Journal of the American College of Cardiology Vol. 51, No. 24, 2008

Published by Elsevier Inc.
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2008.02.068

STATE-OF-THE-ART PAPER

Long QT Syndrome

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The hereditary long QT syndrome (LQTS) is a genetic channelopathy with variable penetrance that is associated with increased propensity to syncope, polymorphous ventricular tachycardia (torsades de pointes), and sudden arrhythmic death. This inherited cardiac disorder constitutes an important cause of malignant ventricular arrhythmias and sudden cardiac death in young individuals with normal cardiac morphology. Risk assessment in affected LQTS patients relies upon a constellation of electrocardiographic, clinical, and genetic factors. Administration of beta-blockers is the mainstay therapy in affected patients, and primary prevention with an implantable cardioverter defibrillator or left cervicothoracic sympathetic denervation are therapeutic options in patients who remain symptomatic despite beta-blocker therapy. Accumulating data from the International LQTS Registry have recently facilitated a comprehensive analysis of risk factors for aborted cardiac arrest or sudden cardiac death in pre-specified age groups, including the childhood, adolescence, adulthood, and post-40 periods. These analyses have consistently indicated that the phenotypic expression of LQTS is time dependent and age specific, warranting continuous risk assessment in affected patients. Furthermore, the biophysical function, type, and location of the ion-channel mutation are currently emerging as important determinants of outcome in genotyped patients. These new data may be used to improve risk stratification and for the development of gene-specific therapies that may reduce the risk of life-threatening cardiac events in patients with this inherited cardiac disorder.
(J Am Coll Cardiol 2008;51:2291–300) © 2008 by the American College of Cardiology Foundation

This review focuses on the inherited form of the long QT syndrome (LQTS) and will not cover acquired causes of QT prolongation. Hereditary LQTS is a familial disorder in which most affected family members have delayed ventricular repolarization as manifest on the electrocardiogram (ECG) as QT prolongation. This genetic channelopathy has variable penetrance, with affected individuals having an increased propensity to syncope, polymorphous ventricular tachycardia (torsades de pointes), and sudden arrhythmic death. The estimated overt prevalence of this disorder is in the range of about 1:5,000 subjects. However, because the number of genotyped LQTS patients having 2 LQTS mutations is approximately 10%, the prevalence of LQTS patients with overt or subclinical disorders is likely to be considerably greater than the currently estimated prevalence.

The first family with LQTS, described by Jervell and Lange-Nielsen in 1957, consisted of 4 children with deafness, recurrent syncope, sudden cardiac death, and QT prolongation on the ECG (1). Subsequently, this disorder was found to be due to homozygous mutations of the KCNQ1 gene, with the deafness being a recessive manifestation of the reduced potassium current (I_{Kr}). Romano et al. in 1963 (2) and Ward in 1964 (3) described families in which affected members had QT prolongation, recurrent syncope, and sudden death without deafness with an autosomal dominance pattern of inheritance. The first therapy for this disorder was reported in 1971 with the introduction of left cervicothoracic sympathetic denervation (LCSD) (4). The usefulness of beta-blockers in the treatment of this disorder was appreciated in the mid-1970s. The International Long QT Syndrome Registry was established in 1979, and extensive clinical and genetic studies have been and are derived from this Registry (5). The Registry currently involves 1,276 proband-identified LQTS families involving over 3,600 clinically or borderline affected family members with about 2,000 of these family members with genetically confirmed LQTS mutations. Publications from the International LQTS Registry have provided insight into risk mechanisms; genotype-phenotype associations; risk stratification by age, gender, and genotype; and the importance of syncope as a cardiac event that frequently precedes aborted cardiac arrest (ACA) or sudden cardiac death (SCD).

Genetic and Molecular Understanding

Clinically, LQTS is identified by abnormal QT interval prolongation on the ECG. The QT prolongation may arise from either a decrease in repolarizing potassium currents or an inappropriate late entry of sodium into the myocyte (6). Most commonly, QT prolongation is produced by delayed repolar-

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Manuscript received December 31, 2007; revised manuscript received February 19, 2008, accepted February 26, 2008.

JACC Vol. 51, No. 24, 2008
June 17, 2008:2291–300

Abbreviations and Acronyms

ACA = aborted cardiac arrest

ECG = electrocardiogram

ICD = implantable cardioverter-defibrillator

LCSD = left cervicothoracic sympathetic denervation

LQTS = long QT syndrome

QTc = corrected QT

SCD = sudden cardiac death

ization due to mutations in the α-subunit of ion channels involving either the slowly (I_{Ks}, KCNQ1, LQT1) or rapidly (I_{Kr}, KCNH2, LQT2) acting repolarizing cardiac potassium currents (7). Infrequent forms of LQTS may result from mutations involving the auxiliary β-subunits to KCNQ1 (minK, LQT5) (8) and KCNH2 (MiRP1, LQT6) (9), although there is not full agreement regarding the function of MiRP1. Mutations of the sodium-channel protein are associated with prolonged depolarization due to a small persistent inward "leak" in cardiac sodium (Na^+) current I_{Na} (SCN5A, LQT3) (10). The LQT1, LQT2, LQT3, LQT5, and LQT6 genes make up the classic genetic forms of LQTS. At the present time, over 300 different LQTS-related mutations have been identified on these 5 genes (11), and it is this group of ion-channel genes that has characterized LQTS as a channelopathy. During the past few years, mutations in other genes have been identified in single individuals or just a few families in what can be categorized as "LQTS-related" disorders. These disorders involve mutations in the following genes: ankyrin-B gene, which functions as a cytoskeletal membrane adapter (LQT4) (12); KCNJ2 gene, with reduction in Kir2.1 current and a phenotype dominated by skeletal abnormalities (Andersen-Tawil syndrome) (LQT7) (13); CACNA1C gene, with increase in $Ca_v1.2$ current and associated with syndactyly in both hands and feet (Timothy syndrome) (LQT8) (14); cavelolin-3 gene, with increase in late sodium current (LQT9) (15); and SCN4B gene, also with increase in late sodium current (LQT10) (16). Whether these genes should be categorized as LQTS4, LQTS7, LQTS8, LQTS9, and LQTS10 genotypes, respectively, is somewhat controversial at this time.

The protein structure of each of the ion channels (KCNQ1, KCNH2, SCN5A) consists of a series of aminio acids with an N-terminus region, the 6 membrane-spanning segments with connecting intracellular cytoplamic loops (S2–S3 and S4–S5) and a pore area (S5–S6), and a C-terminus region. The KCNQ1 (LQT1) and KCNH2 (LQT2) genes belong to the family of voltage-gated potassium ion channels in which a tetramer of 4 α-subunits makes up each channel. The SCN5A sodium channel is a single protein, a conjoined tetramer with 4 α-subunit divisions. Two distinct biophysical mechanisms mediate the reduced repolarizing current in patients with potassium-channel mutations: 1) coassembly or trafficking defects, in which mutant subunits are not transported properly to the cell membrane and fail to incorporate into the tetrameric channel, with the net effect being a $\leq$50% reduction in channel function (haploinsufficiency); and 2) formation of defective channels involving mutant subunits, with the altered channel protein transported to the cell membrane and resulting in a dysfunctional channel having >50% reduction in channel current (dominant-negative effect). In patients with SCN5A sodium-channel mutations, the channel fails to close properly after initial depolarization and continued leakage of sodium into the channel results in prolongation of the action potential.

Genotype-phenotype studies of LQTS have provided new insights into risk mechanisms, electrocardiographic features, and long-term clinical course associated with this inherited disorder. For example, each of the 3 major genotypes (LQT1 to LQT3) seems to have a distinctive T-wave repolarization pattern on the ECG, as shown in Figure 1 (17,18).

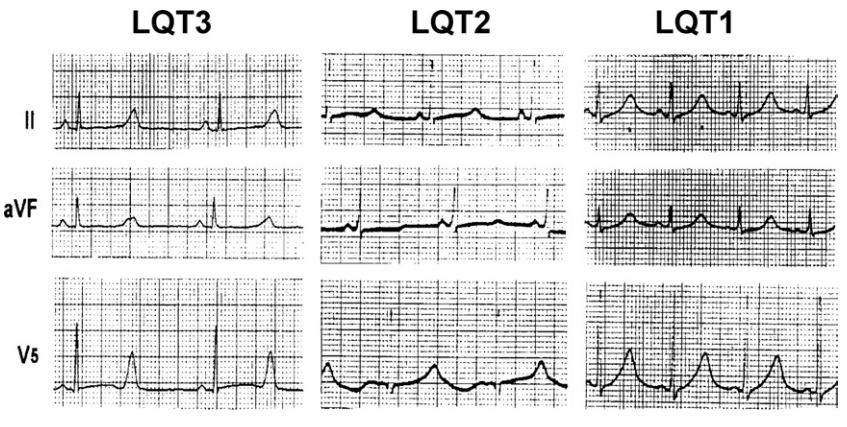

Figure 1 **Distinctive T-Wave Patterns in the 3 Major LQTS Genotypes**

T-wave morphology by LQTS genotype: LQT1: typical broad-based T-wave pattern (corrected QT [QTc] 570 ms); LQT2: typical bifid T-wave (QTc 583 ms); and LQT3: typical late-onset peaked/biphasic T-wave (QTc 573 ms). Reprinted, with permission, from Moss et al. (17).

Diagnosis

The diagnosis of LQTS relies mainly on ECG findings and clinical history. When marked corrected QT (QTc) prolongation is present, the diagnosis is straightforward. For less clear cases, a scoring system has been introduced in which other characteristics are taken into account.

ECG assessment. An accurate measurement of the QT interval is valuable for the diagnosis of LQTS. The QT interval should be determined as a mean value derived from at least 3 to 5 cardiac cycles (heart beats), and is measured from the beginning of the earliest onset of the QRS complex to the end of the T-wave. The QT measurement should be made in leads II and V_5 or V_6, with the longest value being used. The QT interval is usually corrected for heart rate using the Bazett formula ($QTc = QT/RR^{0.5}$, with all intervals in seconds) which remains the standard for clinical use despite some limitations at particularly fast or slow heart rates (in which the formula may overcorrect or undercorrect, respectively). Based on analysis of digitized data for QT and RR interval measurements in healthy individuals, a simple 3-level ECG classification was developed (Table 1) (19).

Clinical assessment. When a prolonged QTc is identified after a syncopal event in the absence of acquired causes of QT prolongation (see subsequent text) the diagnosis of LQTS can be made, and ECGs should be obtained on all first-degree family members to determine whether others are affected. Unexplained sudden death in a young individual should trigger a similar evaluation to determine if LQTS is present in the family. Rarely, an asymptomatic individual is identified with LQTS by QTc prolongation on an ECG obtained for another reason.

Gathering detailed information regarding family history in a suspected individual is essential because careful questioning may reveal a long-term pattern of similar episodes (syncope, sudden death), not only in first-degree relatives (mother, father, siblings, children), but also in more remote relatives in the family. Data on comorbidities in evaluated individuals or family members (such as congenital deafness) should also be acquired.

It is important to distinguish acquired factors that result in QT prolongation from the inherited form of LQTS through careful history. Causes of abnormal prolongation of the QT interval include myocardial ischemia, cardiomyopathies, hypokalemia, hypocalcemia, hypomagnesemia, autonomic influences, drug effects, and hypothermia.

Table 1 Suggested Bazett-Corrected QTc Values for Diagnosing QT Prolongation

Rating	1–15 yrs	Adult Male	Adult Female
Normal	<440	<430	<450
Borderline	440–460	430–450	450–470
Prolonged	>460	>450	>470

Values are given in ms. Reprinted, with permission, from Goldenberg et al. (19).

When the diagnosis is not clear, a clinical scoring system based on personal and family history, symptomatology, and ECG has been developed (Table 2) (20). Additional methods of testing, including Holter and exercise testing, have been suggested to improve diagnosis in borderline cases. Holter monitoring is not sufficiently well standardized to serve in the primary assessment for ventricular repolarization analysis. However, this method can sometimes be used for the detection of extreme QT interval events that occur infrequently during the day (21). Exercise testing, with a standard activity protocol, can be used for the evaluation of QT prolongation during the exercise and recovery periods (22). However, the adaptation of QT interval duration to heart rate is not instantaneous, and substantial errors may be introduced if nonstationary episodes are analyzed. A differential response of LQT1 and LQT2 patients to epinephrine infusion has been reported, and epinephrine challenge was suggested to be a significant provocative test in the unmasking of low-penetrance KCNQ1 mutation carriers (23).

Role of genetic testing. Genetic testing has so far largely been used for research purposes, making the phenotypic assessment cited in the preceding text the mainstay in the diagnosis of this genetic disorder. The recent commercial marketing of short-turnaround-time (approximately 6 weeks) LQTS genetic diagnostic testing, and increasing availability of testing through university-affiliated laboratories, may establish genetic testing as a clinical tool. However, before widespread use, the clinical validity of LQTS genetic testing needs to be more widely established. In a recent study of 541 consecutive unrelated patients referred to the Mayo Clinic's Sudden Death Genomics Laboratory for LQTS genetic testing (24), the yield of genetic testing was shown to be highest (72%) among tested individuals with the highest clinical probability. Thus, the current genetic test can be expected to capture approximately three-fourths of phenotypically affected LQTS individuals, whereas a negative genetic test in a subject with clinical LQTS (i.e., genotype-negative/phenotype-positive LQTS) provides no basis for removing the diagnosis (25). Despite this, a positive genetic test may influence treatment decisions (see subsequent text) and may provide the means for precise "carrier" status classification of potentially at-risk relatives. Furthermore, genetic testing may be important in the identification of concealed LQTS, because a significant minority (25% to 50%) of individuals with genetically proven LQTS have a nondiagnostic QTc (26).

Clinical Course

The clinical course of patients with LQTS is variable, owing to incomplete penetrance. It is influenced by age, genotype, gender, environmental factors, therapy, and possibly other modifier genes (27–29). Importantly, the clinical risk in LQTS is age specific. Therefore, continuous risk assessment is warranted in patients with this genetic disorder. The main

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Table 2 Diagnostic Criteria for LQTS

Finding	Score
Electrocardiographic†	
Corrected QT interval, ms	
≥480	3
460–470	2
450 (in males)	1
Torsades de pointes‡	2
T-wave alternans	1
Notched T-wave in 3 leads	1
Low heart rate for age§	0.5
Clinical history	
Syncope‡	
With stress	2
Without stress	1
Congenital deafness	0.5
Family history‖	
Family members with definite LQTS	1
Unexplained SCD in immediate family members <30 yrs old	0.5

Scoring: ≤1 point, low probability of long QT syndrome (LQTS); 2 to 3 points, intermediate probability of LQTS; and ≥4 points, high probability of LQTS. †Findings in the absence of medications or disorders known to affect these electrocardiographic findings. The corrected QT interval is calculated by Bazett's formula: $QT/RR^{0.5}$. ‡Torsades de pointes and syncope are mutually exclusive. §Resting heart rate below the second percentile for age. ‖The same family member cannot be counted in both categories. Reprinted, with permission, from Schwartz et al. (20).

SCD = sudden cardiac death.

clinical and genetic risk factors in LQTS are considered separately in the following sections.

Gender. Accumulating data from the International LQTS Registry demonstrate that the phenotypic expression of LQTS displays major time-dependent gender differences in the risk of nonfatal and life-threatening cardiac events (Fig. 2) (30). Locati et al. (31) showed that male gender is independently associated with a significant 85% and 72% increase among probands and affected family members, respectively, in the risk of cardiac events (comprising syncope, ACA, or SCD) before age 15 years, whereas a gender risk reversal was shown to occur after age 14 years, in which girls displayed an 87% increase in the risk of cardiac events compared with boys among probands and a 3.3-fold increase in the risk among affected family members. Zareba et al. (32) showed that during childhood, LQT1 boys exhibited a 71% increase in the risk of a first cardiac event compared with corresponding girls, whereas no significant gender-related difference in the risk was shown among LQT2 and LQT3 carriers during the same time period. Consistent with the results of Locati et al. (31), that study demonstrated gender risk reversal after age 16 years, in which the risk of cardiac events was more than 3-fold higher among both LQT1 and LQT2 girls compared with the respective boys.

More recent studies from the International LQTS Registry, in which risk factors for life-threatening cardiac events (ACA or SCD) were assessed (28,29,33), demonstrated that the onset of gender risk reversal for this more severe end point occurs at a later age (Fig 2B). In a study of 3,015 LQTS children, the cumulative probability of a first life-threatening cardiac event from age 1 to 12 years was 5% in boys compared with only 1% among girls ($p < 0.001$) (33), whereas in the age range of 12 to 20 years, Hobbs et al. (28) showed that there is no significant gender difference in the risk. Risk reversal for the end point of ACA or SCD was shown to occur after the age of 20 years. Sauer et al. (29), in an analysis of 812 mutation-confirmed LQTS patients, showed that during adulthood, women have nearly a 3-fold increase in the risk of ACA or SCD compared with men. The risk associated with female gender in the post-adolescence period may be related to hormonal factors. Androgens were shown to blunt QT-interval prolongation in response to quinidine (34) and therefore may be associated with QT shortening in men after childhood. In contrast, estrogens were demonstrated to modify the expression of potassium channels and may have a dose-dependent blocking effect on I_{Ks} (35). The possible relationship between female hormones and arrhythmic risk is also supported by a recent study from the Registry that showed a significant increase in the risk of cardiac events in the 9-month post-partum period, mainly among women who were identified as LQT2 genotype carriers (36).

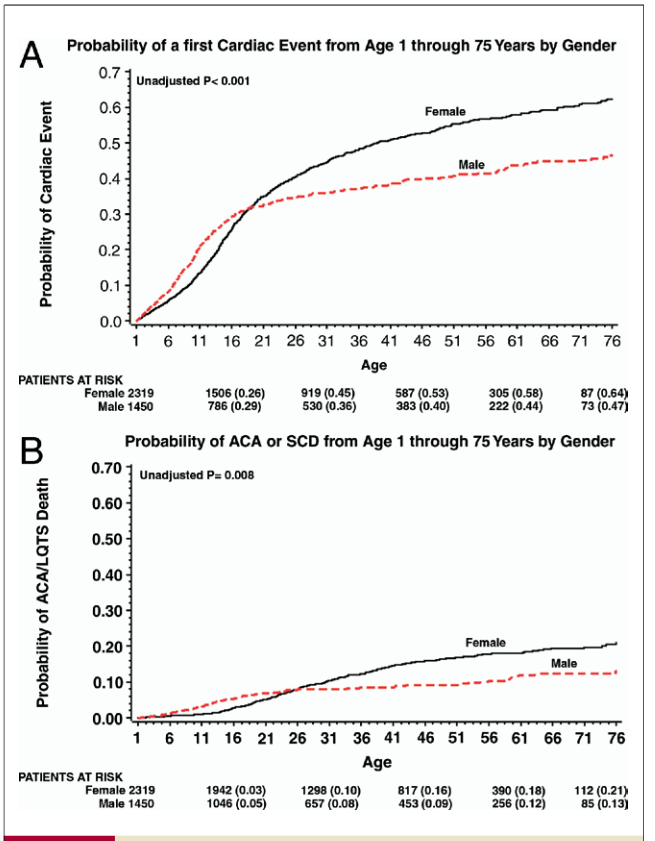

Figure 2 Probability of LQTS-Related Events by Gender

Kaplan-Meier estimates of the cumulative probability of **(A)** a first cardiac event (syncope, aborted cardiac arrest [ACA], or sudden cardiac death [SCD]) and **(B)** a first life-threatening cardiac event (ACA or SCD) from age 1 through 75 years by gender in 3,779 long QT syndrome (LQTS) patients from the International LQTS Registry. Reprinted, with permission, from Goldenberg et al. (30).

QTc duration. A baseline QTc interval of ≥500 ms has consistently been shown to be associated with a high risk of cardiac events (comprising syncope ACA or SCD) in LQTS patients (37–41). More recent data regarding risk factors for life-threatening cardiac events (ACA or SCD) have confirmed the role of baseline QTc duration as a major risk factor for this end point (28,29,33). In the study by Hobbs et al. in LQTS adolescents (age 28), a baseline QTc duration of ≥530 ms was shown to be independently associated with a 2.3-fold ($p = 0.001$) increase in the risk of ACA or SCD compared with shorter QTc values. Consistently, Sauer et al. (29) demonstrated that in LQTS adults, baseline QTc durations between 500 and 549 ms were associated with a 3.3-fold increase in the risk of ACA or SCD compared with shorter QTc values, and QTc ≥550 ms was associated with a 6.3-fold increase in the risk. These studies, however, assessed only the risk associated with QTc duration that was measured at the baseline, first recorded ECG. We have recently shown that follow-up ECG recordings provide important incremental prognostic information in LQTS patients (42). In a study of 375 children with ECG follow-up data, we showed that there is considerable variability in QTc interval duration when serial ECGs are recorded, and that the maximum QTc duration measured at any time during follow-up is the most powerful predictor of subsequent cardiac events, regardless of baseline QTc values (42). These findings further demonstrate that the phenotypic expression of LQTS is dynamic and suggest that QTc data from follow-up ECG recordings should be incorporated into the risk assessment of LQTS patients.

Time-dependent syncope. Early LQTS studies have traditionally assessed the combined end point of a first cardiac event (comprising syncope, ACA, or LQTS-related SCD). In these studies, the predominant component in the combined end point was syncope, mainly owing to sample size limitations. Recent data from the International LQTS Registry have facilitated a comprehensive analysis of risk factors for the more severe end point of ACA or SCD that is clinically more important in the affected population (28,29,33). These studies have consistently demonstrated that a history of syncope, assessed as a time-dependent factor, is the most powerful predictor of subsequent life-threatening cardiac events in LQTS patients. Furthermore, the timing and frequency of the syncopal events were also shown to affect outcome. Thus, in LQTS adolescents (age 10 to 20 years), patients with 2 or more syncopal episodes in the last 2 years were shown to have an 18-fold increase in the risk of subsequent life-threatening cardiac events ($p < 0.001$), those with 1 syncopal episode in the last 2 years had a 12-fold increase in the risk ($p < 0.001$), and those with 1 or 2 or more episodes of syncope 2 to 10 years before (but none in the last 2 years) had a 3-fold increase in the risk compared with patients without a history of syncope in the past 10 years (Table 3) (28). Similarly, in LQTS adults (age 18 to 40 years) time-dependent syncope after age 18 years was shown to be associated with >5-fold increase in the risk of subsequent life-threatening cardiac events, whereas more distant syncopal history (before age 18 years) was not a significant risk factor (29). These findings further stress the importance of dynamic risk assessment in LQTS patients.

Table 3 Age-Specific Risk Factors for Life-Threatening Cardiac Events in LQTS Patients*

Age Group (Ref. #)	Risk Factor	Hazard Ratio (p Value)	Beta-Blocker Efficacy, % Reduction (p Value)
Childhood (1–12 yrs) (33)	Male gender	3.96 (<0.001)	73% (0.002)
	QTc >500 ms	2.12 (0.02)	
	Prior syncope		
	Recent (<2 yrs)	14.34 (<0.001)	
	Remote (≥2 yrs)	6.45 (<0.001)	
Adolescence (10–20 yrs) (28)	QTc >530 ms	2.3 (<0.001)	64% (0.01)
	Syncope		
	≥2 syncopal events in past 2 yrs	18.1 (<0.001)	
	1 syncopal event in past 2 yrs	11.7 (<0.001)	
	≥2 syncopal events in past 2–10 yrs	5.8 (<0.001)	
	1 syncopal events in past 2–10 yrs	2.7 (<0.001)	
Adulthood (18–40 yrs) (29)	Female gender	2.68 (<0.05)	60% (<0.01)
	QTc duration		
	QTc ≥500 ms	6.35 (<0.01)	
	QTc 500–549 ms	3.34 (<0.01)	
	Prior syncope	5.10 (<0.01)	
Adulthood (41–60 yrs) (53)†	Recent syncope (<2 yrs)	9.92 (<0.001)	42% (0.40)‡
	QTc >530 ms	1.68 (0.06)	
	LQT3 genotype	4.76 (0.02)	

*Findings are from separate multivariable Cox models in each age group for the end point of aborted cardiac arrest or sudden cardiac death. †Because long QT syndrome (LQTS)–related events are more difficult to delineate in the older age group, the end point in the 41 to 60 years age group comprised aborted cardiac arrest or death from any cause. ‡Lack of a statistically significant beta-blocker effect in this age group may relate to the broad end point of death from any cause.

QTc = corrected QT interval.

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LQTS genotypes. Gene-specific differences have been described in terms of morphology of the ST–T wave complex (Fig. 1) (17,18), triggers for cardiac events (43–45), and risk of cardiac events (38–40). Life-threatening cardiac events have been shown to occur under specific circumstances in a gene-specific manner. Patients with the LQT1 genotype seem to have a high frequency of cardiac events associated with vigorous physical activities, whereas patients with the LQT2 genotype are at high risk of having arrhythmic events triggered by a sudden loud noise, such as the ringing of an alarm clock. Patients with the LQT3 genotype experience events without emotional arousal during sleep or at rest (43–45). Swimming has been described as an LQT1-specific arrhythmogenic trigger (45). It has been suggested that arrhythmic risk is related to the presence of specific LQTS genotypes. A previous study, which assessed the risk of cardiac events of any type, demonstrated a significantly higher risk among patients with LQT1 and LQT2 mutations compared with those with LQT3 mutations (39). However, the lethality of cardiac events was found to be significantly higher in LQT3 than in LQT2 and LQT1 family members (39). More recent reports that assessed the end point of ACA or SCD suggest that data regarding a specific genotype (LQT1, LQT2, or LQT3) do not contribute significantly to outcome after adjustment for clinical risk factors, including gender, QTc duration, and time-dependent syncope (28,29,33). This may be related to variable penetrance among patients carrying the same genotype (46). Several modifier factors, including genetic polymorphisms in the same gene carrying the primary genetic defect and environmental factors have been implicated as determinant of incomplete penetrance (27).

Biophysical function and location of LQTS mutations. Recent genotype-phenotype studies from the International LQTS Registry have provided important information regarding the effect of location, coding type, and biophysical function of the channel mutations on the phenotypic manifestations and clinical course of LQTS patients (Fig. 3) (47,48). In a study of 600 patients with 77 different KCNQ1 mutations, the biophysical function of the mutations, categorized according to dominant-negative (>50%) or haploinsufficiency (≤50%) reduction in cardiac repolarizing I_{Ks} potassium channel current, was shown to be an important determinant of outcome. Patients with dominant-negative ion channel dysfunction had a >2-fold increase in the risk of cardiac events compared with those who harbored mutations with haploinsufficiency effects ($p < 0.001$), and patients with transmembrane mutations had a significantly higher risk of cardiac events compared with C-terminus mutations (hazard ratio 2.06; $p < 0.001$) (47). Notably, several recent studies have reported that the dominant-negative KCNQ1-A341V mutation is associated with a particularly high clinical severity independently of the ethnic origin of the families (49–51). The location of the mutation was also shown to be an important determinant of arrhythmic risk in LQT2 patients (48). Patients with pore mutations in the LQT2 gene were shown to have more severe electrocardiographic and clinical manifestations compared with subjects with nonpore mutations, resulting in a higher frequency of arrhythmia-related cardiac events (74% vs. 35%, respectively; $p < 0.001$) occurring at an earlier age (48). The U.S., Japan, and the Netherlands LQTS registries are currently cooperating in the analysis of the risk associated with additional mutation sites in LQT2 patients and of the phenotypic expression of different ion-channel mutations in LQT3 patients.

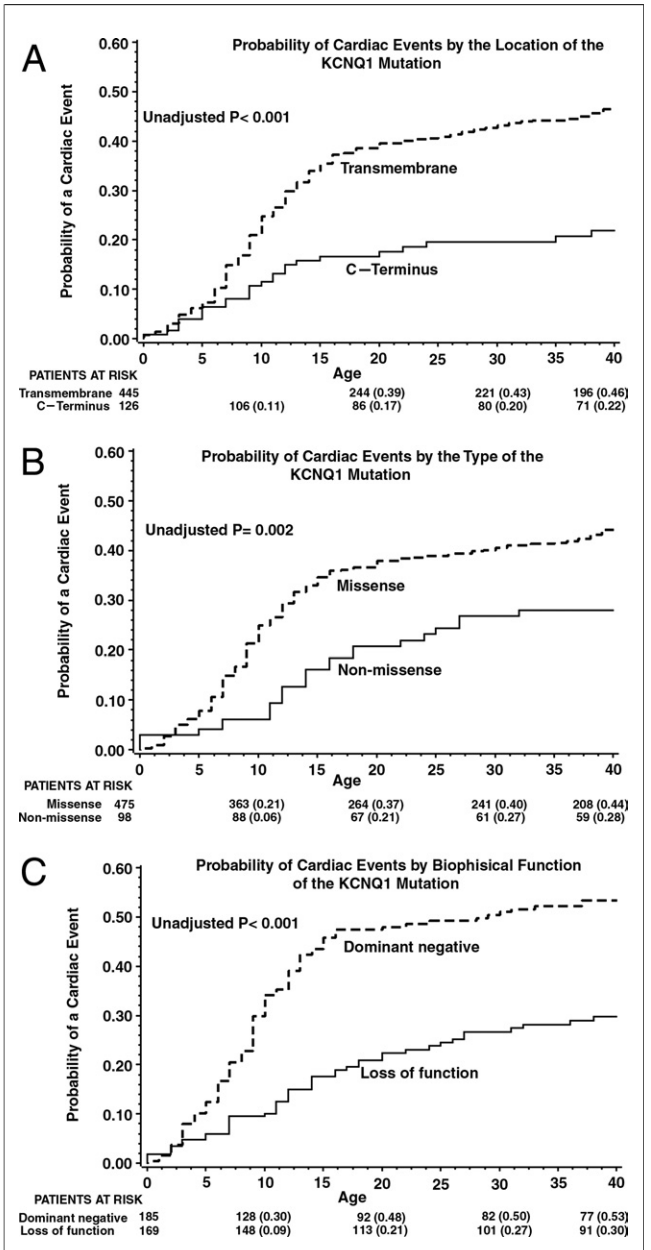

Figure 3 **Probability of Cardiac Events in LQT1 Patients**

Kaplan-Meier estimates of the cumulative probability of a first cardiac event in KCNQ1 mutation carriers (LQT1 genotype) by **(A)** location, **(B)** type, and **(C)** biophysical function of the mutation. Reprinted, with permission, from Moss et al. (47).

Risk stratification for life-threatening cardiac events in LQTS patients. Based on published mortality rates, LQTS risk groups may be categorized as high (history of aborted cardiac arrest and/or ECG-documented episodes of torsades de pointes), intermediate (time-dependent syncopal history and/or QTc prolongation >0.50 s), and low (affected subjects without history of prior syncope and with QTc duration ≤0.50 s) risk (Fig. 4) (52). It should be remembered, however, that these risk groups represent a simplified approach, because risk factors in LQTS are time dependent and age specific. More specific data from recent Registry studies regarding high-risk subsets for life-threatening cardiac events in each age group are presented in Table 3 (28,29,33,53).

Therapeutic Consideration

Owing to the low prevalence of LQTS, it is not possible to assess the benefit of suggested therapies through prospective randomized trials. Therefore, data regarding therapeutic efficacy in affected patients are based on observational long-term studies in heterogeneous risk subsets, necessitating complex statistical analyses to avoid possible bias related to nonrandomized administration of proposed LQTS-related therapies to high-risk patients. Medical, device, and surgical therapies have been evaluated for the primary and secondary prevention of LQTS-related cardiac events. These are considered separately in the following sections.

Beta-blockers. Medical therapy with beta-blockers is considered to be first-line prophylactic therapy. These drugs should be administered to all intermediate- or high-risk affected individuals and considered on an individual basis in low-risk patients (Fig. 4). An alternative therapeutic approach, recommended by some physician-investigators, is to administer beta-blockers in all LQTS patients, even those at very low risk, unless there is a contraindication. Their mechanism of action is probably related to the attenuation of adrenergic-mediated triggers in this disorder, especially in individuals with the LQT1 and LQT2 genotypes (43). In a study of 139 genotyped patients, beta-blocker therapy was associated with a significant reduction in the rate of cardiac events in patients with LQT1 and LQT2 mutations, but no evident reduction in those with LQT3 mutations (52). More recent analyses from the International LQTS Registry have attempted to adjust for the fact that in an observational cohort, beta-blockers are given at the discretion of each subject's attending physician to those considered to be at high risk by assessing the benefit of time-dependent beta-blocker therapy in pre-defined risk subsets for each age group (28,29,33). The results of these studies have consistently demonstrated that beta-blocker therapy is associated with a significant and pronounced reduction in the risk of life-threatening cardiac events in high-risk LQTS patients (Table 3). However, despite these beneficial effects, a high rate of residual cardiac events has been reported in patients receiving beta-blocker therapy (28,29,33,52,54). Priori et al. (54) recently showed that, in a cohort of 335 genotyped LQTS patients receiving beta-blocker therapy, cardiac events occurred in 10%, 23%, and 32% of LQT1, LQT2, and LQT3 patients, respectively. Therefore, patients who remain symptomatic despite treatment with beta-blockers should be considered for other, more invasive, therapies.

Implantable cardioverter-defibrillator (ICD). Implantation of an ICD was shown to be highly effective in high-risk LQTS patients (55,56). In a study of 125 LQTS patients with ICDs (55), there was 1 death (1.3%) in 73 high-risk ICD patients, compared with 26 deaths (16%) in 161 non-ICD patients during mean 8-year follow-up ($p = 0.07$). Further

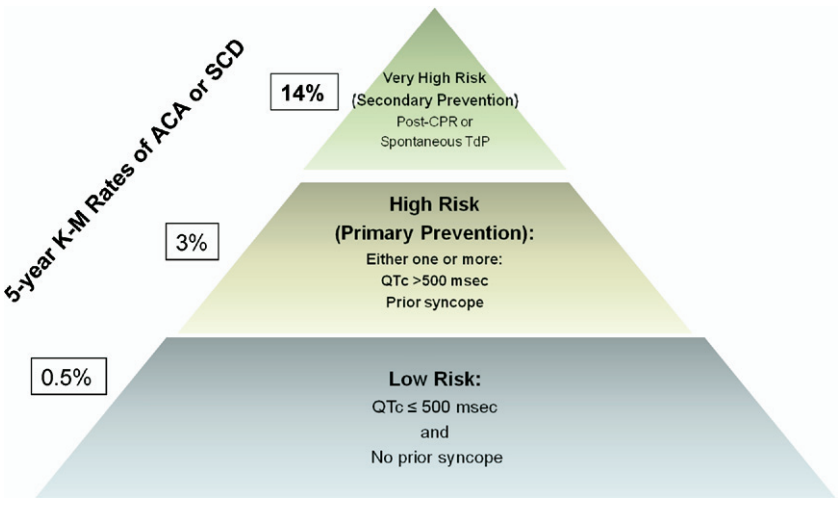

Figure 4 Suggested Risk-Stratification Scheme for ACA or SCD in LQTS Patients

Risk stratification categories for LQTS patients based on published event rates; more specific risk subsets by age group are detailed in Table 3. Kaplan-Meier (K-M) estimates are based on a series of 869 LQTS patients (52). CPR = cardiopulmonary resuscitation; TdP = torsades de pointes; other abbreviations as in Figure 2.

analysis of these data demonstrated a 4% annual rate of ICD shocks in this high-risk subset (57). Implanted defibrillators in combination with beta-blockers are indicated for secondary prevention in LQTS patients and for primary prevention in high-risk patients who remain symptomatic despite beta-blocker therapy. Early therapy with an ICD should also be considered in high-risk Jervell and Lange-Nielsen patients, because the efficacy of beta-blocker therapy was found to be limited in this population (58,59). Recent studies indicate that a family history of premature SCD is not an independent risk factor for subsequent lethal events in an affected individual (28,29,33,60). Thus, the risk to the remaining family members is dependent on the surviving family members' risk factors (QTc duration, history of syncope, gender, and age). Accordingly, our recommendation is that ICD therapy is indicated only in high-risk surviving members.

We recently developed a computer-based analytic model to compare non-ICD with ICD therapy in LQTS patients (age range 10 to 75 years) and showed that primary ICD therapy is cost-effective in high-risk LQTS males (incremental cost-effectiveness ratio [ICER] $3,328 per quality-adjusted life-year saved.) and cost-saving in high-risk LQTS females (ICER $7,102 gained per quality-adjusted life-year saved) (61). This is in contrast to adult patients with high-risk acquired cardiac disease, in whom an ICER in the range of $30,000 to $185,000 per quality-adjusted life-year saved was reported (62,63).

Surgical left cervicothoracic sympathetic denervation. This surgical procedure was introduced for the treatment of LQTS before beta-blockers became available (4). LCSD should be considered in patients with recurrent syncope despite beta-blocker therapy and in patients who experience arrhythmia storms with an ICD. A recent study comprising 147 LQTS high-risk patients showed that after LCSD, 46% remained asymptomatic. Furthermore, the mean yearly number of LQTS-related cardiac events per patient declined by 91% ($p < 0.001$), and in 5 patients with preoperative ICDs and multiple discharges the post-LCSD count of shocks decreased by 95% ($p = 0.02$). However, cardiac events, including SCD, after LCSD occurred in 54% of the study population during long-term follow-up, suggesting a relatively high rate of residual risk in treated patients (64).

Other therapeutic considerations. Pacemakers have been used in selected LQTS patients with sinus bradycardia, but long-term follow-up studies indicate an inappropriately high rate of SCD in this group of patients (65). A recent report points to focal radiofrequency ablation as a potentially valuable tool in controlling arrhythmogenesis by focal ablation of the ventricular premature beats that trigger tachycardia/fibrillation in LQTS patients (66). Further experience with this type of therapy is needed. Gene-specific LQTS therapies, including sodium-channel blockers, potassium-channel activators, alpha-adrenergic receptor blockers, protein-kinase inhibitors, and atropine, appear to be promising additions to the standard therapy for LQTS (67). However, current experience with these drugs is limited. Preventive measures are important in LQTS, and adrenergic-type stimuli, alarm clocks, and QT-prolonging drugs should be avoided.

Conclusions and Future Directions

Investigations of clinical aspects and basic causal mechanisms of LQTS have provided novel and important insight into the fundamental nature of the electrical activity of the human heart and to the relationship between disturbances in ion flow and cardiac disease. In the past few years, accumulating data from the International LQTS Registry have facilitated a comprehensive analysis of risk factors for life-threatening cardiac events, using syncopal history as a time-dependent risk factor rather than a predominant component of the cardiac event end point. Emerging data from these studies have indicated that the phenotypic expression of this genetic disorder is time dependent and age specific, displaying important gender differences in the risk among different age groups. Recent, ongoing, and cooperative studies from the U.S., Japan, and the Netherlands LQTS registries are providing important genotype-phenotype information regarding the association between the biophysical function, type, and location of the ion-channel mutation and outcome in each of the 3 major LQTS genotypes. This information is likely to provide improved criteria for risk assessment in affected patients and the background for innovative therapeutic strategies involving mutation-specific medications and possibly gene therapy.

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