTS, an inherent limitation of this study is still the relatively small number of cardiac events, in particular, in males, and the small number of patients receiving therapies despite an international collaboration. The assumption that the deceased young individuals carried the familial mutation is reasonable but not certified, yet removing them from the analysis did not change the results. In addition, the generalizability even within LQT3 is limited somewhat because the study population was dominated by 5 specific mutations. Although we excluded families with obvious evidence of an overlap syndrome, any of the 36 functionally uncharacterized *SCN5A* mutations (of the 51 LQT3-associated mutations represented in this study) might potentially exhibit an expressed phenotype of overlap if the families were large enough or followed for longer durations. The E1784K mutation is an example of this,[35] but we stress that patients with an overt overlap syndrome (ie, signs of right precordial ST elevation) were excluded. Another limitation was the nonrandomized use of β-blockers and that less than one-third of the patients in this cohort were ever treated with β-blockers. Last, follow-up was censored at age 41 years, and cardiac events may continue

Table 4. Numbers of Subjects and Events While on β-Blocker Therapy

β-Blocker Therapy	No. of Patients Treated with β-Blockers	Follow-up Duration in Months After Treatment, 25th–75th Quartile; Median	Syncope, ACA, or Death, n (% of treated)	Death, n (% of treated)	ACA/SCD, n (% of treated)
All patients	111	36–161; 87	15 (14)	3 (3)	5 (5)
Male patients	51	40–180; 92	8 (16)	2 (4)	2 (4)
Female patients	60	34–144; 86	7 (12)	1 (2)	3 (5)

ACA indicates aborted cardiac arrest; and SCD, sudden cardiac death.

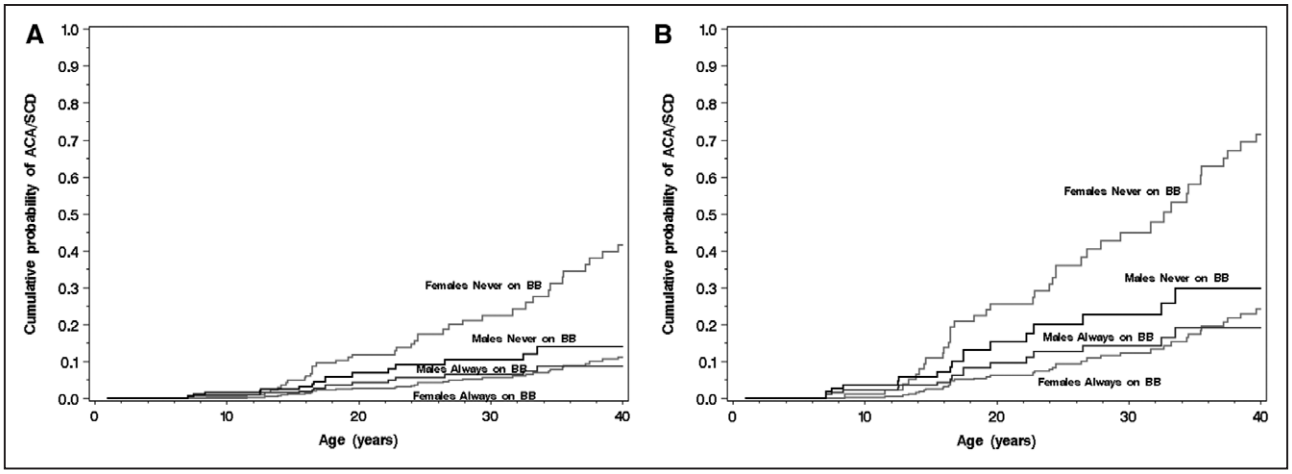

Figure 4. Plots for medium- and high-risk patients.
A, Plot for medium-risk patients. Cox model–based predicted distributions of the age at first ACA or SCD, conditional on event-free survival to age 1 year, by BB and sex for asymptomatic patients (no prior syncope) born in 1971 (median) with a QTc of 470 ms (median) and neither lower-risk mutation (neither E1784K nor D1790G). See online-only Data Supplement comment. **B,** Plot for high-risk patients. Cox model–based predicted distributions of the age at first ACA or SCD, conditional on event-free survival to age 1 year, by BB and sex for asymptomatic patients (no prior syncope) born in 1971 (median) with a QTc≥500 ms and neither lower risk mutation (neither E1784K nor D1790G). See online-only Data Supplement comment. ACA indicates aborted cardiac arrest; BB, β-blocker; and SCD, sudden cardiac death.

later in life in LQT3, especially if the patient acquires concomitant coronary artery disease.

Conclusions

Patients with LQT3 can be stratified as to their risk of life-threatening cardiac events on the basis of clinical and genetic characteristics. A high-risk subpopulation of LQT3 patients with QTc ≥500 ms and a history of syncope can be identified, and this population may require adjunctive therapy. β-Blocker therapy significantly reduces the risk for cardiac events.

SOURCES OF FUNDING

This work was supported in part by the Health Sciences Research Grant (H18 - Research on Human Genome - 002) and the Research Grant for the Cardiovascular Diseases (21C-8, 22-4-7, H24-033, H26-040) from the Ministry of Health, Labor and Welfare, Japan (to Dr Shimizu); research grants HL-33843, HL-51618, and HL-123483 from the National Institutes of Health, Bethesda, MD (to Dr Moss); grants 2000.059 and 2005T024 from the Nederlandse Hartstichting, The Netherlands (to Drs Wilde and Bezzina), and the Cardiovascular Onderzoek Nederland and Netherlands Heart Foundation project PREDICT (Drs Wilde and Bezzina); NIH grant HL68880 and Telethon grant GGP09247 (to Drs Schwartz and Crotti), and the Windland Smith Rice Comprehensive Sudden Cardiac Death Program (Dr Ackerman).

DISCLOSURES

Dr Wilde serves on the scientific advisory board of Lilanova. Dr Ackerman is a consultant for Boston Scientific, Gilead Sciences, Medtronic, and St. Jude Medical. Dr Ackerman and Mayo Clinic receive royalties from Transgenomic for their FAMILION-LQTS and FAMILION-CPVT genetic tests. None of these entities provided financial support for this study. The other authors report no conflicts.

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FOOTNOTES

Received February 3, 2016; accepted August 5, 2016.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.116.021823/-/DC1.

Circulation is available at http://circ.ahajournals.org.

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Clinical Aspects of Type 3 Long-QT Syndrome: An International Multicenter Study

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Circulation. 2016;134:872-882; originally published online August 26, 2016;
doi: 10.1161/CIRCULATIONAHA.116.021823
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

SUPPLEMENTAL MATERIAL

SUPPLEMENTAL TABLES

Table S1: List of Mutations by Coding Effect, Location, and Frequency in 406 LQT3 Patients. The different regions of the *SCN5A*-encoded Nav1.5 channel were defined as the coding sequence involving amino acid (aa) residues from N-terminus (aa1-126), DI (aa127-415), IDL I-II (aa416-711), DII (aa712-939), IDL II-III (aa940-1200), DIII (aa1201-1470), IDL III-IV (aa1471-1523), DIV (aa1524-1772) and C-terminus (aa1773-2016).

Coding Effect	Location	COUNT
V125L	N-term	1
Q245K	DI-S4/S5	3
R340W	DI-S4/S5	7
T370M	DI-S5/S6	9
N406K	DI-S6	1
V411M	DI-S6	7
A413T	DI-S6	3
L604V	DI/DII	2
G615E	DI/DII	2
P627L	DI/DII	2
Q692K	DI/DII	1
S941N	DII/DIII	1
R971C	DII/DIII	1
P1008S	DII/DIII	1
P1021S	DII/DIII	5
T1069M	DII/DIII	1
D1114E	DII/DIII	15
E1208K	DIII-S1	1
N1269S	DIII-S2/S3	6
I1278N	DIII-S3	5
T1304M	DIII-S4	9
N1325S	DIII-S4/S5	21
A1330D	DIII-S4/S5	1
A1330T	DIII-S4/S5	5
I1448L	DIII-S6	1
L1501V	DIII/DIV	13
K1505_Q1507del	DIII/DIV	9
Q1507_P1509del	DIII/DIV	55
L1560F	DIV-S2	1
F1596I	DIV-S3	5
F1617del	DIV-S3/S4	5
R1623L	DIV-S4	3

Coding Effect	Location	COUNT
R1623Q	DIV-S4	1
G1631D	DIV-S4	2
R1644H	DIV-S4	2
V1667I	DIV-S5	2
A1746T	DIV-S6	4
I1762del	DIV-S6	1
V1763M	DIV-S6	2
M1766L	DIV-S6	1
M1766V	DIV-S6	10
Y1767C	DIV-S6	4
I1768V	DIV-S6	58
V1777M	Cterm	2
T1779M	C-term	5
E1781G	C-term	3
E1784K	C-term	70
L1786Q	C-term	3
D1790G	C-term	30
Y1795C	C-term	3
R1991Q	C-term	1
TOTAL		**406**

Supplemental Table S2. LQT3 subjects with events before age 1 or no follow-up after Age 1.

Center	Gender	QTc (ms)	Syncope (Age)	ACA (Age)	Sudden Cardiac Death (Age)	Coding Effect	Mutation Location
Denmark	Male	No ECG	No	No	No	R340W	IS5-IS6
Mayo Clinic	Female	460	Yes (0)	No	No	N406K	IS6
Italy	Male	442	No	No	No	A413T	IS6
Italy	Male	550	No	Yes (0)	Yes (4)	S941N	IIS6-IIIS1
Rochester	Male	380	Yes (0)	No	No	T1304M	IIIS4
Italy	Male	520	Yes (0)	Yes (0)	Yes (0)	A1330D	IIIS4-IIIS5
Rochester	Female	440	Yes (0)	No	No	Q1507-P1509del	IIIS6-IVS1
Rochester	Female	590	Yes (0)	Yes (0)	No	R1623Q	IVS4
Italy	Male	520	No	Yes (0)	No	G1631D	IVS4
Japan	Male	550	Yes (0)	Yes (0)	No	G1631D	IVS4
Italy	Male	No ECG	No	Yes (0)	Yes (0)	V1763M	IVS6
Mayo Clinic	Male	490	No	Yes (1.5)	Yes (1.5)	M1766L	DIV-S6
Netherlands	Female	420	No	No	No	I1768V	IVS6
Rochester	Female	510	Yes (0)	No	No	E1784K	C-TERM
Israel	Male	470	No	No	Yes (0)	D1790G	C-TERM

Supplemental Table S3. Numbers of Subjects and Events by Time-Dependent ß-Blocker Status (BB).

	No CE (no ACA/SCD)	1st CE on BB (1st ACA/SCD on BB)	1st CE off BB (1st ACA/SCD off BB)	Total
All Patients				
Never on BB during follow-up to 1st CE (1st ACA/SCD)	205 (241)	0 (0)	107 (49)	312 (290)
Ever on BB during follow-up to 1st CE (1st ACA/SCD)	69 (95)	9 (5)	2 (2)	80 (102)
Total # Subjects	274 (336)	9 (5)	109 (51)	392 (392)
Males				
Never on BB during follow-up to 1st CE (1st ACA/SCD)	100 (112)	0 (0)	32 (14)	132 (126)
Ever on BB during follow-up to 1st CE (1st ACA/SCD)	33 (45)	7 (3)	2 (0)	43 (48)
Total # Male Subjects	133 (157)	7 (3)	34 (14)	174 (174)
Females				
Never on BB during follow-up to 1st CE (1st ACA/SCD)	105 (129)	0 (0)	75 (35)	180 (164)
Ever on BB during follow-up to 1st CE (1st ACA/SCD)	36 (50)	2 (2)	0 (2)	38 (54)
Total # Female Subjects	141 (179)	2 (2)	75 (37)	218 (218)

Note: numbers not in parentheses refer to cardiac events (CE) including syncope, aborted cardiac arrest (ACA), or sudden cardiac death (SCD) whichever came first as categorized as No CE, 1st CE on BB, and 1st CE off BB. Numbers in parentheses refer to ACA or SCD whichever occurred first as categorized as No ACA/SCD, 1st ACA/SCD on BB, and 1st ACA/SCD off BB. This table provides rough background information on numbers of patients in the time-dependent ß-blocker Cox multivariate analyses by gender. See Table 2 in the main manuscript for specific hazard ratios, confidence intervals, and p-values.

Supplemental Comment Regarding Interpretation of the Cox Model and the Derived Figures 4A and 4B.

This was a focused, pre-specified analysis with only a small number of candidate predictors, all of which were included in the final Cox models, irrespective of statistical significance.

In Cox analyses, if properly specified, adjusting for QTc, birth year, gender, mutation and time-dependent syncope means that comparisons between patients on versus off beta-blockers are only made between matched subgroups of patients with identical QTc values, birth year, age (since age is the time scale), gender, mutation, and syncopal history. For example, female patients with the I1768V mutation and a QTc of 470 ms who were born in 1971 who are asymptomatic and *on* ß-blockers at age 29 are effectively matched and compared to female patients with the I1768V mutation and a QTc of 470 ms who were born in 1971 who are asymptomatic and *off* ß-blockers at age 29. This is what is meant by the covariate-adjusted hazard ratio for beta-blockers. Thus, one need not be concerned with any potential differences -- at baseline or at any other point during follow-up -- in QTc, birth year, gender, mutation, or syncopal history when the model is properly specified.

The figures shown here are not Kaplan-Meier curves, but rather predicted event rates. Each male contributes information to both "always on" and "never on" ß-blocker curves, as does each female. Furthermore, predicted event rates depend strongly on all significant risk factors in the Cox model (Table 2). As shown in Figure 4B, QTc $\geq$ 500 ms approximately doubles the 40-year event rates to >70% for females never on BB and about 25% for others. Prior syncope, especially at a young age, would further increase the event rates. On the other hand, 40-year event rates for those with the lower risk D1790G mutation are < 5% for most subjects and < 15% even for females never on ß-blockers, while event rates are even lower among those with the E1784K mutation.

An example on how these curves can be used and interpreted is provided in the following description: the absolute risk predicted by the model for an asymptomatic woman age 25 in the medium risk profile group off ß-blockers (figure 4a) is ±20% and in the high-risk group ±40% (figure 4b). ß-blocker therapy would reduce that risk to ±5% and ±10% in the medium- and high-risk groups, respectively.