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Long QT Syndrome in Adults

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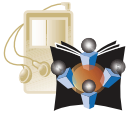
Objectives The aims of this study were: 1) to evaluate risk factors influencing the clinical course of mutation-confirmed adult patients with long QT syndrome (LQTS), 2) to study life-threatening cardiac events as a specific end point in adults, and 3) to examine the protective effect of beta-blocker therapy on cardiac events in adult LQTS patients with known cardiac channel mutations.

Background The clinical course and risk factors for cardiac events in genotype-confirmed adult patients with LQTS have not been previously investigated.

Methods The clinical characteristics of 812 mutation-confirmed LQTS patients age 18 years or older were studied with both univariate and multivariate analyses to determine the genotype-phenotype factors that influence the clinical course of adult patients with this disorder.

Results Female gender, corrected QT (QTc) interval, LQT2 genotype, and frequency of cardiac events before age 18 years were associated with increased risk of having any cardiac events between the ages of 18 and 40 years. Female gender, QTc interval ≥500 ms, and interim syncopal events during follow-up after age 18 years were associated with significantly increased risk of life-threatening cardiac events in adulthood. Beta-blockers provided a 60% reduction in risk of any cardiac event and life-threatening events, with somewhat greater effect in higher-risk subjects.

Conclusions The severity of LQTS in adulthood can be risk stratified with information regarding genotype, gender, QTc duration, and history of cardiac events. Beta-blockers effectively reduce but do not eliminate the risk of both syncopal and life-threatening cardiac events in adult patients with mutation-confirmed LQTS. (J Am Coll Cardiol 2007;49:329–37) © 2007 by the American College of Cardiology Foundation



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The long QT syndrome (LQTS) is a genetic cardiac channelopathy in which most affected individuals have delayed ventricular repolarization manifest with prolongation of the corrected QT (QTc) interval on the electrocardiogram. Prior studies have focused on birth as time origin, with events occurring most frequently during adolescence. The major factor contributing to an increased risk of cardiac events (syncope, aborted cardiac arrest, or LQTS-related death) during childhood and/or adolescence is a QTc interval >500 ms (1–3). Many patients affected with LQTS possess mutations in genes encoding cardiac potassium or sodium ion channels (4–7). The clinical course of LQTS throughout an affected patient's lifetime is thought to be significantly influenced by genotype, and risk stratification has been done on the basis of LQTS subjects with events mostly occurring before reaching adulthood (4–5,7). Earlier

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Abbreviations and Acronyms

ACA = aborted cardiac arrest

HR = hazard ratio

LQTS = long QT syndrome

QTc = corrected QT (interval)

observations indicated that LQT1- and LQT2-genotyped patients carrying the KCNQ1 and KCNH2 potassium channel gene mutations, respectively, have a higher lifetime risk of cardiac events than LQT3-genotyped patients carrying the SCN5A sodium channel gene mutation (5). Gender and age also play significant roles in influencing the clinical course of LQTS in that cardiac events tend to occur more frequently in children, with males having an increased risk of events during preadolescence and females having higher event rates in adolescence and beyond (8). Previous studies have suggested that the rate of increase in cardiac events generally plateaus in adult men (8,9). Event manifestations, specifically in LQT1 and LQT2 patients, might be modulated differently by age and gender (9). However, the existing literature provides limited risk stratification for patients who survive LQTS into adulthood or are diagnosed with LQTS after adolescence. Also, there is minimal evidence regarding the risk of lethal events or the magnitude of beta-blocker protection during adulthood. The purpose of the present study is to evaluate the clinical course and identify risk predictors for subsequent cardiac events—including lethal or potentially lethal outcomes—in a large population of genotype-confirmed adult patients with LQTS.

Methods

Study population. The subjects within the study population were enrolled in the International Long-QT Syndrome Registry (1). The time origin for analyzing the study population was age 18 years, with follow-up through age 40 years. Genetic testing was performed on 1,627 members of 221 families enrolled in the registry. Genetic testing identified 812 subjects with genotype positive LQTS: 428 LQT1 gene carriers from 88 families with the KCNQ1 mutations, 302 LQT2 gene carriers from 93 families with the KCNH2 mutations, and 82 LQT3 gene carriers from 11 families with the SCN5A mutations. Members of known genotype-positive LQTS families who were not identified as having their respective family mutation were considered non-carriers, and these non-carriers were not routinely screened for independent mutations in the 3 major genes. Informed consent for genetic and clinical studies was obtained from all subjects. Mutations were identified by standard genetic tests (10–12).

Phenotypic characterization. A clinical history and a 12-lead electrocardiogram were obtained on all study subjects. In addition, detailed pedigrees were constructed for each family to further characterize inheritance information. The first recorded electrocardiogram in each subject was used to determine the Bazett-corrected QTc interval (13). The QTc interval for each subject was then categorized into 1 of 5 prespecified categories: ≤439 ms; 440 to 469 ms; 470 to 499 ms; 500 to 549 ms; and ≥550 ms. Additional pertinent baseline clinical information at age 18 years included gender, genotype, history of syncope and/or aborted cardiac arrest (ACA), frequency and timing of prior syncope and/or ACA, and the LQTS therapy the patient was receiving at age 18 years (i.e., beta-blockers, pacemaker, implantable defibrillator). To make comparisons in our analysis, the number and timing of cardiac events (syncope and/or ACA) before and after age 18 years were categorized in advance of the analysis into specific subsets.

End points. The cardiac event end points included syncope (transient abrupt onset and offset of loss of consciousness), ACA (requiring defibrillation), and LQTS-related sudden death. Follow-up was censored after age 40 years to minimize the influence of coronary disease on cardiac events.

Statistical analysis. The statistical software used in the analyses involved SAS version 9.1.3 (SAS, Cary, North Carolina). The clinical characteristics of the genotype-positive study groups were compared with the Kruskal-Wallis test for continuous variables and Fisher exact test for categorical variables. The unadjusted cumulative probability of first cardiac event (syncope, ACA, or LQTS-related death) between ages 18 and 40 years, separately stratified by each baseline covariate, was assessed with the Kaplan-Meier estimator and the log-rank test (14). The Cox model (15) with time-dependent covariates was used to evaluate the influence of clinical and genetic factors as well as time-dependent beta-blocker therapy on the distribution of the time to the first cardiac event between ages 18 and 40 years. Relevant interactions of time-dependent beta-blocker therapy with QTc interval dichotomized at 500 ms, LQTS genotype, and history of cardiac events (yes/no) were evaluated.

Results

Clinical characteristics. The clinical characteristics of the 812 genotyped subjects are shown in Table 1. Women predominated as the majority of the study group. The mean QTc interval was significantly different among the 3 LQTS genotypes, with the QTc interval longest in LQT3. Cardiac therapy was similar among all 3 LQTS groups at baseline. The overall percentages of genotyped subjects receiving beta-blockers at age 18, 30, and 40 years were 18%, 17%, and 18%, respectively, with similar percentage use by age across all 3 genotypes. The proportion of subjects with a history of a cardiac event before age 18 differed among the 3 genotypes, with LQT1 having the highest proportion (34%) of subjects with a prior event. The percentage of subjects who experienced at least 1 cardiac event after age 18 also differed among the genotypes, with LQT2 having the highest percentage (33%). The frequency of ACA before age 18 and the frequency of ACA and/or LQTS-related death after age 18 were similar among the 3 genotypes. There were 64 patients who had ACA before age 18 or

Table 1 Clinical Characteristics in 812 Genotyped Patients

Characteristic	LQT1 (n = 428)	LQT2 (n = 302)	LQT3 (n = 82)
Families, n	88	93	11
Median age at baseline ECG, yrs	31	33	30
Female gender, n (%)	249 (58)	178 (59)	42 (51)
Baseline QTc findings			
Subjects with baseline ECG, n	370	261	78
QTc* mean ± SD, ms	485 ± 49	492 ± 52	506 ± 46
95% CI of mean QTc, ms	480–490	486–499	495–516
≤439 ms, n (%)	41 (11)	21 (8)	5 (6)
440–469 ms, n (%)	103 (28)	64 (25)	13 (17)
470–499 ms, n (%)	102 (28)	81 (31)	13 (17)
500–549 ms, n (%)	85 (23)	58 (22)	30 (38)
≥550* ms, n (%)	39 (11)	37 (14)	17 (22)
Cardiac therapy at age 18 yrs, n (%)			
Beta-blockers	85 (20)	53 (18)	11 (13)
Pacemaker	3 (1)	10 (3)	2 (2)
Sympathectomy	9 (2)	4 (1)	1 (1)
Implantable defibrillator	4 (1)	4 (1)	1 (1)
Cardiac events ≥1, n (%)			
Syncope/ACA before age 18 yrs	142 (34)	75 (25)	10 (12)
Syncope/ACA/LQTS-death after age 18 yrs	83 (20)	97 (33)	12 (15)
ACA/LQTS-death, n (%)			
ACA before age 18 yrs	7 (2)	9 (3)	0
ACA after age 18 yrs	16 (3.7)	13 (4.3)	1 (1.2)
Death after age 18 yrs	5 (1.2)	12 (3.7)	3 (3.7)
ACA or death after age 18 yrs	21 (4.9)	25 (8.0)	4 (4.9)

*$p < 0.01$ for comparison of baseline parameters among all 3 long QT syndrome (LQTS) subtypes. No significance-level comparisons are provided for the distribution of events among the genotypes, because these end point analyses are provided in the multivariate analyses in Tables 2 and 3.

ACA = aborted cardiac arrest; CI = confidence interval; ECG = electrocardiogram; QTc = corrected QT interval.

ACA/LQTS-related death between ages 18 to 40, and 34% (22 of 64) experienced these events as their first symptom.

Clinical course on the basis of Kaplan-Meier univariate analyses. ANY CARDIAC EVENT (SYNCOPE, ACA, OR LQTS-RELATED DEATH). With age 18 years as the time origin, the cumulative probability of experiencing any cardiac event (including syncope) during adulthood was higher for longer QTc intervals (Fig. 1A) and for more frequent events before age 18 years (Fig. 1B). Patients with no cardiac events before age 18 had the lowest cumulative event rate, with a 20% event rate by age 40. Women had a higher event rate than men (Fig. 1C). The cardiac event rate also differed by genotype, with the LQT2 subjects having the highest cumulative probability of cardiac events (Fig. 1D) among the 3 genotypes.

ABORTED CARDIAC ARREST OR LQTS-RELATED DEATH. The combination of all 3 LQTS genotypes together showed a higher rate of ACA or LQTS-related sudden death with longer QTc intervals (Fig. 2A) and with more frequent events before age 18 (Fig. 2B). Also, the cumulative probability of ACA or LQTS-related death was increased in women (Fig. 2C) when compared with men. However, there was no significant difference in cumulative probability of ACA or LQTS-related sudden death by genotype (Fig. 2D).

Risk stratification on the basis of Cox proportional hazards analyses. ANY CARDIAC EVENT (SYNCOPE, ACA, OR LQTS-RELATED DEATH). The relative magnitude, independence, and significance of the risk of any cardiac event stratified by history of cardiac events before age 18, genotype, gender, and QTc duration were compared with the lowest risk group in each category with multivariate Cox survivorship analysis (Table 2). Hazard ratios (HRs) ranged from approximately 2.3 to 12, depending on the risk category, with the highest risks for those with a history of more than 10 cardiac events before age 18 (HR = 12.01), female gender (HR = 3.05), QTc interval ≥550 ms (HR = 10.08), and LQT2 genotype (HR = 2.27) versus LQT1. No statistically significant difference in HR was observed in genotype LQT3 versus LQT1. Time-dependent beta-blocker use during follow-up was associated with a significant 59% reduction in the risk of a subsequent cardiac event (HR = 0.41).

Interaction analyses involving the combined end point syncope/ACA/LQTS-related sudden death showed that the benefit from beta-blocker therapy was better: 1) in subjects with QTc interval ≥500 ms (HR 0.27, $p < 0.001$) than for those with QTc interval <500 ms (HR 0.67, $p = 0.14$); 2) in subjects with LQT1 (HR 0.29, $p < 0.001$) and LQT2 (HR 0.47, $p = 0.01$) than in subjects with LQT3 (HR 1.67, $p = 0.44$); and 3) in subjects with a prior cardiac event before age 18 (HR 0.45, $p < 0.001$) than those without a prior cardiac event (HR 0.66, $p = 0.33$). Beta-blocker efficacy was similar in subjects with LQT1 and LQT2 genotypes (interaction $p = 0.28$), but efficacy of beta-blockers in those with either LQT1 or LQT2 genotype was significantly better than in those with LQT3 (interaction $p = 0.04$).

We evaluated the risk factors for any cardiac event in a subset of 570 adults who were asymptomatic before age 18. As shown in (Table 3), the risk factors were similar to those found in the entire study population (Table 2), but beta-blockers showed only a weak trend toward reduction in cardiac events in this lower-risk group (HR 0.68, $p = 0.37$).

ACA OR LQTS-RELATED DEATH. When analyzing for ACA or LQTS-related death (excluding syncope) after age 18 years (Table 4), we found that women maintained an increased relative risk compared with men (HR = 2.68). Also, a QTc interval of 500 to 549 ms (vs. ≤499 ms) was associated with an HR of 3.34, whereas a QTc interval ≥550 ms (vs. ≤499 ms) contributed an HR of 6.35. Moreover, any QTc interval ≤499 ms was found not to contribute independently to an increased risk of a lethal event (compared with QTc interval ≤439 ms). The history of a cardiac event before age 18 was not a risk factor for a potentially lethal cardiac event, but time-dependent interim syncope after age 18 years was a risk factor for ACA or LQTS-related death (HR = 5.10). Time-dependent beta-blocker therapy during follow-up was associated with a

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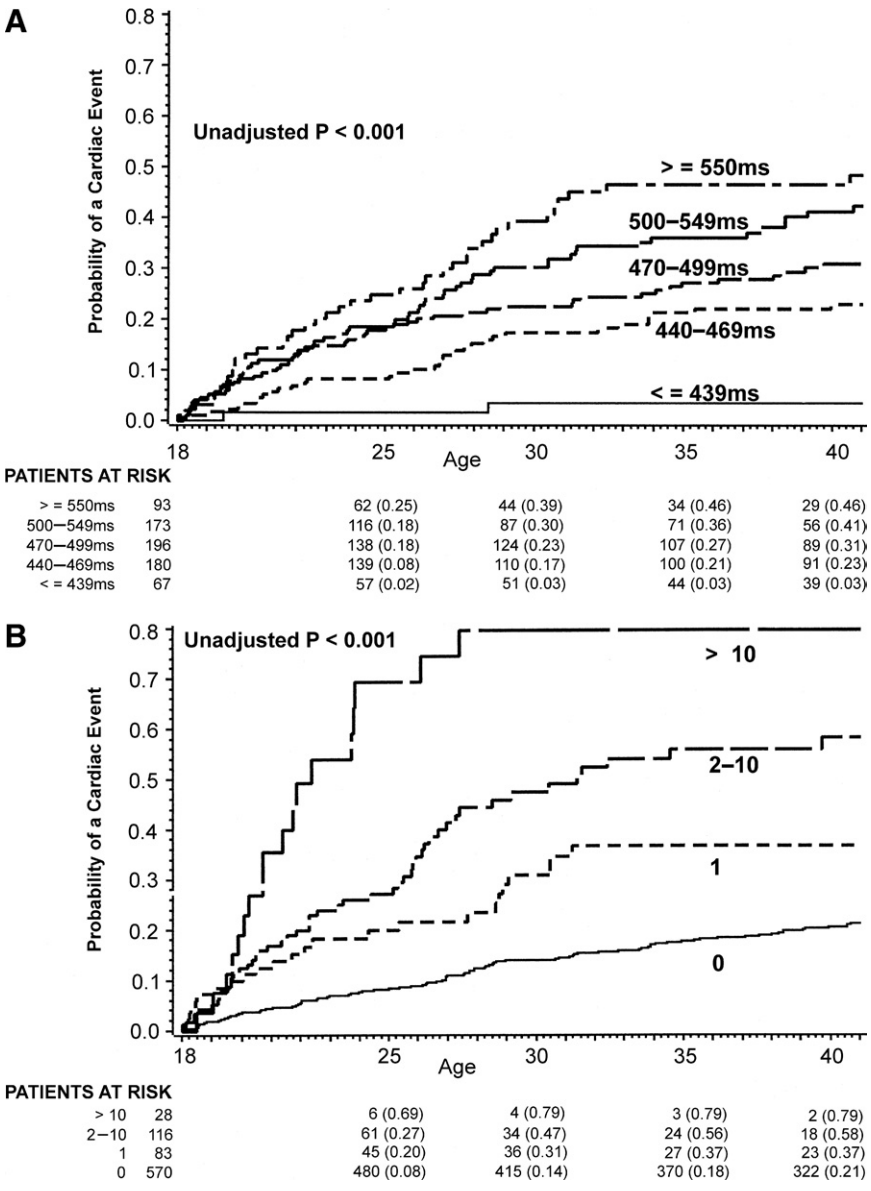

Figure 1 **Probability of Any Cardiac Event**

Kaplan-Meier estimate of the cumulative probability of any cardiac event (syncope/aborted cardiac arrest [ACA]/long QT syndrome [LQTS]-related sudden death) after age 18 years among mutation-carrying subjects on the basis of: **(A)** corrected QT interval; **(B)** number of cardiac events before age 18 years; **(C)** gender; and **(D)** genotype. The p value was computed with the log-rank test, and they are unadjusted for covariates. The numbers of subjects remaining at risk are given at 5-year intervals beginning at age 25 years, with the numbers in parentheses indicating the cumulative probability of a cardiac event at the specified age. *Continued on next page.*

significant 60% reduction in the risk for ACA or LQTS-related sudden death (HR = 0.40), but interaction analyses did not reveal a significant difference in the life-saving benefit of beta-blocker therapy between the LQT1 and LQT2 genotypes. There were insufficient numbers of ACA/LQTS-related sudden death events in LQT3 to evaluate a difference in beta-blocker efficacy between LQT1 and/or LQT2 and LQT3.

In the subgroup of 570 patients who were asymptomatic before age 18 years, the risk factors for ACA or LQTS-related sudden death (Table 5) were similar to the total population (Table 4). Interim beta-blocker therapy had a borderline significant effect in reducing fatal or near-fatal cardiac events (HR 0.22, p = 0.05).

Discussion

We found that adult patients with mutation-confirmed LQTS can be risk-stratified by genotype, gender, QTc duration, and history of a cardiac event—with clear

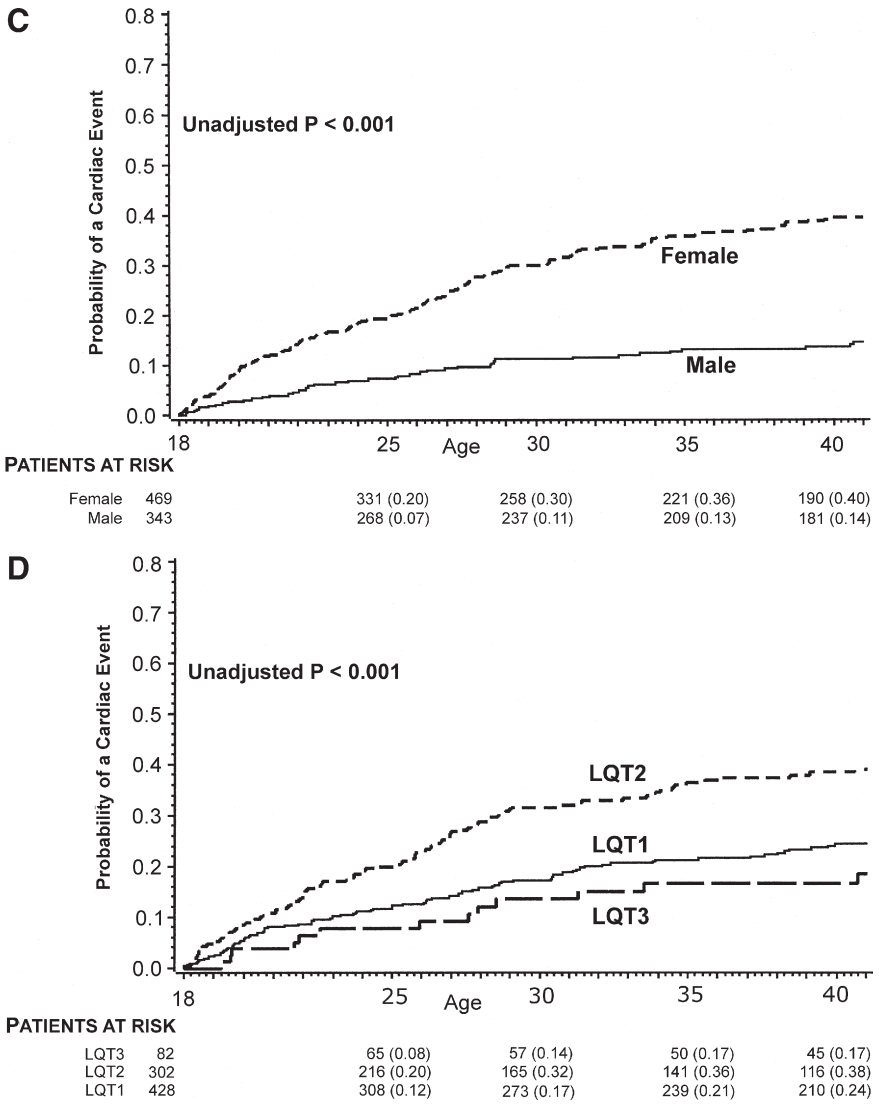

Figure 1 Continued

evidence of risk reduction by beta-blocker therapy. In 2003, Priori et al. (4) developed a risk stratification scheme (with birth as time origin and first cardiac event before therapy as the primary end point) among patients with LQT1-3. Priori et al. and Zareba et al. (4,9) demonstrated that genotype, QTc interval, and gender (in some cases) were important predictors of a first cardiac event during childhood and adolescence when using birth as the time-origin. Of note, our study is a contingent analysis that provides new findings regarding LQTS risk stratification among adult patients and extends the findings from our prior report that dealt with the modulating effect of age on outcome in LQTS (9). The current analysis examines the more important ACA or LQTS-related death end points that have not been specifically examined in adult subjects. Furthermore, our study considered time-dependent beta-blocker therapy and history of cardiac events as significant contributors to appropriate risk stratification in adult LQTS subjects with known mutations, whereas previous studies did not include these variables in risk stratification (4,5).

Risk stratification regarding any cardiac event. Our findings are consistent with existing evidence that genotype is an important independent risk factor among genotype-positive patients when looking at any first cardiac event during adulthood. Patients with LQT2 mutations are at a greater risk for a cardiac event than patients with LQT1 or LQT3 genotypes (9). Women had a significantly elevated risk and increased rate of cardiac events when compared with male adult patients. Priori et al. (4) demonstrated that gender was not an independent predictor of risk except when coexistent with an LQT3 mutation, in which case men were at increased risk. The differing results can be explained by noting that Priori used birth as time-origin and most of the

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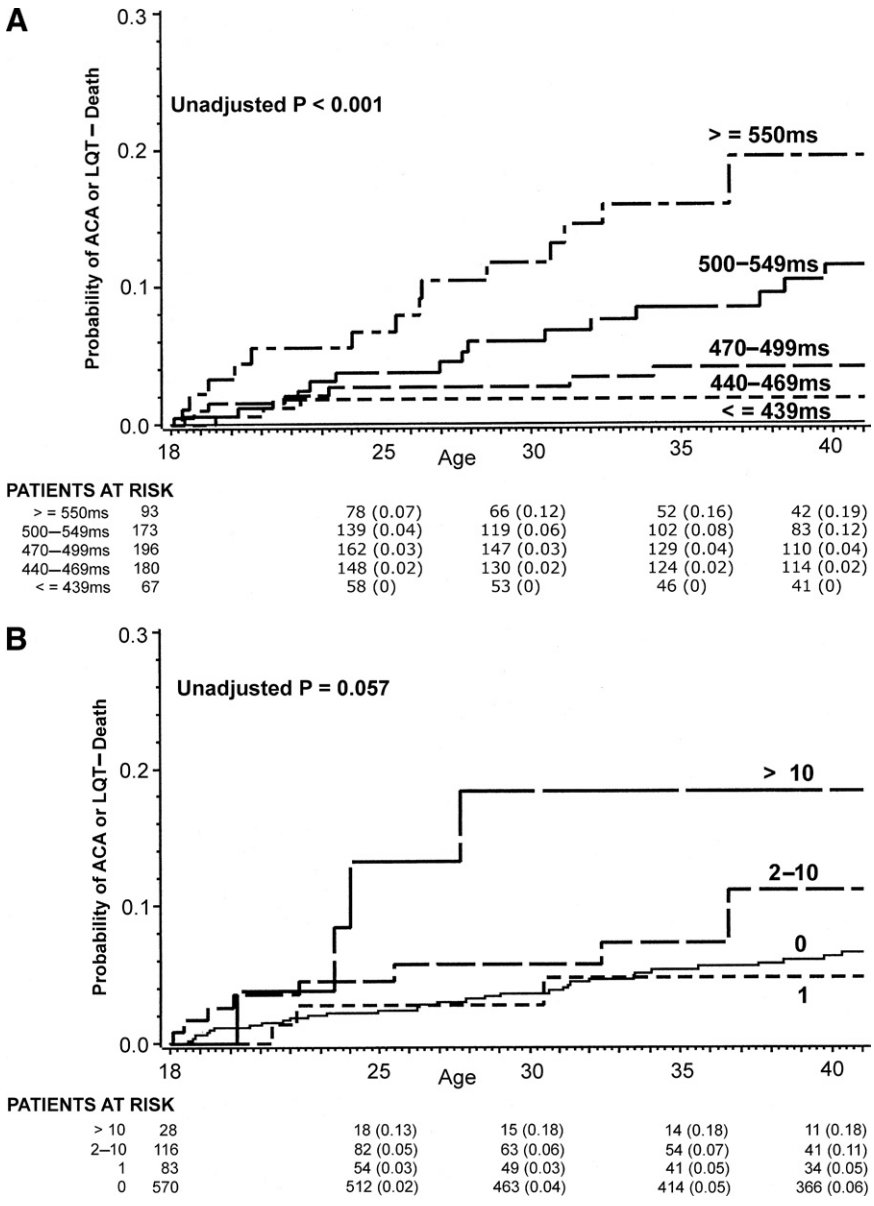

Figure 2 **Probability of ACA or LQTS-Related Death**

Kaplan-Meier estimate of the cumulative probability of aborted cardiac arrest (ACA) or long QT syndrome (LQTS)-related sudden death (syncope excluded) after age 18 years among mutation-carrying subjects on the basis of: **(A)** corrected QT interval; **(B)** number of cardiac events before age 18 years; **(C)** gender; and **(D)** genotype. The p value was computed with the log-rank test and is unadjusted for covariates. The numbers of subjects remaining at risk are given at 5-year intervals beginning at age 25 years, with the numbers in parentheses indicating the cumulative probability of a cardiac event at the specified age. *Continued on next page.*

first events occurred in childhood or adolescence, a time-period when boys have been found to be at increased risk (8,9). Also, Locati et al. (8) demonstrated in 1998 that gender-related differences in cardiac events were age-dependent in LQTS, with girls experiencing an increasing risk of cardiac events compared with boys during adolescence. A clear explanation does not exist regarding the age-related difference in the risk of cardiac events by gender, but several studies have pointed toward the influence of sex hormones that might modulate ion-channel kinetics (16–19).

In adulthood, an increased QTc interval remains a significant independent predictor of cardiac events. Patients who had experienced more than 1 syncopal event before age 18 years had HRs ranging from 5.4 to 12.0, depending on the number of previous events. Patients without cardiac events before age 18 were at reduced risk for subsequent cardiac events, but these patients still experienced LQTS-related events in their adult years.

Risk stratification regarding life-threatening events. Potential lethality of LQTS in adulthood, measured by ACA

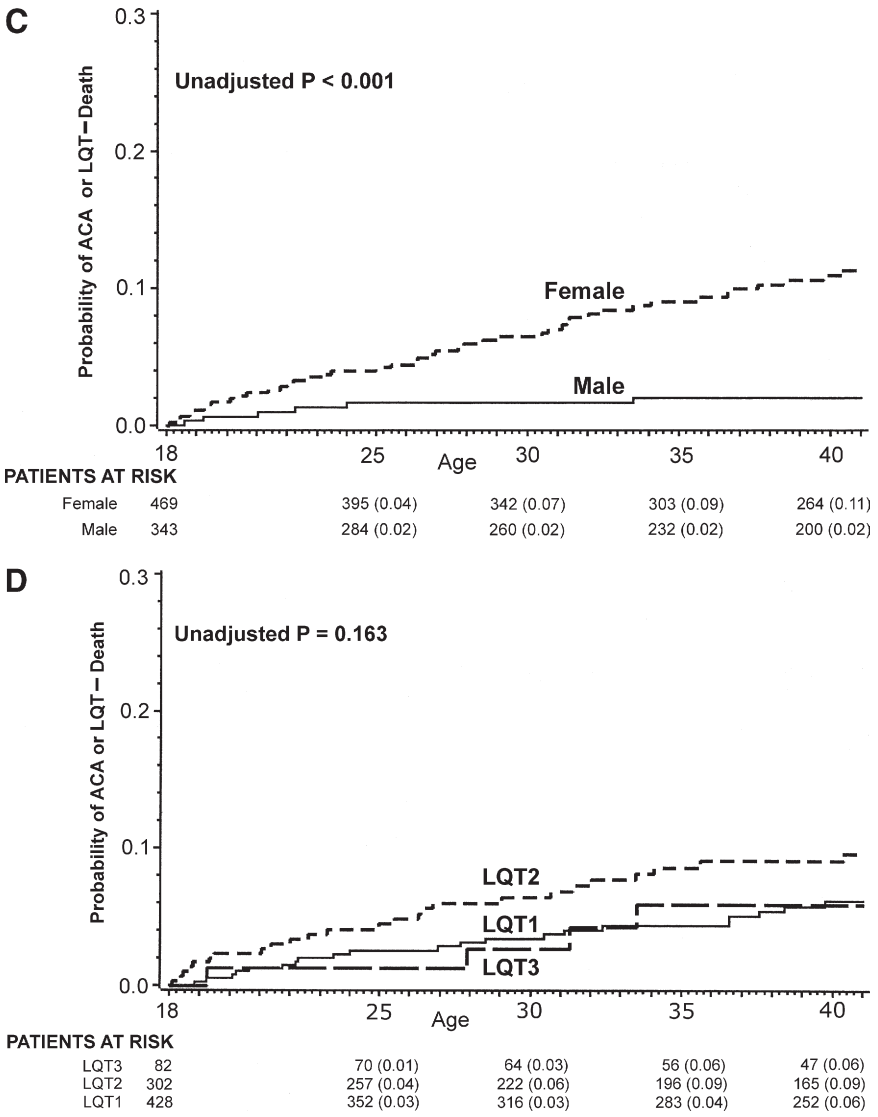

Figure 2 Continued

or LQTS-related sudden death, was related to female gender, QTc duration of ≥500 ms, and interim syncope after age 18. No previous study included interim syncope as a risk factor in the proportional hazards model (4,5), because syncope during adulthood cannot be used as a covariate risk factor when syncope is also used as an end point event. In our large population, we had an adequate number of ACA/LQTS-related sudden death end point events exclusive of syncope to evaluate time-dependent syncope as a risk factor in the risk-stratification model. Genotype, history of syncope before age 18, and a QTc interval <500 ms were not independent predictors of ACA/LQTS-related death. We speculate that although genotype has been considered an important predictor of cardiac events in prior studies looking at younger populations (4,5), the risks of female gender, prolonged QTc interval, and interim time-dependent syncope supersede genotype as more significant contributing risk factors for lethal cardiac events in adulthood.

Beta-blocker therapy. Previous observations in 2000 by Moss et al. (20) found that LQT1 and LQT2 patients benefited significantly from beta-blocker therapy (as represented by a reduction in cardiac events during adolescence), whereas patients with LQT3 genotype were not shown to have a significant benefit from beta-blockers. In that publication, some patients with LQT1, LQT2, and LQT3 died suddenly while receiving beta-blockers (20). Clearly, beta-blockers do not prevent sudden cardiac death in all LQTS patients. In the current study, beta-blocker usage is more effective in preventing cardiac events in LQT1 and LQT2 than in LQT3. In 2004, Priori et al. (21) demonstrated differing event rates among patients receiving beta-blocker therapy on the basis of genotype, with LQT2 and LQT3 subjects having higher risk when compared with LQT1

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Table 2 Hazard Ratios for First Cardiac Event Age 18 to 40 Years

Factor	Hazard Ratio	95% CI	p Value
History of a cardiac event before age 18 yrs			
1 cardiac event (vs. no event)	2.43	1.53–3.87	<0.01
2–10 cardiac events (vs. no event)	5.36	3.64–7.91	<0.01
>10 cardiac events (vs. no event)	12.01	6.93–20.80	<0.01
Genotype			
LQT2 vs. LQT1	2.27	1.67–3.10	<0.01
LQT3 vs. LQT1	1.15	0.63–2.12	0.65
LQT2 vs. LQT3	1.97	1.08–3.58	0.03
Gender			
Female (vs. male)	3.05	2.13–4.38	<0.01
QTc category			
440–469 ms (vs. ≤439 ms)	4.93	1.18–20.57	<0.05
470–499 ms (vs. ≤439 ms)	6.71	1.63–27.67	<0.01
500–549 ms (vs. ≤439 ms)	9.58	2.33–39.47	<0.01
≥550 ms (vs. ≤439 ms)	10.07	2.41–42.16	<0.01
Time-dependent beta-blocker therapy			
Beta-blockers (vs. no beta-blockers)	0.41	0.27–0.64	<0.01

CI = confidence interval; QTc = corrected QT interval.

subjects. These earlier studies were significant for noting both the effectiveness and limitations of beta-blocker therapy in mutation-confirmed LQTS patients. However, prior investigators did not specifically restrict their analyses to adult subjects, nor were they able to look at potential lethality (particularly in adults) as an expressly defined end point for multivariate analysis to assess for independent predictors of life-threatening events. In our study of patients over the age of 18 years, beta-blockers provided approximately a 60% overall reduction in the risk of syncope/ACA/LQTS-related sudden death and in the risk of ACA/LQTS-related sudden death in adulthood, with a greater beneficial effect in those with longer QTc intervals. Identified high-risk patients, especially those having cardiac events while taking beta-blockers, might benefit from an implantable defibrillator (22) or left cardiac sympathetic denervation (23) for the prevention of fatal events.

Table 3 Hazard Ratios for First Cardiac Event Age 18 to 40 Years in 570 Patients Without Cardiac Events Before Age 18 Years

Factor	Hazard Ratio	95% CI	p Value
Genotype			
LQT2 vs. LQT1	2.42	1.54–3.79	<0.01
LQT3 vs. LQT1	0.98	0.47–2.03	0.96
LQT2 vs. LQT3	2.46	1.23–4.92	0.01
Gender			
Female (vs. male)	2.77	1.66–4.62	<0.01
QTc Category			
440–469 ms (vs. ≤439 ms)	7.74	1.04–57.84	<0.05
470–499 ms (vs. ≤439 ms)	8.80	1.19–65.05	<0.05
500–549 ms (vs. ≤439 ms)	14.75	1.99–109.10	<0.01
≥550 ms (vs. ≤439 ms)	21.29	2.85–159.38	<0.01
Time-dependent beta-blocker therapy			
Beta-blockers (vs. no beta-blockers)	0.68	0.30–1.57	0.37

Abbreviations as in Table 2.

Table 4 Hazard Ratios for Aborted Cardiac Arrest or LQTS-Related Death Age 18 to 40 Years

Factor	Hazard Ratio	95% CI	p Value
Gender			
Female (vs. male)	2.68	1.10–6.50	<0.05
QTc category			
500–549 ms (vs. ≤499 ms)	3.34	1.49–7.49	<0.01
≥550 ms (vs. ≤499 ms)	6.35	2.82–14.32	<0.01
Time-dependent interim syncope age 18–40 yrs			
Interim syncope (vs. no interim syncope)	5.10	2.50–10.39	<0.01
Time-dependent beta-blocker therapy			
Beta-blockers (vs. no beta-blockers)	0.40	0.17–0.98	<0.05

LQTS = long QT syndrome; other abbreviations as in Table 2.

Study limitations. Our study included only subjects with mutations involving the 3 major genotypes, and these genotypes are thought to account for the majority of LQTS patients. The selection of mutation-confirmed subjects might have contributed to a selection bias, with inclusion of subjects at increased risk for cardiac events. In the analyses, beta-blocker therapy was modeled as a time covariate. This means that at each point in time (age), those receiving beta-blockers were compared with those not receiving beta-blockers within each covariate pattern. If a patient was not taking beta-blockers at the time of event, his/her event would count in the off beta-blocker group, regardless of whether he/she had ever been taking beta-blockers in the past. By the same token, if a patient began taking beta-blockers and then died the next day, his/her event would count in the on beta-blocker group. Although we know whether subjects were prescribed beta-blockers, we do not know for sure whether they actually took the beta-blocker on the day of a fatal event, so the therapy analysis in this

Table 5 Hazard Ratios for Aborted Cardiac Arrest or LQTS-Related Death Age 18 to 40 Years in 570 Patients Without Cardiac Events Before Age 18 Years

Factor	Hazard Ratio	95% CI	p Value
Gender			
Female (vs. male)	3.34	0.98–11.43	0.05
QTc category			
500–549 ms (vs. ≤499 ms)	3.27	1.18–9.02	<0.05
≥550 ms (vs. ≤499 ms)	6.52	2.33–18.28	<0.01
Time-dependent interim syncope age 18–40 yrs			
Interim syncope (vs. no interim syncope)	9.76	3.86–24.65	<0.01
Time-dependent beta-blocker therapy			
Beta-blockers (vs. no beta-blockers)	0.22	0.05–1.01	0.05

Abbreviations as in Tables 2 and 4.

study follows the intention-to-treat principle. Although syncopal events can be due to causes other than LQTS-related cardiac arrhythmias, we considered sudden onset and offset of loss of consciousness in an LQTS subject as syncope due to an arrhythmia unless there was evidence by history for another explanation.

The study included LQTS families of various sizes, and a few large families could dominate the results. As a secondary analysis, we removed these large families from the study population and repeated the major analyses with remarkably similar findings.

Conclusions. This study has identified risk factors associated with fatal or near-fatal cardiac events in adult subjects with genotype-positive LQTS. Beta-blocker therapy is effective in reducing the frequency of potentially fatal events and should remain a mainstay of therapy in adults with this disorder.

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