Long QT Syndrome

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Abstract: The hereditary Long QT syndrome (LQTS) is a genetic channelopathy with variable penetrance that is associated with increased propensity for polymorphic ventricular tachyarrhythmias and sudden cardiac death in young individuals with normal cardiac morphology. The diagnosis of this genetic disorder relies on a constellation of electrocardiographic, clinical, and genetic factors. Accumulating data from recent studies indicate that the clinical course of affected LQTS patients is time-dependent and age-specific, demonstrating important gender differences among age groups. Risk assessment should consider age–gender interactions, prior syncopal history, QT-interval duration, and genetic factors. Beta-blockers constitute the mainstay therapy for LQTS, while left cardiac sympathetic denervation and implantation of a cardioverter defibrillator should be considered in patients who remain symptomatic despite beta-blocker therapy. Current and ongoing studies are also evaluating genotype-specific therapies that may reduce the risk for life-threatening cardiac events in high-risk LQTS patients. (Curr Probl Cardiol 2008;33:629-694.)

Melvin M. Scheinman: The comment that beta-blockers remain the mainstay of therapy for patients with the Long QT syndrome (LQTS) is true as a generalization. As will be made abundantly clear by the authors, beta-blockers appear to be less effective in some forms of the Long QT syndrome (LQT2) and are without value for other forms (LQT3).
The Long QT syndrome (LQTS) is a hereditary disorder in which most affected family members have delayed ventricular repolarization manifest on the electrocardiogram (ECG) as QT prolongation.\textsuperscript{1,2} The disorder is associated with an increased propensity to arrhythmogenic syncope, polymorphous ventricular tachycardia (torsade de pointes), and sudden arrhythmic death. LQTS is due to mutations involving principally the myocyte ion-channels, and this monogenetic disorder has an autosomal-dominant inheritance pattern. About 85% of the reported cases are inherited from one of the parents, with the remaining 15% of the affected patients having de novo mutations. The disease is relatively infrequent with an overt prevalence estimated at about 1:3,000-1:5,000 in the general population. The disorder has variable penetrance. In recent studies, two LQTS mutations were identified in approximately 10% of genotyped LQTS patients,\textsuperscript{3} and this finding suggests that this genetic disorder may be considerably more frequent than is generally appreciated. LQTS patients may be especially susceptible to drug-induced cardiac arrhythmias. Clinical and genetic studies of patients with LQTS have provided unique insight into the electrophysiology of the heart and basic arrhythmogenic mechanisms.\textsuperscript{4}

In 1957, two Norwegian physicians, Drs. A. Jervell and F. Lange-Nielsen, reported a family of six siblings, four of whom were deaf with recurrent fainting attacks.\textsuperscript{5} One of the deaf children died suddenly before the family was evaluated. The other three deaf children had QT prolongation on the ECG, and two of them died suddenly. A copy of the ECG recorded a few months before one of the children died suddenly during a syncopal episode is presented in Fig 1. The parents and the two non-deaf children were healthy with normal ECGs. The very next year, Levine and Woodworth published a similar case in a deaf patient with syncopal attacks, QT prolongation, and sudden death.\textsuperscript{6} The disorder was initially described as the surdo-cardiac syndrome\textsuperscript{7} but subsequently was referred to as the Jervell and Lange-Nielsen syndrome (JLS). It is now appreciated that this syndrome is due to homogygous mutations involving the KCNQ1 gene in which the extreme severity of the cardiac condition is due to inheritance of two KCNQ1 mutations (one from each parent, ie, a double-dominant disorder). The deafness reflects a recessive disorder with the two KCNQ1 mutations resulting in sensory hearing loss due to involvement of the auditory nerves.\textsuperscript{8}

A few years after the Jervell and Lange-Nielsen publication, Romano et al in 1963\textsuperscript{9} and Ward in 1964\textsuperscript{10} reported independent families in which affected members had QT prolongation, recurrent syncope, and sudden
FIG 1. ECG recorded on July 20, 1953 in the first reported patient with deafness, recurrent syncope, and QT prolongation. The paper speed is 50 mm/s, QT = 0.48 s, RR = 0.90 s, and QTc (Bazett) = 0.51 s. (Reproduced with permission from Jervell A, Lange-Nielsen F. Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval and sudden death. Am Heart J 1957;54:59-68.)

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death without deafness, with an autosomal-dominant pattern of inheritance. This LQTS disorder without deafness was considerably more frequent than the Jervell and Lange-Nielsen syndrome and has been referred to as the Romano–Ward syndrome.

During the 1960s several individuals and families with LQTS, mostly with the Romano–Ward variant, were reported in the literature. In 1969, one of the authors of this publication (A.J.M.) saw in consultation a 39-year-old woman with normal hearing who experienced recurrent syncope and had marked QT prolongation (QTc = corrected QT = 0.69 s). With knowledge of the report by Yanowitz et al in 1966\(^1\) that left stellate stimulation in canine studies prolonged the QT interval, a left cervico-thoracic sympathetic ganglionectomy (left 7th cervical through left 2nd thoracic, including the stellate ganglion) was performed through a left supraclavicular approach.\(^{12}\) The ECG-QT findings before any interventions, with local left and right stellate block, and 6 months after left cervicothoracic sympathetic ganglionectomy are presented in Fig 2. The patient remains alive and well with modest QT prolongation and without recurrent syncpe 37 years after the ganglionectomy surgery. In a recent report relating the clinical experience with left cervicothoracic sympathetic ganglionectomy surgery for refractory LQTS in 147 patients, the overall long-term experience has been very favorable.\(^{13}\)

Melvin M. Scheinman: The original article by Yanowitz relative to the effects of left stellate stimulation was transient and, although left stellate ganglion resection has been used therapeutically, the genesis of the LQTS is clearly not due to sympathetic imbalance, as was postulated in the 1970s.

The effectiveness of beta-blockers in the treatment of LQTS was appreciated in the mid-1970s, and it has now become the treatment of choice for this disorder.\(^{14}\)

Following the report by the Rochester, NY group of the successful therapy of LQTS with left cervicothoracic sympathetic ganglionectomy in 1971,\(^{12}\) a large number of patients with LQTS were referred to the authors for clinical evaluation and therapy. About this same time, Dr. Peter Schwartz in Milan, Italy and Dr. Richard Crampton in Charlottesville, Virginia reported their experience with LQTS and the link between the left stellate ganglion and this disorder.\(^{15,16}\)

Melvin M. Scheinman: A positive experience with left stellate ganglion resection has not been universal. In a joint experience between ourselves and
FIG 2. Lead II of ECGs (paper speed, 25 mm/s) taken at rest 1 day after syncopal episode (A: QT = 0.64 s); after local left stellate-ganglion block (B: QT = 0.46 s); after local right stellate-ganglion block (C: QT = 0.72 s); and 6 months after left cervicothoracic sympathetic ganglionectomy (D: QT = 0.44 s). (Reproduced with permission from Moss AJ, McDonald J. Unilateral cervicothoracic sympathetic ganglionectomy for the treatment of long QT interval syndrome. N Engl J Med 1971;285:903-4).12
In 1979, the three of us (Moss, Schwartz, and Crampton) established the International Long QT Syndrome Registry. During the past 28 years, the Registry has enrolled 1276 proband-identified LQTS families involving over 3600 clinically or borderline-affected family members, with over 2000 of these family members having 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).

Molecular-Genetic Aspects of LQTS

Ion-Channel Genes and Currents

QT prolongation is the hallmark of LQTS and may arise from either a reduction in the outward potassium current during phase 3 of the action potential (referred to as a “loss of function”) or an augmented late entry of sodium or calcium ions into the myocytes due to malfunctioning sodium or calcium channels (referred to as a “gain of function”). The most common genetic causes of LQTS involve mutations in genes regulating the α-subunits of the following: (1) the slowly activating potassium repolarization channel (KCNQ1; LQT1) resulting in a reduction in IKs current; (2) the rapidly activating potassium repolarization channel (KCNH2; LQT2) resulting in a reduction in IKr current; or (3) the sodium channel (SCN5A; LQT3) resulting in an increase in late INa current. LQTS has been identified infrequently in patients with mutations involving the auxiliary β-subunits of KCNQ1 (minK; LQT5) and of KCNH2 (MiRP1; LQT6), although there is not full agreement regarding the function of MiRP1. A summary of LQT1, LQT2, LQT3, LQT5, and LQT6 genotypes, their altered ion-channel currents, and their relative frequency in mutation-identified LQTS patients is presented in Table 1. At the present time, several hundred different mutations have been identified in these five LQTS genes, and it is this group of ion-channel genes that has characterized LQTS as a “channelopathy.” LQT1, LQT2, and LQT3 genotypes account for 97% of the mutations identified in LQTS patients. A schematic diagram of the prolongation of the myocyte
action potential that results from a reduction in IKs (LQT1) or IKr (LQT2) currents or from an increase in late INa (LQT3) current is presented in Fig 3.

During the past few years, mutations in three other ion-channel genes have been identified in a small number of LQTS families (LQT7, −8, and −10; Table 1): (1) mutation in the KCNJ2 gene results in a reduction in Kir2.1 current, QT prolongation, and a phenotype dominated by skeletal
abnormalities (Andersen–Tawil syndrome) (LQT7)\textsuperscript{19}; (2) mutation in the CACNA1C gene results in an increase in Cav1.2 current, QT prolongation, and a phenotype characterized by syndactyly in both hands and feet and multiorgan dysfunction (Timothy’s syndrome) (LQT8)\textsuperscript{20}; and (3) mutation in the SCN4B gene (LQT10), one of the \(H9252\)/\(H11002\)-subunits of SCN5A, results in an increased late entry of sodium current into the cell with associated QT prolongation.\textsuperscript{21}

It is now appreciated that mutations in non-ion channel genes can affect ion-channel currents with resultant prolongation in ventricular repolarization and the QT interval. LQT4 is caused by mutations in the ankyrin B gene\textsuperscript{22} that produces a protein that functions as a cytoskeletal membrane adapter and is involved in the cellular organization of the

![Figure 3](https://example.com/figure3.png)

**FIG 3.** Schematic diagram of the influence of altered ion-channel currents on the action potential duration in LQTS. Inward currents are indicated below the line and outward currents are indicated above the line. The hatched rectangles denote the timing location of the effect of mutations in LQT1, −2, and −3 genes on sodium and potassium ion-channel currents. The action potential is prolonged (horizontal arrow) when there is inappropriate gain of function (GOF) in late sodium current \(I_{Na}\) or loss of function (LOF) in slowly \(I_{Ks}\) or rapidly \(I_{Kr}\) acting repolarizing potassium currents.
sodium pump, the sodium/calcium exchanger, and the inositol-1,4,5-triphosphate receptors. Recently, mutations in caveolin-3 were identified in patients with LQTS, and this new LQTS-related gene has been labeled LQT9. Electrophysiologic studies have revealed altered gating kinetics in the cardiac sodium channel with resultant increase in sustained late sodium current (Na\textsubscript{1.5}) probably due to direct protein–protein interactions. Thus, LQT4 and LQT9 may be considered “channelopathic-related disorders” (Table 2), and it is likely that mutations in other channelopathic-related genes will be identified in the future to account for some of the 25% or so LQTS patients who are negative for mutations in the eight classical channelopathy genes.

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**Melvin M. Scheinman:** In addition to the 10 recognized genetic mutations causing LQTS, two additional genetic mutations were described at the last American Heart Association meeting. One involved the Yotiao protein complex (Chen M, Marquardt ML, Tester DJ, et al. Circulation 2007;116:11-653; abstract), which produces abnormalities in the IKs current and mutations in alpha-1-syntrophin (Vatta M, Ai T, Wu G, et al. Circulation 2007;116:11-653; abstract), which produced abnormality in the Na\textsubscript{+} channel. More genetic abnormalities will likely be discovered as 25% of patients with the LQTS currently do not have a specific mutation.

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**Ion-Channel Structure and Function**

Ion channels are formed by transcription of exonic DNA from the gene into mRNA with translation into a sequence of amino acids that make up channel-protein subunits (Fig 4). The subunits are co-assembled into a structural channel protein that is transported to the cell surface through a process called trafficking. The protein is then anchored into the myocyte membrane so it can function as an ion channel. The protein channel undergoes controlled degradation and appropriate replacement. Thus, a mutation in the genetic DNA can produce an abnormal or deficient ion channel.
channel through a variety of processes that may include altered subunit assembly, trafficking deficiencies, impaired anchoring of the channel in the myocyte membrane, abnormal amino acid sequence in the protein channel, or an imbalance in the degradation-formation rates of the channel protein. Trafficking deficiencies are especially common in LQTS patients with mutations in the KCNH2 (LQT2) gene.26

The putative topology of each voltage-gated cardiac ion channel consists of a pore-forming $\alpha$-subunit and one or more attached $\beta$-subunits. The protein structure of the $\alpha$-subunits of the LQT1 and LQT2 potassium channels (KCNQ1, KCNH2) are similar and consist of a series of amino acids with an N-terminus region, six membrane-spanning segments (S1-S6) with connecting intracellular cytoplasmic loops (S2-S3 and S4-S5) and a pore area (S5-loop-S6), and a C-terminus region. Four $\alpha$-subunits join together to form a tetrameric potassium channel around a
central pore (Fig 5). The LQT7 potassium channel (KCNJ2) is a simpler channel with just two transmembrane segments that embrace a pore region. The LQT3 sodium channel (SCN5A) consists of a single protein involving four conjoined, homologous repeat α-subunits (24 membrane-spanning segments) assembled around a central permeation pathway plus one β-subunit. The LQT8 calcium channel (CACNA1C) consists of α1-subunit (24 membrane-spanning segments plus four subunits). The voltage gating, selectivity filter, inactivation plugging of the pore, role of the N- and C-terminus regions, and the modifying function of the attached subunits vary among and between the potassium, sodium, and calcium ion channels, resulting in their unique and specific functional characteristics. Recent resolution X-ray crystallographic analysis of the ion channels has provided unique insight into the structural alterations associated with specific ion-channel mutations. It is clear from the complexity of the structure of the individual ion channels that LQTS mutations that result in altered amino-acid sequences in various portions of the structural ion-channel protein can have a spectrum of effects on the channel function with mild to severe alterations in ion-channel kinetics and the phenotypic manifestations of the disorder. Genotype–phenotype studies in LQTS have revealed distinctive electrocardiographic T-wave patterns (Fig 6).
and different long-term outcomes in the LQT1, −2, and −3 genotypes (see Clinical Course and Risk Stratification section).  

**Diagnosing LQTS Patients**

**Clinical Approach**

Suspected LQTS patients are usually referred to a cardiologist or an electrophysiologist early after recently experiencing a cardiac arrhythmia, syncope, an aborted cardiac arrest, episode of palpitation, or sudden death/cardiac arrest in a relative. Since the majority of such individuals come to the physician’s attention during adolescence or early adulthood, the differential diagnosis includes a spectrum of arrhythmogenic disorders including hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), long QT syndrome, drug-induced QT prolongation, Brugada syndrome (BS), and some other even less frequent causes of sudden death in young age groups. The role of the clinician is to develop diagnostic strategies leading to a proper diagnosis, either by confirming LQTS or at least by ruling out other possible causes.
Among possible arrhythmogenic inheritable disorders, hypertrophic cardiomyopathy is the most frequent entity with an estimated 1:500 individuals affected by this disorder, whereas LQTS is estimated to be present in 1:3000 individuals. The ARVC/D and Brugada syndromes are less frequent with estimated occurrence of 1:10,000; however, the latter two disorders are associated with higher mortality. Diagnosing a patient suspected of an arrhythmogenic origin of the symptoms requires comprehensive testing to confirm or rule out the above disorders.

A 22-year-old female college athlete with recent episodes of syncope during physical training and a family history of sudden death at age <45 years might serve as a typical case. A physician evaluating this patient needs to collect more precise information about the nature of the episodes, whether they were abrupt in onset and offset, associated with a complete loss of consciousness, or presyncopal in nature. Were they preceded or not by palpitations felt shortly prior to syncope, were the episodes witnessed, and if yes, how long did they last? Was resuscitation attempted/needed, was external defibrillation used? Was there any ECG rhythm recorded during the episode, or immediately after the episode? These questions lead to the understanding of the nature and severity of the syncopal episode. Information regarding lifetime history of similar episodes should be acquired: at what age they started, was triggering factors similar, was there ECG documentation of prior episodes? History of medications taken on a continuous basis or occasionally needs to be acquired since temporary administration of a drug may contribute to significant QT prolongation and life-threatening torsades de pointes ventricular tachycardia or ventricular fibrillation.

The conditions under which the syncopal episodes occurred may also be suggestive, since arrhythmic/syncopal events occurring during exercise are more frequently observed in patients with hypertrophic cardiomyopathy, LQT1 (swimming, in particular), and catecholaminergic polymorphic ventricular tachycardia, whereas such events occur more frequently at rest in patients with LQT2, LQT3, Brugada syndrome, and ARVC/D.

Melvin M. Scheinman: Exercise-induced syncope may be a truly difficult clinical problem. In some, a vagal reaction may occur usually in the immediate recovery period but can occur at peak exercise. In addition, it is important to remember that patients with either right or left outflow tract tachycardia may present with exercise-induced ventricular arrhythmias. In children it is important to remember that serious ventricular arrhythmias may result in exercise-induced ischemia for those with aberrant origin of the coronary arteries from the aortic coronary sinuses. A cardiac echo or MRI is useful in defining the site of origin of the coronary vessels.
Gathering detailed information regarding family history is essential since 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 (like congenital deafness) should also be acquired.

Once these clinical historical data are obtained, physical examination should be performed. In cases of arrhythmogenic disorders, physical examination infrequently adds to the diagnosis, with the exception of advanced hypertrophic cardiomyopathies where sign and symptoms of heart enlargement and auscultatory evidence for obstructive flow might be present. Profound bradycardia is a feature that occurs in many patients with LQTS, but it is also frequently seen in well-trained athletes, and is therefore of limited clinical value.

**QTc Duration in Standard 12-lead ECG**

A standard 12-lead ECG is the most useful everyday tool for a clinician evaluating such a case of a 22-year-old female with recent syncope. Focusing directly on features of arrhythmogenic disorders, HCM might manifest with signs of left ventricular enlargement, including high QRS voltage criteria or an elevated QRS voltage-duration product, usually without or (at later stages) with a strain pattern. The presence of broad negative T-waves in several leads, including left precordial leads, may also be indicative of HCM. The ARVC/D is frequently characterized by negative T-waves in V2-V4, and these repolarization changes may be accompanied by QRS prolongation >110 ms that is more pronounced in the right versus left precordial leads. In both these disorders, QTc duration may be normal/borderline, or sometimes mildly prolonged. Patients with the Brugada syndrome may demonstrate spontaneous or drug-induced ST-segment elevations in leads V1-V3 with cove-type or saddleback-type morphology. Since some of the ECG patterns described above have a varying nature, it is important to obtain all ECGs ever performed to determine whether there were signs clearly indicative of, for example, the Brugada syndrome, or showing clear QTc prolongation. Any suspicion of HCM, ARVC/D, or the Brugada syndrome usually triggers further testing consisting of cardiac Echo, cardiac magnetic resonance imaging, or pharmacologic challenge with sodium-channel blockers to rule out/confirm these respective entities. Detailed description of these tests and their results relevant for diagnosing HCM, ARVC/D, or BS goes beyond the scope of this review. A comprehensive analysis of all
available ECGs in addition to the above additional testing is needed to focus on the LQTS as a primary suspect, unless one deals with a patient having a QTc >550 ms, a finding indicating LQTS as the origin of the clinical problem.

An LQTS patient may present with a QTc interval duration that is in the normal range, borderline, or prolonged, following the criteria proposed by Moss and Robinson (Table 3). The values of QTc (corrected using Bazett’s formula) are gender- and age-dependent with adult women and children showing longer values than male adults. Rautaharju et al studied over 13,000 subjects representing both males and females across ages from birth until elderly and they demonstrated that heart rate decreasing with age in males at the time of puberty contributes to gender-related difference in QTc values. The changes in heart rate (and consequently in QTc) were observed between ages 17 and 55 years, whereas in younger individuals and in individuals >55 years of age both heart rate and QTc values were similar in both males and females, indicating the potential underlying role of sex hormones.

Diagnosing patients with QTc >470 ms, especially >500 ms, is usually easier after some additional underlying causes including comorbidities, cardiomyopathies, and drugs are ruled out. The major challenge of LQTS diagnosis is related to the substantial overlap observed in genetically affected and unaffected individuals. In 1991, Vincent et al demonstrated that QTc durations ranging from 410 to 470 ms may be observed among both carriers and noncarriers in LQT1 families. This substantial overlap relates to a number of factors, including varying penetrance of genes, possible effect of modifying genes, and inadequacy of the Bazett correction formula that overcorrects QTc duration during slower heart rates that are frequently observed in LQTS patients. With increasing knowledge regarding the genetic types of LQTS, we are learning that about 50% of carriers and noncarriers may present with QTc in the gray-zone range. These patients are particularly difficult to diagnose. Such patients may benefit from analyses of multiple ECG recordings (if available), for they may show consistency of QTc prolongation or clear evidence of QTc prolongation at somewhat faster heart rates.

<table>
<thead>
<tr>
<th>Rating</th>
<th>1-15 y (ms)</th>
<th>Adult male (ms)</th>
<th>Adult female (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;440</td>
<td>&lt;430</td>
<td>&lt;450</td>
</tr>
<tr>
<td>Borderline</td>
<td>440-460</td>
<td>430-450</td>
<td>450-470</td>
</tr>
<tr>
<td>Prolonged</td>
<td>&gt;460</td>
<td>&gt;450</td>
<td>&gt;470</td>
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</table>

The diagnosis of LQTS based on QTc duration is particularly difficult in newborns. The question whether a newborn child inherited the disease is crucial for parents and for physicians taking care of LQTS families. As demonstrated by Schwartz et al., healthy newborns up to about 1 month of age frequently show a QTc interval duration that exceeds 470 ms, partially due to immaturity of the ion channels, but also because Bazett’s formula may overestimate QTc at fast heart rates in the newborn. Fridericia’s formula works somewhat better at fast heart rates.

**T-wave Morphology**

Careful analysis of T-wave morphology in a 12-lead ECG may be beneficial in the diagnosis of LQTS patients. Even in the pregenetic era, Moss et al. described different patterns of repolarization morphology in LQTS including flat T-waves, bifid/notched T-waves, broad-based T-waves with slow upslope of the initial segment, peaked T-waves, and more complex patterns reflecting merged or overlapping T- and u-waves. Malfato et al. and Lehmann et al. stressed the presence of notched T-waves in LQTS patients. Zareba et al. emphasized the presence and role of beat-to-beat changes in T-wave morphology classified as T-wave alternans (2:1 changes in repolarization morphology) and as non-2:1 T-wave alternans (now called T-wave variability). In 1995, Moss et al. evaluated the relationship between T-wave morphology and genotype and, as shown in Fig 6, specific patterns were associated with distinct genetic types of the disorder. LQT1 was found to be associated with wide, broad-based T-waves, LQT2 patients usually had low amplitude and frequently notched T-waves, and LQT3 patients were categorized with a relatively long ST segment followed by a peaked, frequently tall, T-wave. These initial observations were confirmed and further expanded on by Zhang and coworkers, who emphasized that LQT1 patients may present with normally looking T-waves. Following these findings, the identification of T-wave morphology has been used to predict genotype in the era of limited genetic testing. The genotype suggested by the T-wave morphology may provide useful information to laboratories involved in screening genes for LQTS mutations, for it could save time and effort in the genetic screening process. Currently, most laboratories favor sequential testing of all major LQTS genes.

LQTS patients frequently show abnormal T-wave morphology, and careful evaluation of all 12 leads is recommended to determine the presence or absence of even subtle changes in T-wave shape. This is particularly important and useful in patients with QTc durations in the gray zone of 420-470 ms, where the diagnosis is uncertain based on just
QTc. In patients with QTc <440 ms (which is considered normal by clinicians), abnormal T-wave morphology may provide an important hint regarding the possibility of LQTS. Abnormal, mostly flat and notched T-waves are the most pathognomonic for LQT2, especially in adolescents and adults. However, it is worth stressing that T-wave notches can occur in unaffected young children. Similar to the point made regarding QTc duration, access to multiple ECGs and careful evaluation of T-wave morphology in these ECGs may help in the diagnosis of suspected individuals.

**Melvin M. Scheinman:** The authors have well described the problem relating to proper diagnoses of the LQTS for patients in the gray zone (QTc 420-470 ms). A major problem relative to accurate measurement of the QT is the confounding influence of the u-wave. A normal u-wave is usually found in leads V2-V3; hence, measurement of the QT is best taken from leads II or V6. In addition, the average of at least three QT measurements should be taken from the lead with the longest QT interval.

**LQTS Score**

The above changes in QTc duration and T-wave morphology should be analyzed in light of the clinical history of the evaluated individual. The meaning of a QTc duration of 460 ms will be different if there is a history of frequent syncopal episodes in the past or if there is sudden death at a young age in the family. This clinical approach is reflected by a LQTS diagnostic score published by Schwartz and colleagues in the pregenetic era of LQTS diagnosis. The score, shown in Table 4, proposes that a high probability of LQTS diagnosis is present if it reaches a value of at least 4, whereas in the case of score values of 2 to 3, the likelihood of diagnosis is lower. It is important to stress that the score not only relies on QTc duration but also accounts for documented torsade de pointes, T-wave alternans, T-wave notches, as well as for bradycardia, findings frequently seen in LQTS patients. A personal history of cardiac events, diagnosis of LQTS in first-degree family members, as well as a sudden unexpected death <30 years of age further enrich the system based on ECG findings.

Tester et al studied the correlation between the LQTS score and results of genetic testing in 541 patients. In patients with a score >4, indicating a high probability of LQTS diagnosis, 72% of patients were found to be genotype-positive, whereas among patients with a score <4,
indicating lower probability of the diagnosis, 44% were positive by genetic testing. These data emphasize important limitations of phenotypic evaluation using the LQTS score.

**Other ECG Modalities for the Diagnosis of LQTS**

In the case of clear-cut QTc prolongation >500 ms, usually there is little doubt regarding the diagnosis. However, individuals with QTc <500 ms are frequently referred for exercise ECG testing, 24-hour Holter monitoring, or sometimes event monitoring. The diagnostic value of these modalities in borderline cases is still controversial. Krahn et al. demonstrated that QT hysteresis, evaluation based on a response of QT to changing heart rate during exercise testing, may be helpful in the diagnosis of suspected cases. A distinct adaptation to increased heart rate on the upslope of exercise activity compared with the early recovery period at a similar heart rate was found useful. The authors postulated that a difference in QT >21 ms between 1 minute into recovery and early exercise measured in matched heart rates may be indicative of LQTS.

### TABLE 4. Diagnostic criteria for Long QT syndrome*

<table>
<thead>
<tr>
<th>Findings</th>
<th>Score</th>
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<tbody>
<tr>
<td>Electrocardiographic†</td>
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<tr>
<td>Corrected QT interval, ms</td>
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</tr>
<tr>
<td>≥480</td>
<td>3</td>
</tr>
<tr>
<td>460-470</td>
<td>2</td>
</tr>
<tr>
<td>450 (in males)</td>
<td>1</td>
</tr>
<tr>
<td>Torsade de pointes ‡</td>
<td>2</td>
</tr>
<tr>
<td>T-wave alternans</td>
<td>1</td>
</tr>
<tr>
<td>Notched T-wave in three leads</td>
<td>1</td>
</tr>
<tr>
<td>Low heart rate for age¶</td>
<td>0.5</td>
</tr>
<tr>
<td>Clinical history</td>
<td></td>
</tr>
<tr>
<td>Syncope ‡</td>
<td></td>
</tr>
<tr>
<td>With stress</td>
<td>2</td>
</tr>
<tr>
<td>Without stress</td>
<td>1</td>
</tr>
<tr>
<td>Congenital deafness</td>
<td>0.5</td>
</tr>
<tr>
<td>Family history §</td>
<td></td>
</tr>
<tr>
<td>Family members with definite LQTS</td>
<td>1</td>
</tr>
<tr>
<td>Unexplained SCD in immediate family members &lt;30 y</td>
<td>0.5</td>
</tr>
</tbody>
</table>


†Findings in the absence of medications or disorders known to affect these electrocardiographic findings. The corrected QT interval (QTc) is calculated by Bazett’s formula: QT/RR1/2.

‡Torsade 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.
Takenaka et al\textsuperscript{40} analyzed exercise-induced repolarization changes in a cohort of 51 LQT1 and 31 LQT2 patients. The QTc and TpTec (the interval between the peak and the end of the T-wave) were $510 \pm 68$ and $143 \pm 53$ ms in LQT1 and $520 \pm 61$ and $195 \pm 69$ ms in LQT2, respectively, at baseline. These measures were both significantly larger than those observed in control subjects ($402 \pm 36$ and $99 \pm 36$ ms). Both QTc and TpTec were significantly prolonged during exercise in LQT1 patients ($599 \pm 54$ and $215 \pm 46$ ms) in whom a morphological change into a broad-based T-wave pattern was observed. In contrast, in LQT2 patients, exercise produced a prominent notch on the descending limb of the T-wave, with no significant changes in the QTc and TpTec ($502 \pm 82$ and $163 \pm 86$ ms). QT adaptation to changing heart rate was recognized as another method indicative of LQTS. As shown by Takenaka et al\textsuperscript{40}, LQT2 patients have steeper QT-RR slope than LQT1 patients during exercise. In addition, TpTe dynamics were shown to be different among subgroups. In LQT2 patients and controls, the TpTe was reduced in response to shortening of the R-R interval, thereby producing a positive TpTe/R-R slope; among LQT1 patients, the TpTe was significantly prolonged when the R-R interval shortened, resulting in a negative TpTe/R-R slope.\textsuperscript{40}

For diagnostic purposes, it is believed that the presence of QTc $>500$ ms at heart rates $<100$ beats per minute during exercise testing or Holter recordings may be indicative of LQTS, whereas values below $500$ ms are within physiologic range (again using Bazett’s formula, which is inadequate at faster heart rates).

\textbf{Melvin M. Scheinman:} I fully agree with the authors’ contention using QTc $>500$ ms at heart rates $<100$ for exercise protocols. With exercise, the RR interval will shorten much more than the QT because in the Bazett formula the measured QT is divided by the square root of the RR interval. These changes will result in marked overcorrection as the heart rate increases. In addition, with more rapid rates during exercise it becomes difficult to separate the T-wave from the next P-wave.

Holter recordings may also provide information regarding adaptation of T-wave amplitude morphology with changing heart rates.

Nemec et al\textsuperscript{41} studied the heart rate dependence of the QT interval duration in different LQTS genotypes and control subjects using computerized QT measurements obtained from Holter recordings. The dependence of the QT duration on heart rate was steeper in LQTS than in control subjects ($0.347 \pm 0.263$ versus $0.162 \pm 0.083$ at a heart rate of
100 beats/min; \(P < 0.05\)). In addition, the QT interval was significantly longer in LQT2 and LQT3 patients than in those with the LQT1 genotype at slow (533 ± 23 ms versus 468 ± 30 ms at a heart rate of 60 beats/min; \(P < 0.0001\), but not at rapid heart rates. The heart rate dependence of QT interval was steeper in LQT2 and LQT3 than in LQT1 (0.623 ± 0.245 versus 0.19 ± 0.079 at a heart rate of 100 beats/min; \(P < 0.05\)). For a given heart rate, the QT intervals varied more in LQT2 and LQT3 than in LQT1 patients (25.98 ± 11.18 ms versus 14.39 ± 1.55 ms; \(P < 0.01\)).

In a study by Couderc et al\(^4\) the T-amplitude/RR slope was significantly flatter in LQT2 patients (0.31 ± 0.27 \(\mu\)V/ms) than in both LQT1 patients (0.62 ± 0.40 \(\mu\)V/ms) and healthy individuals (0.55 ± 0.29 \(\mu\)V/ms). The above tests evaluating dynamics of repolarization are still considered more useful as research tools than in clinical practice. Nevertheless, the additive information obtained from these tests is valuable when diagnosing patients with LQTS.

Kaufman et al\(^{43}\) studied a series of ECG parameters including exercise-induced T-wave alternans in a cohort of LQTS gene carriers and healthy controls. Standard resting QTc duration was found to be most predictive among individuals with a genotype-positive status; however, there was a 78% overlap between gene carriers and noncarriers. A T-wave alternans test did not contribute to improved LQTS diagnosis.

Epinephrine testing is considered as another test in the diagnosis of LQTS. Experimental studies using pharmacological models of LQTS tests in perfused wedge preparations by Antzelevitch and Shimizu\(^{44}\) demonstrated a differential response of repolarization to epinephrine in different types of LQTS. Clinical evidence subsequently came from studies by Noda et al\(^{45}\) and Ackerman et al.\(^{46}\) The study of Noda et al\(^{45}\) showed that in LQT1 patients QTc was prolonged remarkably (477 ± 42 to 631 ± 59 ms; \(P < 0.0005\), % delta prolongation = +32%) as the RR was maximally decreased (at peak of epinephrine) and remained prolonged at steady-state conditions of epinephrine infusion (556 ± 56 ms; \(P < 0.0005\) versus baseline, +17%). In LQT2 patients, epinephrine also prolonged the QTc dramatically (502 ± 23 to 620 ± 39 ms; \(P < 0.0005\), +24%) at peak epinephrine, but this shortened to baseline levels at steady state (531 ± 25 ms; \(P = \text{ns versus baseline}, +6\%\)). The QTc was much less prolonged at peak epinephrine infusion in LQT3 patients (478 ± 44 to 532 ± 41 ms; \(P < 0.05\), +11%) and controls (394 ± 21 to 456 ± 18 ms; \(P < 0.0005\), +16%) than in LQT1 and LQT2 patients, and shortened to baseline levels (LQT3; 466 ± 49 ms, −3%, controls; 397 ± 16 ms, +1%; \(P = \text{ns versus baseline}\)) at steady state.
Subsequently Shimizu and coworkers reported the responses of 12-lead ECG parameters to epinephrine examined in 31 LQT1, 23 LQT2, 6 LQT3, and 30 control subjects. The sensitivity by ECG diagnostic criteria was lower in LQT1 (68%) than in LQT2 (83%) or LQT3 (83%) before epinephrine, and improved with steady-state epinephrine in LQT1 (87%) and LQT2 (91%) but not in LQT3 (83%), without the expense of specificity (100%).

The above findings and those of Ackerman et al suggest that epinephrine testing may be useful, particularly in differentiating borderline cases of LQTS. However, responses to epinephrine infusion must be interpreted with caution in view of the limited amount of data available involving normal controls.

Melvin M. Scheinman: The introduction of epinephrine testing has provided for a fresh approach to evaluating patients with a borderline QT interval. Several pitfalls should be recognized. It was long recognized that epinephrine infusions accentuate the u-wave and tend to merge the T- and u-waves in normals and this may confound proper measurement. In addition, to my knowledge there has been no controlled study assessing epinephrine infusion response vis-à-vis exercise in the same patient cohort. Specifically, we do not have data on the incremental value of epinephrine infusion versus exercise testing.

Genetic Testing for LQTS Diagnosis

Genetic testing adds significantly to the diagnosis of LQTS. The diagnosis may be straightforward in patients showing QTc >500 ms, and one could argue that genetic testing may offer little diagnostic or prognostic value in such clearly affected individuals. Nevertheless, there are data indicating that the clinical course is different by genotype, and the effectiveness of therapy with beta-blockers also differs in LQT1 than LQT2 and LQT3 patients. Most importantly, knowing the genetic type (mutation) in a proband provides an opportunity to conduct genotyping of family members who frequently cannot be diagnosed just based on ECG findings. Genetic testing of a proband is excessively costly and this high cost and reimbursement issues are factors limiting much wider application of the testing in clinical practice. Testing of family members for mutation(s) found in a proband should become routine to diminish overall costs of unnecessary multiple clinical testing frequently used for diagnosing individuals.

Genetic testing of individuals suspected for LQTS with QTc <500 ms is particularly useful since an overlap between affected and unaffected
individuals in this category of patients is very substantial. Standard genotyping usually focuses on the most frequent LQTS genes: LQT1, LQT2, LQT3, LQT5, LQT6, whereas the remaining genes (LQT4, LQT7-10) are tested less frequently since mutations of these genes are very infrequent. Current state of genotyping LQTS patients leads to identification of gene mutations in about 70-75% of those tested. The fact that a majority of patients can be identified with specific mutation(s) should be encouraging to both physicians and patients who should pursue this testing. Splawski et al \(^5^1\) reported, that among genotyped patients, about 45% of tested patients were identified with LQT1; another 45% of patients were identified with LQT2, and about 5-8% of patients were identified with LQT3. The remaining 1-3% were in LQT5 and LQT6 genes. Napolitano et al \(^5^2\) evaluated the yield of genetic testing in 430 consecutive patients, with 310 (72%) patients having 235 different mutations, 138 of which were novel. The distribution of detected LQTS genotypes was as follows: 49% LQT1, 39% LQT2, 10% LQT3, 1.7% LQT5, and 0.7% LQT6. Importantly, they showed that by using the sex-based cutoff values for QTc, 40% of affected individuals (ie, carriers of a genetic defect) were not identified by clinical assessment, further reinforcing the need for genetic testing.

Recent data from Taggart et al \(^5^3\) demonstrate that genetic testing supported by expert clinical evaluation may improve the diagnostic strategy of identifying LQTS patients. The authors have found that about 40% of individuals referred as having LQTS were found to be unaffected based on miscalculation of QTc or misinterpretation of symptoms. Again, genetic testing may be helpful in avoiding misdiagnoses, which carry lifelong consequences for LQTS-labeled individuals.

An additional benefit of comprehensive genetic testing may come from testing other non-LQTS genes of interest in suspected individuals. Tester et al \(^5^4\) found ryanodine receptor gene mutations responsible for the catechoaminergic polymorphic ventricular tachycardia in 17 (6.3%) of 269 patients with negative LQTS genetic testing.

The cost-effectiveness of genetic testing for LQTS is of concern. Philips et al \(^5^5\) found that genetic testing is more cost-effective than not testing for symptomatic index cases at an estimated cost of $2500 US dollar per life-year saved.

**Clinical Course and Risk Stratification**

The clinical manifestations of affected LQTS patients may span from completely asymptomatic individuals to fully penetrant and symptomatic forms, even among patients harboring the same mutation. This phenom-
enon is defined as variable penetrance, and it represents a landmark feature of LQTS that may have a profound effect on clinical presentation, risk assessment, and management. Vincent et al\textsuperscript{31,56} described the first evidence of incomplete penetrance by demonstrating a large range of QT durations among genotyped patients and proposed the existence of “silent gene carriers.” Subsequently, Priori et al\textsuperscript{57} reported families in which only 17% of carriers showed clinical signs of the disease. It was also reported that subclinical mutations may generate the substrate for drug-induced torsades de pointes.\textsuperscript{58} Several modifier factors, including genetic polymorphisms in the same gene carrying the primary genetic defect and environmental factors, have been implicated as determinants of incomplete penetrance.\textsuperscript{58} Independently from its causes, variable penetrance makes it difficult to predict the clinical outcome in each specific subject based on genetic data alone. Thus, at birth when the full clinical phenotype is not yet manifest, the predictive information can only be based on genotype and gender, whereas time-dependent clinical factors (ie, a patient’s phenotype) provide incremental prognostic information to genotype as the patient ages. Early studies that assessed the clinical course of LQTS patients were limited in two important aspects: first, the endpoint that was evaluated in these analyses comprised cardiac events of any type, in which syncope was the predominant component in the composite endpoint possibly due to sample size limitations; and second, these prior analyses used birth as the time of origin, thereby precluding an evaluation of time-dependent changes in the clinical course of affected patients. To provide a more accurate description of the phenotypic expression of LQTS, recent studies from the expanding International LQTS Registry have focused on identifying risk factors for ACA or SCD in specific age groups, with syncope assessed as a time-dependent risk factor for this more severe endpoint.\textsuperscript{59-63}

The clinical course of LQTS has been shown to be influenced by many factors, including gender, prior syncope, family history, QT-interval duration, genotype, the biophysical function, type, and location of the ion-channel mutation, and congenital deafness.\textsuperscript{2,48,49,59-70} Data regarding the effect of each of these factors on the outcome of LQTS patients are considered separately below, with a focus on age-specific risk for life-threatening cardiac events.

\textit{Time-Dependent Effect of Gender on the Clinical Course of LQTS Patients}

We recently analyzed the clinical course of 3779 LQTS patients enrolled in the Registry, of whom 2319 patients (60%) were females.\textsuperscript{61}
The cumulative probabilities of the considered two endpoints (eg, a first cardiac event of any type and a first ACA or SCD) during the childhood, adolescence, adulthood, and the >40 age groups are shown in Fig 7A-D, respectively. The results of this analysis, together with data from recent studies,\textsuperscript{59-63} consistently demonstrate that during childhood, male patients display a higher event rate than females, whereas after this time period, risk-reversal occurs, and females maintain a higher risk than males during adulthood. Notably, when the combined endpoint of any cardiac event is considered, gender risk-reversal is shown to occur during adolescence (Fig 7B), whereas when the more severe endpoint of ACA or SCD is evaluated, the change in the male–female risk occurs after the adolescence period (Fig 7C), and females continue to exhibit a significantly higher event rate throughout adulthood (Fig 7C and D).

**Gender-Related Risk During Childhood (Fig 7A).** In a study of 479 probands (70% females) and 1041 affected family members (QTc >440 ms, 58% females) from the registry, Locati et al\textsuperscript{64} showed that male gender was independently associated with a significant 85 and 72% increase in the risk of cardiac events before age 15 years among probands and affected family members, respectively. Zareba et al\textsuperscript{65} studied 533 genotyped patients from the Registry and showed that during childhood, LQT1 males experienced a significant 71% increase in the risk of a first cardiac event as compared with the corresponding females, whereas there was no significant gender-related difference in the risk of cardiac events among LQT2 and LQT3 carriers during the same time-period. In a recent analysis from the International LQTS Registry, we assessed the endpoint of ACA or SCD in 3015 LQTS children (1893 males and 1122 females) diagnosed by QTc criteria and demonstrated that male gender is associated with a 3-fold increase in the risk of life-threatening cardiac events during childhood.\textsuperscript{62}

**Gender-Related Risk During Adolescence (Fig 7B).** When the endpoint of a first cardiac event is assessed, a gender risk-reversal is consistently shown to occur with the onset of the adolescence. In the registry analysis of 479 probands and 1041 affected family members, Locati et al\textsuperscript{64} showed that in the age range of 15 through 40 years, females had a significant 87% increase in the risk of cardiac events as compared with males among probands, and a 3.3-fold increase in the risk among affected family members. Similar findings were shown by Zareba et al.\textsuperscript{65} The study demonstrated that in the age range of 16 through 40 years, the risk of cardiac events of any type was more than 3-fold higher among both LQT1 and LQT2 females as compared with the respective males. In contrast, when the more severe endpoint of a first life-threatening cardiac
event was assessed, the male versus female risk of ACA or SCD was shown to be similar during the adolescence period. Thus, in a recent study of 2772 registry patients that were followed between the ages of 10 and 20 years, Hobbs et al\textsuperscript{59} showed that males 10 to 12 years old had a 4-fold increase in the risk of ACA or SCD and an 11-fold increase in the risk of SCD compared with respective females, whereas in the age range of 12 to 20 years no significant gender difference in the risk of life-threatening of cardiac events was observed.

**Gender-Related Risk During Adulthood (Fig 7C).** Gender risk-reversal for the more severe endpoint of ACA or SCD was shown to occur after adolescence. Sauer et al,\textsuperscript{60} in an analysis of 812 mutation-confirmed LQTS patients from the registry who were followed-up between the ages of 18 and 40 years, showed that during adulthood females had a significant 3-fold increase in the risk of a first cardiac event of any type and a significant 2.7-fold increase in the risk of ACA or SCD as compared with males. Fig 7C consistently demonstrates that the cumulative probability of a first cardiac event from age 18 through 40 years is significantly higher among females (39\%) as compared with males (16\%), and the corresponding probabilities of ACA or SCD (11 and 3\%) are also higher among females than males in this age group.

**Gender-Related Risk After Age 40 Years (Fig 7D).** Published studies on the clinical course of LQTS patients are limited mostly to the first four decades of life due to lack of appropriate follow-up information in the older age group. The International LQTS Registry has recently expanded the duration of follow-up in enrolled subjects, and current updated information now facilitates a comprehensive analysis of the clinical course of affected patients beyond the age of 40 years.\textsuperscript{63} Our data indicate the risk conferred by LQTS continues to be higher among females as compared with females. Fig 7D demonstrates that during this time period the cumulative probability of a first cardiac event is significantly higher among LQTS females (31\%) as compared with LQTS males (14\%), and females also experience a marginally significant rate of life-threatening cardiac events as compared with males (7\% versus 4\%, respectively; $P = 0.05$).

**Possible Mechanisms for Gender-Related Risk in LQTS.** Interactions among genetic, hormonal, and environmental factors may contribute to the age-dependent gender-related risk among LQTS patients. Ventricular tachyarrhythmias have been shown to occur more frequently during physical effort in patients carrying the common LQT1 genotype with mutations that impair the IKs current. It has been shown that 79\% of the lethal arrhythmic episodes in LQT1 patients are associated with exercise.
FIG 7. Kaplan–Meier estimate of the cumulative probability of (i) a cardiac event of any type and (ii) a life-threatening cardiac event (aborted cardiac arrest [ACA] or sudden cardiac death [SCD]) by gender during (A) childhood; (B) adolescence; (C) adulthood; (D) after 40 years of age among 3774 LQTS patients from the International LQTS Registry. (Color version of figure is available online.)
and faster heart rates, and that LQT1 males have an earlier onset of cardiac events than the respective females. Environmental factors may predispose boys to more intensive physical activity during childhood than girls, possibly leading to a higher risk of life-threatening cardiac events.
that are associated with fast heart rates in males during this time period. With the onset of adolescence, hormonal factors may affect the clinical course of LQTS males and females. Androgens were shown to blunt QT interval prolongation to quinidine and thus may be associated with
D(i) Risk of Cardiac Events by Gender after Age 40 years

Unadjusted $P < 0.001$

Age 40—75

PATIENTS AT RISK
Female 1045
Male 527

417 (0.07)
458 (0.02)
376 (0.05)
309 (0.06)
252 (0.10)
202 (0.12)
170 (0.12)
119 (0.14)

D(ii) Risk of ACA or SCD by Gender after Age 40 Years

Unadjusted $P = 0.050$

Age 40—75

PATIENTS AT RISK
Female 1045
Male 527

876 (0.02)
498 (0.03)
622 (0.04)
415 (0.06)
330 (0.06)
250 (0.06)
180 (0.07)
129 (0.04)
QT shortening in males after childhood. In contrast, estrogens were demonstrated to modify the expression of potassium channels and may have a dose-dependent blocking effect on IKs.\textsuperscript{73} Female LQTS patients with mutations impairing potassium channel activity may therefore be specifically sensitive to estrogen activity. Furthermore, adult female patients may be exposed to conditions, such as menses and pregnancy, in which hormonal changes favor QT prolongation and vulnerability to arrhythmias.\textsuperscript{75,76} 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 postpartum period, mainly among females who were identified as LQT2 genotype carriers.\textsuperscript{77}

**QTc Interval Duration and the Risk of LQTS-Related Cardiac Events**

A prolonged QTc interval duration has been consistently demonstrated to be a major risk factor in LQTS patients.\textsuperscript{2,48,49,59,60,62,63,80} Early studies assessed the effect of this risk factor on the development of cardiac events (syncope, aborted cardiac arrest, or LQTS-related death).\textsuperscript{2,48,49} Moss et al\textsuperscript{2} showed, among 3343 individuals from 328 LQTS families, that 1-ms increments in QTc were independently associated with a 5.5% increase in the risk of cardiac events. Subsequently, Priori et al\textsuperscript{49} showed that increasing quartiles of QTc were directly correlated with the rate of cardiac events in LQTS patients. In this analysis the cumulative probability of a first cardiac event from birth through age 40 years in patients with QTc >500 ms was shown to be 70%. More recent studies from the International LQTS Registry provided important information regarding the relationship between QTc duration and the risk of life-threatening cardiac events in specific age groups of LQTS patients,\textsuperscript{59,60,62,63} and on the importance of follow-up QTc assessment in this population.\textsuperscript{81}

**QTc and the Risk of ACA or SCD During Childhood (Fig 8A).** In our recent analysis of 3015 LQTS children (ages 1 through 12 years) from the International LQTS Registry\textsuperscript{62} we have shown that the risk associated with QTc duration during this time period is related to gender. A QTc duration >500 ms was associated with nearly a 3-fold increase in the risk of fatal or near-fatal events in LQTS males, whereas QTc duration was not a significant risk factor among females. Notably, asymptomatic LQTS males (eg, who did not experience prior syncope) with a prolonged QTc duration exhibited more than a 12-fold increase in the risk of life-threatening cardiac events as compared with the respective females during childhood. Accordingly, the cumulative rate of ACA or SCD...
during childhood was significantly higher among boys with a QTc duration >500 ms than among boys with a shorter QTc duration, or girls regardless of their QTc duration (Fig 8A). These QTc–gender interactions should be considered in risk assessment during childhood.

**QTc and the Risk of ACA or SCD During Adolescence.** In the study of 2772 LQTS adolescents (age 10 through 20 years) from the International LQTS Registry Hobbs et al\(^5\) identified that the most predictive threshold for QTc prolongation in this population was 530 ms. Patients with a QTc ≥530 ms had more than a 2-fold increase in the risk for ACA or SCD compared with those with a QTc <530 ms (HR = 2.3 [95% CI 1.6-3.3]; \(P < 0.001\)), and more than a 3-fold increase in the risk of SCD alone (HR = 3.1 [95% CI 1.8-5.3]; \(P < 0.001\)). Similar, although slightly less significant, results were shown when the more traditional QTc threshold of >500 ms was considered. Thus, a prolonged QTc duration should be considered a major risk factor in both male and female LQTS adolescents.

**QTc and the Risk of ACA or SCD During Adulthood.** In the study of 812 mutation-confirmed adult LQTS Registry patients (ages 18 through 40 years),\(^6\) the cumulative probability of experiencing a first life-threatening cardiac event (eg, ACA or SCD) during this time period was shown to be directly correlated with increasing QTc intervals (Fig 8B). Consistently a QTc duration between 500 and 549 ms was shown to be associated with more than a 3-fold increase in the risk of ACA or SCD compared with shorter QTc values (HR = 3.34 [95% CI 1.49-7.49]; \(P < 0.01\)) and a QTc ≥550 ms was shown to be associated with more than a 6-fold increase in the risk of this endpoint (HR = 6.35 [95% CI 2.82-14.32]; \(P < 0.01\)).\(^6\)

**QTc and the Risk of ACA or Death After Age 40 Years.** In the recent analysis of 2759 subjects from the International LQTS Registry,\(^6\) we categorized study subjects into electrocardiographically affected (QTc ≥470 ms), borderline (QTc 440-469 ms), and unaffected (QTc <440 ms) subgroups. The affected versus unaffected adjusted hazard ratio for ACA or death was 2.65 (\(P < 0.001\)) in the age range of 41-60 and 1.23 (\(P = 0.31\)) in the age range of 61-75. Consistently, the cumulative probability of a fatal or near fatal event from age 41 through 75 years was significantly higher among subjects with QTc ≥470 ms (28%) as compared with those with QTc 440-469 ms or <440 ms (20 and 21%, respectively, \(P = 0.02\)) (Fig 8C). Thus, it appears that a prolonged QTc continues to confer increased risk in the older age group.

**Importance of Serial QTc Measurements in LQTS Patients.** In the studies described above the relationship between QTc interval duration and the risk of cardiac events was evaluated primarily for the first
recorded ECG, whereas the incremental prognostic information provided by follow-up ECGs was not assessed. To determine the importance of serial QTc measurements during long-term follow-up, we evaluated the risk of cardiac events during adolescence among 375 Registry patients for whom serial follow-up ECGs were recorded before age 10 years. The results of this study showed that there is considerable variability in serial QTc measures during follow-up (the mean ± SD difference between the minimum and maximum QTc values on serial ECGs recorded in study patients was 47 ± 40 ms), and that follow-up QTc values are clinically important and better define subsequent risk of cardiac events than a single baseline QTc value. The study demonstrated that the change in QTc values is not age-related or linear. Rather, the maximum QTc duration obtained at any time during follow-up was shown to be the best indicator of risk. These findings further stress the importance of continuous risk assessment in LQTS patients and suggest that affected patients with a single recorded QTc value <500 ms, who are currently considered to be at a lower risk, should be continually assessed since the phenotypic expression of this disease entity is dynamic and can change during follow-up.
Time-Dependent Syncope and the Risk of Subsequent ACA or SCD

Accumulating data from the International LQTS Registry has recently facilitated a comprehensive analysis of risk factors for the more severe endpoint of ACA or SCD in prespecified age groups (Table 5). These analyses have consistently demonstrated that syncope, assessed as a time-dependent risk factor, is the most powerful predictor of subsequent life-threatening cardiac events in affected patients. Furthermore, the studies showed that the timing and frequency of the syncopal event are also important determinants of outcome. These new data further stress the importance of follow-up information in LQTS patients.

Syncope and Subsequent ACA or SCD During Childhood. In our recent analysis of 3015 Registry LQTS children, time-dependent syncope was shown to be the most powerful predictor of outcome during childhood among both LQTS males and females (Table 5). Notably, the risk associated with a history of syncope was significantly higher in females than in males (P value for gender × prior syncope interaction = 0.01), and most pronounced when the event occurred within the past 2 years. Thus, in males recent syncope (<2 years) was associated with more than a 6-fold increase in the risk of subsequent ACA or SCD (P <

**Table 5. Effect of syncopal events on the development of subsequent life-threatening cardiac events in LQTS age-groups**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Syncope (timing/frequency)</th>
<th>Hazard ratio (95% confidence interval)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood</td>
<td>Males Recent syncope (&lt;2 years)</td>
<td>6.16 (3.41-11.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Remote syncope (≥2 years)</td>
<td>2.67 (1.22-5.85)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Females Recent syncope (&lt;2 years)</td>
<td>27.82 (9.72-79.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Remote syncope (≥2 years)</td>
<td>12.04 (3.79-38.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adolescence</td>
<td>1 Syncopal event in past 2 y</td>
<td>18.1 (10.4-31.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>1 Syncopal event in past 2-10</td>
<td>11.7 (7.0-19.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2 Syncopal events in past 2-10</td>
<td>5.8 (3.6-9.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>1 Syncopal events in past 2-10</td>
<td>2.7 (1.3-5.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Adulthood</td>
<td>Time-dependent syncope</td>
<td>5.10 (2.50-10.39)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>41-60 y</td>
<td>Recent syncope (&lt;2 y)</td>
<td>9.92 (4.99-19.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>61-75 y</td>
<td>Recent syncope (&lt;2 y)</td>
<td>2.13 (0.51-8.85)</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>Remote syncope (2-10 y)</td>
<td>2.76 (1.35-5.63)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*Findings are from separate multivariable Cox models in each age group for the endpoint of aborted cardiac arrest or sudden cardiac death.
†Since LQTS-related events are more difficult to delineate in the older age group, the endpoint in the 41-60 and 61-75 age groups comprised aborted cardiac arrest or death from any cause.
and more remote syncope (≥2 years) was associated with a 2.7-fold increase in the risk \( (P < 0.001) \), whereas among females recent syncope was associated with nearly a 28-fold increase in the risk and more remote syncope was associated with a 12-fold increase in the risk as compared with no syncope during follow-up. These data suggest that both QTc and prior syncope should be considered in risk assessment in LQTS boys, whereas in LQTS girls risk assessment should rely on a history of symptoms. To further confirm these findings by obtaining an estimate of event rates during childhood for patients who experienced syncope during this time period, we identified time-independent risk groups at age 6 years, stratified by the occurrence of syncope prior to age 6, and evaluated the cumulative probability of ACA or SCD from age 6 through 12 years (Fig 9A). This analysis demonstrated that the rate of life-threatening events during childhood was highest among boys who experienced prior syncope (15%), intermediate in girls with a history of syncope and asymptomatic boys (4 and 3%, respectively), and lowest in girls without a history of prior syncope (0.6%; \( P < 0.001 \)).

**Syncope and Subsequent ACA or SCD During Adolescence.** Hobbs et al\(^{59}\) showed that both the timing and the frequency of recent syncopal events are related to the risk of subsequent ACA or SCD during the adolescence period (Table 5). Compared with patients who did not experience prior syncope or experienced the event more than 10 year ago, those with one episode of syncope between 2 and 10 years ago (but none in the last 2 years) had a significant 4-fold increase in the risk \( (P < 0.001) \); those with two or more syncopal episodes in this period had a 6-fold increase in the risk \( (P < 0.001) \), and the greatest risk was observed in LQTS adolescents who experienced 1 and ≥2 syncopal events in the last 2 years (8-fold \( [P < 0.001] \) and 15-fold \( [P < 0.001] \) increase, respectively). These time-dependent events should be considered in risk assessment during the high-risk adolescence period.

**Syncope and Subsequent ACA or SCD During Adulthood.** Sauer et al\(^{60}\) showed that a history of a cardiac event before age 18 was not a significant risk factor for the development of life-threatening cardiac events in the age group of 18-40 years, whereas time-dependent syncope after age 18 years was associated with a significant 5-fold increase in the risk for subsequent ACA or SCD (Table 5). Of note, the number of syncopal events before age 18 years displayed a direct correlation with the rate of life-threatening cardiac events during adulthood (Fig 9B).

**Syncope and Subsequent ACA or SCD After Age 40 Years.** The timing of syncope was also shown to be an important risk factor in LQTS patients after age 40 years (Table 5).\(^{63}\) In the analysis of 925 LQTS
patients >40 years with QTc ≥470 ms, the risk associated with syncope was highest when it occurred within the past 2 years during follow-up (10-fold increase, \( P < 0.001 \)) and intermediate when it occurred in the past 2-10 years (3-fold increase, \( P = 0.005 \)) in the age range of 41-60 years, whereas in the age range of 61-75 years syncope in the past 2-10 years had a significant effect on outcome (3-fold increase, \( P = 0.01 \)). Syncope that occurred >10 years in the past was not a risk factor in either age group.\(^{63}\) These findings indicate that the phenotypic expression remains an important factor in predicting life-threatening cardiac events even in the older age group.

**Family History of Death in a Sibling**

The death of a sibling may be a marker of a more severe mutation, and, thus, a higher risk. However, LQTS patients demonstrate variable penetrance within families, with a wide range of QT intervals and symptoms.\(^{57}\) Accordingly, a history of sudden cardiac death in a first-degree relative was not identified in previous studies as a significant risk factor.\(^{59,60,62,63,82}\) In a recent study from the International LQTS Registry we examined 1915 LQTS probands and first- and second-degree relatives from birth through age 40 years.\(^{70}\) In this analysis, death of a sibling was assessed as a time-dependent risk factor in the multivariate model. The study showed that sibling death is not significantly associated with an increase in the rate of subsequent life-threatening cardiac events (eg, ACA or LQTS-related SCD) (Fig 10A) but is associated with an increased rate of a first cardiac event of any type (predominantly syncope) (Fig 10B). These findings suggest that SCD in a sibling does not add to risk of subsequent life-threatening cardiac events. Thus, LQTS family members in whom a sibling experienced LQTS-related death should receive treatment based on individual risk assessment.

**Genotype–Phenotype Correlations**

Genotype–phenotype correlation in the LQTS has been one of the most active lines of research in the past few years.\(^{83}\) Available evidence indicates that there is a remarkable degree of phenotypic variability as part of LQTS clinical presentation. Gene-specific differences have been reported in terms of morphology of the ST-T wave complex (Fig 6),\(^{27,36}\) triggers for cardiac events,\(^{71,84-86}\) and risk of cardiac events.\(^{48,49}\)

**Genotype-Specific Triggers for Cardiac Events.** Life-threatening cardiac events (syncope or sudden death) tend to occur under specific circumstances in a gene-specific manner (Fig 11).\(^{71}\) In a study of 670 LQTS symptomatic patients identified as carriers of one of the three main
FIG 10. Mantel–Byar graphs showing time-dependent risk of (A) ACA or SCD and (B) any cardiac event in the absence of and following the death of a sibling. Only the total number of available subjects at birth is provided, since sibling death is a time-varying risk factor in this analysis. (Color version of figure is available online.)
LQTS genotypes, LQT1 patients were shown to experience 68% of their lethal events during exercise, whereas this never occurred for LQT2 and occurred in only 4% of cases for LQT3 patients. By contrast, 49 and 64% of lethal events occurred during rest/sleep without arousal for LQT2 and LQT3 patients, respectively, whereas this occurred in only 9% of cases for LQT1 patients. Thus, sympathetic activation, induced by exercise, appears to be the most common trigger for lethal events in LQT1 patients. Among the different types of exercise, swimming was shown to be an important risk factor in the premolecular era for LQTS in general, and more recently as a specific trigger for LQT1 patients. The triggering role of sympathetic activation in LQT1 patients has important therapeutic implications, as it suggests that protection could be expected by the use of anti-adrenergic interventions. It should also be noted that, although most events in LQT2 and LQT3 patients occur at rest or during sleep, the triggers associated with lethal events for LQT2 and LQT3 patients show a different pattern (Fig 11). LQT2 patients are particularly sensitive to startling and sudden noises, such as a telephone or alarm clock ring, and

![Triggers for Lethal Events in the 3 Main LQTS Genotypes](image-url)

**Fig 11.** Triggers for lethal cardiac events according to three genotypes. Numbers in parentheses indicate number of triggers, not number of patients. (Reproduced with permission from Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome: genotype-specific triggers for life-threatening arrhythmias. Circulation 2001;103:89-95).
females with the LQT2 genotype appear to be at higher risk also in the postpartum period.\textsuperscript{77} The low rate of lethal events associated with exercise in LQT2 and LQT3 patients may be explained by the fact that these two genotypes both have a normal IKs current, which is activated by sympathetic stimuli and is responsible for the shortening of ventricular repolarization with increasing heart rate. Possibly related to the increased sympathetic activation and faster heart rates during exercise, LQT1 males were shown to have a high rate of cardiac events during childhood.\textsuperscript{86}

\textbf{Genotype-Specific Risk of Cardiac Events.} Early studies that assessed the endpoint of cardiac events among genotyped patients suggested that genotype data can be utilized for risk stratification in this population.\textsuperscript{48,49} Zareba et al\textsuperscript{48} studied 541 genotyped patients from 38 families enrolled in the International Long-QT Syndrome Registry: The study showed that the cumulative probability of cardiac events from birth through age 40 years was higher among LQT1 (63\%) or LQT2 (46\%) than among LQT3 subjects (18\%; \(P < 0.001\) for the comparison among the three genotype groups). However, the likelihood of dying during a cardiac event was significantly higher in LQT3 subjects (20\%) than among LQT1 (4\%) or LQT2 (4\%) subjects (\(P < 0.001\)). Subsequently, Priori et al\textsuperscript{49} studied 647 LQTS patients from 193 genotyped families and reported that the cumulative event rate was lowest among LQT1 patients (30\%) as compared with LQT2 (46\%) and LQT3 (42\%) patients. The lack of a consistent genotype effect in these studies may be related to the long-term follow-up in these studies that does not take into account important age-specific genotype interactions that occur during this time period. To evaluate these factors, we assessed the age-specific clinical course of 1368 genotyped patients from the International LQTS Registry for the endpoints of (i) a first cardiac event of any type and (ii) ACA or SCD, within specific age groups (Fig 12A-C). The analysis showed that LQT1 patients exhibit a high rate of cardiac events during the childhood and adolescence periods (Fig 12A), whereas after this time period a genotype–age crossover occurs, and LQT2 patients maintain a high event rate throughout adulthood (Fig 12B and C). Notably, when the endpoint of ACA or SCD was assessed, the difference in event rate among the three genotypes was attenuated before age 40 years (Fig 12A and B), whereas after age 40 years LQT3 patients were shown to have a significantly higher rate of life-threatening cardiac events. Recent reports from the International LQTS Registry that assessed the endpoint of ACA or SCD demonstrate that data regarding a specific genotype (LQT1, −2, or −3) do not contribute significantly to outcome after adjustment for clinical risk factors, including gender, QTc duration, and time-
dependent syncope. This may be related to variable penetrance among patients carrying the same genotype. Thus, clinical factors (e.g., a patient’s phenotype) may provide a more accurate representation of disease severity than genotype when assessing the risk of fatal or near-fatal events.

**Possible Effect of Modifier Genes on the Phenotypic Expression of LQTS.** As previously mentioned, the clinical manifestations of LQTS patients may span from completely asymptomatic individuals to fully penetrant and symptomatic forms, even among patients harboring the same mutation. This has led to a suggestion that modifier genes may have a possible role in the phenotypic expression of LQTS. In a recent study, Crotti et al showed that the common polymorphism K897T exaggerates the electrophysiological consequences of the LQT2 A1116V mutation. Molecular screening of a family that harbored the two mutations showed that several members had either the mutation or the polymorphism, but only the symptomatic proband had both. The functional effects of both A1116V and K897T include a reduction, by a modest amount, activating and tail IKr current densities (with K897T having a smaller effect), while the coexpression of the two mutations results in a significant and marked reduction in current. Therefore, it appears that common polymorphisms can enhance the consequences of rare LQTS mutations. Modifier genes may also increase the interaction between LQTS mutations and more prevalent arrhythmogenic substrates, such as acute myocardial infarction or heart failure.

**Biophysical Function, Location, and Coding Type of the LQTS Mutation**

Recent data indicate that the biophysical function, location, and type of an LQTS mutation are important independent risk factors influencing the clinical course of this disorder. These findings may be used to further refine risk stratification in LQTS, by including mutation-specific data.

**Mutations in the KCNQ1 Gene.** Two distinct biophysical mechanisms mediate the reduced IKs current in patients with KCNQ1 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 ≤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, resulting in a dysfunctional channel having >50% reduction in channel current (dominant-negative effect). Prior studies
A(i) Probability of Cardiac Events by the 3 Main LQTS Genotypes (Age Group: 1-18 years)

A(ii) Probability of ACA or SCD by the 3 Main LQTS Genotypes (Age Group: 1-18 years)

FIG 12. Cumulative probability of cardiac events (i) and ACA or SCD (ii) by the three main LQTS genotypes in the following age groups: (A) 1-18 years; (B) 19-40 years; and (C) 41-71 years. (Color version of figure is available online.)
B(i) Probability of Cardiac Events by the 3 Main LQTS Genotypes (Age Group: 19-40 years)

PATIENTS AT RISK
LQT1 652 448 (0.10) 362 (0.15) 332 (0.20) 256 (0.23)
LQT2 422 323 (0.15) 262 (0.26) 218 (0.30) 180 (0.24)
LQT3 84 73 (0.08) 61 (0.15) 57 (0.17) 50 (0.17)

Unadjusted P < 0.001

B(ii) Probability of ACA or SCD by the 3 Main LQTS Genotypes (Age Group: 19-40 years)

PATIENTS AT RISK
LQT1 652 488 (0.02) 439 (0.03) 388 (0.03) 340 (0.05)
LQT2 422 377 (0.02) 334 (0.04) 290 (0.06) 261 (0.07)
LQT3 84 78 (0.01) 58 (0.04) 53 (0.05) 54 (0.05)

Unadjusted P = 0.306

FIG 12. (Continued)
C(i) Probability of Cardiac Events by the 3 Main LQTS Genotypes
(Age Group: 41-71 years)

C(ii) Probability of ACA or SCD by the 3 Main LQTS Genotypes
(Age Group: 41-71 years)

PATIENTS AT RISK

FIG 12. (Continued)
that assessed the functional role of LQT1 mutations have yielded conflicting results, possibly due to sample size limitations. However, a recent cooperative study comprising 600 LQT1 patients, derived from the US portion of the International LQTS Registry, the Netherlands’ LQTS Registry, and the Japanese LQTS Registry, has facilitated a comprehensive analysis of the clinical aspects of 77 different KCNQ1 mutations categorized by their location, coding type, and type of biophysical ion channel dysfunction. The study demonstrated that subjects with mutations having dominant-negative ion current effects had a longer QTc interval and a higher cumulative probability of cardiac events than subjects with mutations resulting in haploinsufficiency (Fig 13A). Consistently, subjects with mutations having dominant-negative functional effects exhibited more than a 2-fold increase in the risk for cardiac events compared with those with haploinsufficiency mutations after adjustment for clinical covariates (HR = 2.26 [95% CI 1.56-3.25]; P < 0.001). The study further demonstrated that the cumulative probability of cardiac events in LQT1 patients is also related to the location and type of the KCNQ1 mutation. Subjects with mutations located in the transmembrane region of the channel had a significantly higher rate of cardiac events than those with mutations located in the C-terminus regions (Fig 13B), and those with missense mutations had a significantly higher event rate than those with non-missense mutations (Fig 13C). Of note, the KCNQ1-A341V mutation was associated with a particularly high rate of cardiac events, and several recent studies identified that this dominant-negative mutation is associated with a severe clinical course independently of the ethnic origin of the families.

Mutations in the HERG Gene. The pore region of the HERG channel provides the potassium conductance pathway, and most mutations involving this region are missense mutations with dominant-negative effects on IKr, whereas most mutations in the nonpore regions of HERG are associated with coassembly or trafficking abnormalities resulting in haplotype insufficiency. Accordingly, in a study of 201 subjects with a total of 44 different HERG mutations from the International LQTS Registry, subjects harboring pore mutations exhibited a more severe clinical course and experienced a higher frequency (74% versus 35%; P < 0.001) of arrhythmia-related cardiac events, occurring at earlier age, than did subjects with nonpore mutations. Furthermore, pore mutations were shown to dominate the risk after multivariate adjustment for clinical factors, exhibiting an 11-fold increase in the risk for cardiac events in subjects with QTc at 500 ms, and a 16% increase in the pore hazard ratio for each 10-ms increase in QTc. Cellular expression studies also
FIG 13. Kaplan–Meier estimate of the cumulative probability of a first cardiac event in KCNQ1 mutation carriers (LQT1 genotype) by (A) the biophysical function; (B) location; and (C) coding type of the mutation. (Reproduced with permission from Moss AJ, Shimizu W, Wilde AA, et al. Clinical aspects of type-1 long-QT syndrome by location, coding type, and biophysical function of mutations involving the KCNQ1 gene. Circulation 2007;115:2481-9).

Probability of Cardiac Events by the Biophysical Function of the KCNQ1 Mutation

Unadjusted $P < 0.001$

<table>
<thead>
<tr>
<th>Patiens at Risk</th>
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<td>10</td>
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Probability of Cardiac Events by the Location of the KCNQ1 Mutation

Unadjusted $P < 0.001$

<table>
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<th>Transmembrane</th>
<th>C-Terminus</th>
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<tr>
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<tr>
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<td>0.67</td>
<td>0.67</td>
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<tr>
<td></td>
<td>20</td>
<td>0.83</td>
<td>0.83</td>
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<tr>
<td></td>
<td>25</td>
<td>0.90</td>
<td>0.90</td>
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<tr>
<td></td>
<td>30</td>
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<tr>
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<td>40</td>
<td>1.00</td>
<td>1.00</td>
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</table>
implicate the PAS domain within the N-terminus and the cNBD domain of the C-terminus as important regulators of the biophysical properties of HERG.\textsuperscript{96-98} However, the clinical risk associated with these mutation sites has not yet been assessed. The US, Japanese, and Netherlands LQTS Registries are currently cooperating in the analysis of the risk associated with additional mutation sites in HERG gene, and with the phenotypic expression of different ion-channel mutations in the SCN5A gene.

**The Jervell and Lange-Nielsen Syndrome**

Until recently data on this autosomal-recessive form of LQTS were limited to case reports or case series. A recent study carried out by Schwartz et al\textsuperscript{68} and our recent prospective analysis of 44 JLS patients from the US portion from the International LQTS Registry\textsuperscript{69} more clearly delineate the clinical course of JLS patients from that of patients with the autosomal-dominant form of LQTS (eg, Romano–Ward syndrome [RWS]). The two studies consistently demonstrate that JLS is associated with a significantly higher rate of life-threatening cardiac events than RWS, with a very early onset, and major QTc prolongation. In our analysis of US Registry patients,\textsuperscript{69} the mean ± SD QTc in the JLS patients was 548 ± 73 ms as compared with 500 ± 48 ms in RWS.
patients \( (P < 0.001) \). Furthermore, the cumulative rate of cardiac events from birth through age 40 in JLS patients was 93\% (mean ± SD age: 5.0 ± 7.0 years) as compared with 54\% (mean ± SD age: 14.2 ± 9.3 years) in RWS patients (Fig 14A), and the respective rates of ACA or SCD during this time period were 50 and 15\% (Fig 14B). Notably, both studies reported that beta-blocker therapy is not consistently effective in JLS patients, with approximately one-third of patients experiencing a fatal event during treatment with beta-blockers. Therefore, early primary intervention with an implantable cardioverter defibrillator (ICD) should be considered in high-risk JLS patients.

**Risk Stratification for Fatal or Near-Fatal Events in LQTS Patients**

Recent studies that evaluated the endpoint of ACA or SCD in specific age groups have consistently demonstrated that the risk associated with LQTS genotype is attenuated after adjustment for the occurrence of time-dependent syncope.\(^ {59,60,62} \) Therefore, clinical factors appear to dominate the clinical course of LQTS patients when fatal or near fatal events are considered. Based on published mortality rates, LQTS risk groups may be categorized as high- (a history of aborted cardiac arrest and/or electrocardiographically documented episodes of torsade de pointes); intermediate- (time-dependent syncopal history and/or QTc prolongation >0.50 s); and low- (affected subjects without a history of a prior syncope and with a QTc duration ≤0.50 s) risk (Fig 15).\(^ {14} \) It should be remembered, however, that these risk groups represent a simplified approach since risk factors in LQTS are time-dependent and age-specific, warranting continuous risk assessment in affected patients. A summary of the data from recent studies regarding age-specific risk factors for ACA or SCD is provided in Table 6.

**Therapies for LQTS**

Medical, device, and surgical therapies have been evaluated for the primary and secondary prevention of LQTS-related cardiac events. Due 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. Data from large series have recently more clearly defined the effectiveness and limitations of the various modes of LQTS-related
FIG 14. Kaplan–Meier estimates of (A) a first cardiac event and (B) a first life-threatening event (ACA or SCD) in JLNS, RWS, and genetically diagnosed LQT1 patients; $P < 0.001$ for the comparison between the JLNS group and either the RWS or the LQT1 groups for both endpoints. (Reproduced with permission from Goldenberg I, Moss AJ, Zareba W, et al. Clinical course and risk stratification of patients affected with the Jervell and Lange-Nielsen syndrome. J Cardiovasc Electrophysiol 2006;17:1169-71). ACA, aborted cardiac arrest; JLNS, Jervell and Lange-Nielsen syndrome; LQT1, type 1 long QT syndrome; RWS, Romano–Ward syndrome.
therapy. Furthermore, when the LQTS genotype has been identified, a management may be planned that involves genotype-specific therapeutic and preventive measures. The different types of LQTS-related therapies are considered below.

**Beta-Blockers**

Medical therapy with beta-blockers is considered 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 15). Their mechanism of action is probably related to the attenuation of adrenergic-mediated triggers in this disorder, especially in individuals with the LQT1 genotypes. An early study from the International LQTS Registry, involving 869 patients of whom 69% were symptomatic, assessed the benefit of beta-blocker therapy by evaluating cardiac event rates before and after initiation of beta-blocker therapy. The study showed that beta-blockers reduce the frequency of syncope even though they have little or no effect on QTc duration. Notably, the reduction in the rate of cardiac events in this study was most marked in high-risk patients who experienced the highest event rates.
before beta-blocker therapy was initiated. However, the study observed important limitations of beta-blocker therapy in LQTS patients. Among 33 study patients who died after starting beta-blocker therapy, 76% were receiving beta-blockers at the time of their death. Furthermore, beta-blocker therapy had no evident reduction in cardiac event rates in patients with LQT3 mutations.14 Consistent findings were demonstrated in a study by Priori et al50 of 335 genotyped LQTS patients who were treated with beta-blockers. The study showed a relatively high event rate despite medical therapy in LQT2 (23%) and LQT3 (32%) patients as compared with LQT1 patients (10%; \( P < 0.001 \)). Accordingly, LQT2 patients exhibited nearly a 3-fold increase in the risk of cardiac events while on medical therapy as compared with LQT1 patients (\( P = 0.01 \)), and LQT3 patients who were treated with beta-blockers had a 4-fold increase in the risk compared with the respective LQT1 patients. More recent analyses from the International LQTS Registry have assessed the efficacy of

<table>
<thead>
<tr>
<th>Age group</th>
<th>High-risk subsets</th>
<th>Beta-blocker effect in high-risk patients: % reduction (( P ) value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood62</td>
<td>Males with prior syncope and/or QTc ( \geq 500 ) ms</td>
<td>73 (0.002)</td>
</tr>
<tr>
<td></td>
<td>Females with prior syncope</td>
<td></td>
</tr>
<tr>
<td>Adolescence59</td>
<td>Males and females with either one or two or more of the following: QTc ( \geq 530 ) ms ( \geq 1 ) episode of syncope in the past 1 year. ( \geq 2 ) episodes of syncope in the past 2-10 y</td>
<td>64 (0.01)</td>
</tr>
<tr>
<td>Adulthood60</td>
<td>Either 1 or more of the following: Female gender Interim syncope after age 18 years QTc ( \geq 500 ) ms</td>
<td>60 (&lt;0.01)</td>
</tr>
<tr>
<td>41-60 y63†</td>
<td>Either 1 or more of the following: Female gender Syncope in the past 10 years QTc ( \geq 500 ) msec LQT3 genotype</td>
<td>42 (0.40)‡</td>
</tr>
<tr>
<td>61-75 y63†</td>
<td>Syncope in the past 10 years</td>
<td>86 (0.05)‡</td>
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</table>

*Findings are from separate multivariable Cox models in each age group for the endpoint of aborted cardiac arrest or sudden cardiac death.
†Since LQTS-related events are more difficult to delineate in the older age group, the endpoint in the 41-60 age group comprised aborted cardiac arrest or death from any cause.
‡Lack of statistically significant beta-blocker effect in this age group may relate to the broad endpoint of death from any cause.
beta-blocker therapy in the prevention of the more severe endpoint, comprising ACA or SCD.\textsuperscript{59,60,62,63} These analyses 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 being at high risk, by assessing the benefit of time-dependent beta-blocker therapy in predefined risk subsets in each age group.\textsuperscript{59,60,62,63} 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 6). During childhood, beta-blocker therapy was shown to be independently associated with an overall significant 53% reduction in the risk of ACA or SCD (HR = 0.47 [95% CI 0.26-0.85]; \(P = 0.01\)), with a more pronounced effect among high-risk children who experienced syncope during the past 2 years (HR = 0.27 [95% CI 0.12-0.62]; \(P = 0.002\)). In contrast, the benefit of beta-blocker therapy was significantly attenuated (HR = 0.95 [95% CI 0.41-2.21]; \(P = 0.90\)) in lower risk children with more remote or no syncope (\(P\) value for beta-blocker \(\times\) recent syncope interaction = 0.03).\textsuperscript{62} Similarly, during the high-risk adolescent period beta-blocker therapy was associated with an overall marginally significant risk-reducing effect (HR = 0.69 [95% CI 0.5-1.1]; \(P = 0.08\)), and with a 64% reduction in the risk of ACA or SCD in high-risk participants who experienced recent syncope. In contrast, among those who did not experience recent syncope, beta-blocker use was not associated with reduced risk (HR = 1.2 [95% CI 0.7-2.0]).\textsuperscript{59} It should be noted, however, that the lack of a significant beta-blocker effect in these lower risk groups does not imply that this mode of medical therapy should not be prescribed to lower risk subsets on an individual basis. Prescription of beta-blockers was administered to those considered to be at risk by the treating physician, and unmeasured risk factors may have been present in these patients. Nevertheless, despite the highly significant beneficial effects of beta-blockers in high-risk subsets shown in Table 6, and possible beneficial effects in lower risk subsets, high-risk LQTS patients who were treated with beta-blockers maintained a substantial burden of life-threatening events while on medical therapy. During childhood boys on \(\beta\)-blockers as of age 6 years, who experienced syncope prior to age 6, had a 12% cumulative probability of ACA or SCD during the subsequent 7 years of follow-up, corresponding to an average annual event rate of nearly 2% while on medical therapy.\textsuperscript{62} Similarly, during the adolescence period beta-blocker therapy reduced the risk of ACA or SCD in high-risk LQTS males from 32 to 12%. Thus, a relatively high event rate of life-threatening cardiac events was still observed in high-risk patients.
who were treated with beta-blockers (Fig 16). These findings indicate that patients who remain symptomatic despite treatment with beta-blockers should be considered for other, more invasive therapies, including left cardiac sympathetic denervation (LCSD) or an ICD.

Melvin M. Scheinman: The data presented by the authors and nicely summarized in Fig 16 emphasize the continued risk for those in the very high-risk cohort treated with beta-blockers. It is critical that clinicians be familiar with this data to provide counseling to patients and their families. In some instances either patients or families will opt for the most definitive therapy (ICD) in this setting.

**Left Cardiac Sympathetic Denervation**

This surgical procedure was introduced for the treatment of LQTS before beta-blockers became available. A recent study assessed the role...
of LCSD in 147 high-risk LQTS patients, of whom 99% were symptomatic and 48% experienced prior ACA, with follow-up over a mean period of 8 years after surgery. During long-term follow-up, 46% of patients became asymptomatic; syncope occurred in 31%, ACA in 16%, and SCD in 7% (Fig 17). The mean yearly number of cardiac events decreased by 91% ($P < 0.001$) to a rate of 3.3 events/person/year (95% CI 2.6-4.2), with a median rate of zero events per patient [interquartile range (IQR), 0-10]. LCSD was also shown to shorten QTc duration by an average of 39 ms, thus showing that the procedure may result in electrical remodeling. In five patients with preoperative ICD and multiple discharges, the post-LCSD rate of shocks dropped by 95% ($P = 0.02$) Notably, patients with QTc duration $<500$ ms 6 months after surgery were shown to be at a low risk of subsequent events, whereas those in whom QTc remained
above 500 ms still maintained a high risk for life-threatening cardiac events, suggesting that ICD should be considered in this subset of patients. The findings of this study demonstrate that LCSD is associated with a significant, long-term reduction in the frequency of ACA and syncope. However, the procedure it is not entirely effective in preventing sudden death. This therapy should be considered in LQTS patients who experience syncope despite beta-blocker therapy and in those who have arrhythmia storms and shocks with an ICD.

Melvin M. Scheinman: The experience derived for those with the LQTS treated with left cardiac sympathectomy is instructive. In fact, over 50% will suffer recurrence of symptoms, including ACA and sudden death in 48%. For these reasons, in my opinion, patients who fail beta-blockers therapy should be encouraged to undergo ICD insertion.

Implantable Cardioverter Defibrillator

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. 

Efficacy of ICD Therapy in LQTS Patients. Implantation of an ICD has shown to be an effective mode of primary and secondary prevention in LQTS patients. Groh et al reported early experience with the use of the ICD in patients with this inherited cardiac disorder. The authors identified 35 patients, of whom approximately three-fourths had experienced prior ACA before implantation, and reported that no deaths occurred in this very high-risk population during mean follow-up of 31 ± 21 months. Of the 35 patients, 21 experienced one or more appropriate ICD therapies. Zareba et al reported the largest experience in ICD therapy in LQTS patients involving the Rochester LQTS-ICD registry. The study compared the clinical course of 125 LQTS-ICD recipients, of whom 73 were considered high risk due to either prior ACA (n = 54) or prior syncope despite beta-blocker therapy (n = 19), to that of 161 matched LQTS patients who met identical criteria for ICD implantation but were managed medically without an ICD because of patient or physician preference. In the 73 high-risk ICD-treated patients, one death (1.3%) occurred during an average follow-up of 3 years, whereas in the non-ICD patients, 26 deaths (16%) occurred over a follow-up of 8 years (Fig 18). The death in the ICD-treated high-risk patient occurred during general anesthesia for dental work from incessant torsades de pointes. Beta-blockers were used in nearly all the ICD patients. However, despite
consistent medical therapy with beta-blockers, treated patients were shown to experience a 4% annual rate of ICD shocks.101

**ICD Complications and Issues Related to LQTS.** LQTS patients who receive an ICD are generally younger than ICD recipients with acquired heart disease, and therefore, may be exposed to the downsides or complications of the device for many years. These include the pain of appropriate potentially lifesaving shocks, inappropriate shocks, multiple shocks during a ventricular tachycardia/ventricular fibrillation (VT/VF) storm, lead-related complications, vascular occlusion or stenosis, the need for device replacement, infection, and psychological adjustment due to device therapy in general. Concomitant medical therapy with beta-blockers has been used in most ICD series and is recommended to minimize the incidence of shocks and especially electrical storm. Beta-
blocker therapy is also useful to increase the difference in maximal sinus rate and VT/VF rate to minimize inappropriate shocks. Some patients with a high risk for multiple events, or after one or more ICD shocks, may benefit from the adjuvant surgical procedure of LCSD described above. When programming the device, the duration of detection may be set longer than normal to prevent an intervention for a nonsustained torsades episode that would have terminated spontaneously. Single-shock coil ICD leads may simplify and reduce risk for subsequent ICD extractions, which are likely in the patient who will have an ICD system for many decades. Some experience with nontransvenous shocking electrodes has recently been reported with epicardial placement of standard transvenous ICD shock coils or subcutaneous-only shock coils, especially in pediatric patients, to delay subclavian vein complications of stenosis or occlusion.102-104

Melvin M. Scheinman: The issue relative to minimizing the number of ICDs is particularly important. In addition to use of appropriate beta-blocker therapy, increasing heart rate will serve to shorten the QT interval. In fact, cardiac pacing was shown to augment beta-blocker response for high-risk LQT patients. In my practice, I adjust the paced atrial rate to produce normal or a near normal QTc in an effort to avoid inappropriate discharges. In addition, it is important to remember that children and young adults can generate very high sinus rates during noncompetitive athletics (ie, dancing, surfing, etc); hence, the AICD detect rate should be set at relatively high levels (ie, 200/min) to minimize inappropriate shocks but yet detect torsades.

Cost-Effectiveness of ICD Therapy in LQTS Patients. The absolute protection conferred by ICD therapy in a young and otherwise healthy population with an inherited cardiac disorder results in this mode of therapy being able to provide many decades of productive life, and a possible favorable cost-effectiveness ratio. We recently developed a computer-based analytical model to compare non-ICD with ICD therapy in LQTS patients (age range, 10 to 75 years).105 The analysis showed that primary ICD therapy is cost-effective in high-risk LQTS males (incremental cost-effectiveness ratio [ICER] = $3328 per quality-adjusted-life-year saved) and cost-saving in high-risk LQTS females (ICER = $7102 gained per quality-adjusted-life-year saved).105 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.106,107
Genotype-Specific Considerations

When the LQTS genotype is known, specific therapeutic and preventive measures may be considered.

**LQT1 Patients.** Life-threatening events occur during sympathetic activation in patients with this genotype; therefore, this subset of patients is effectively protected by the use of anti-adrenergic interventions. Priori et al.\(^5\) observed a group of 157 LQT1 patients who were treated with beta-blockers at a very low rate of life-threatening cardiac events (1.2%) during a median-term follow-up period of 4.7 years. Thus, patients who are identified as carriers of the LQT1 genotype should be treated with beta-blockers. In LQT1 patients who remain symptomatic despite beta-blocker therapy, LCSD and ICD have both been shown to be very effective.\(^13,99,100\) LQT1 patients should not be allowed to participate in competitive sports. Swimming is particularly hazardous, as 99% of the arrhythmic episodes associated with swimming were shown to occur in LQT1 patients.

**LQT2 Patients.** The efficacy of beta-blocker therapy in LQT2 patients is lower than in patients with the LQT1 genotype.\(^5\) LQT2 patients who are treated with beta-blockers should be carefully followed up for residual symptoms, and implantation of an ICD should be carried out in LQT2 patients who remain symptomatic despite beta-blocker therapy. Preventive measures in LQT2 patients include avoidance of unexpected auditory stimuli in the bedroom that can cause a startle reaction, since these may be associated with lethal events, especially during rest or sleep. In addition, LQT2 patients are especially vulnerable when their potassium levels are low. Therefore, efforts should be made to maintain a serum potassium level >4 mEq/L.

**LQT3 Patients.** Data regarding management of LQT3 patients are more limited. Beta-blocker therapy in this population was shown to be associated with a relatively high rate of residual events, and the efficacy of this mode of medical therapy was shown to be lower in LQT3 patients compared to the other two main LQTS genotypes.\(^14,5\) LQT3 patients were shown to have excessive further prolongation of the QT intervals at slow heart rates.\(^108\) Subsequently, it was shown that, during the night when heart rate decreases, QTc is prolonged even further.\(^109\) Thus, a reduction in heart rate with beta-blocker therapy may pose a therapeutic problem in this population. Therefore, an early primary ICD intervention should be considered in high-risk LQT3 patients. Since most SCN5A mutations increase a late Na+ inward current, sodium channel blockers may shorten the QT interval in LQT3 patients. Administration of the
sodium-channel blocker mexiletine shortened the QT interval by an average of 90 ms, which is of potential clinical significance. Similarly, low-dose oral flecainide was shown to shorten the QTc interval and to normalize the repolarization T-wave pattern in five LQT3 patients with SCN5A-ΔKPQ mutation. Thus, a possible management strategy in LQT3 patients may be to assess the degree of QT shortening produced by an oral sodium channel blocker and to initiate this mode of medical therapy in patients who respond with a shortening of ≥50 ms. It should be noted, however, that data regarding the clinical efficacy of sodium channel blockers in LQT3 patients are limited, and an electrocardiographic response may not correlate with clinical response in LQT3 carriers. Ranolazine, a novel anti-anginal agent, was reported to decrease the delayed rectifier potassium current, I(Kr), and to reduce late sodium current (late I(Na)), thereby increasing action potential duration. Preliminary data from an in vitro model of LQTS demonstrate that ranolazine reduces the duration of the action potential and ventricular arrhythmias caused by agents that increase late I(Na) and decrease I(K). In five LQT3 patients with the ΔKPQ mutation, 8-hour administration of intravenous ranolazine was associated with significant dose-response shortening of the QTc interval. The clinical response of LQT3 patients to ranolazine needs to be further evaluated.

Summary

The identification of the molecular and clinical determinants of inherited LQTS has been pivotal to the understanding of important aspects of cardiac arrhythmias and sudden death. Data from molecular LQTS studies have provided novel 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. Furthermore, recent studies from the International LQTS Registry that evaluated age-specific risk factors for life-threatening cardiac events have provided important information regarding genotype–phenotype relationship in this inherited cardiac disorder. This information is being utilized to improve the diagnostic criteria, risk assessment, and therapeutic management of affected patients. Importantly, when assessing the risk for life-threatening cardiac events of affected individuals, age-specific and time-dependent clinical and genetic risk factors should be considered. These include primarily age–gender interactions, a prolonged QTc duration observed in serial ECG recordings, and syncopal history. Recent and ongoing and cooperative studies from the US, Japanese, and Netherlands LQTS Registries are currently providing important information regarding the role of the biophysical
function, type, and location of the ion-channel mutation in each of the three major LQTS genotypes in risk assessment and therapeutic considerations. Management of LQTS patients includes genotype-specific preventive measures in genetically tested individuals, and medical therapy with beta-blockers in patients considered to be at risk for life-threatening cardiac events. Among patients who remain symptomatic despite beta-blocker therapy, more invasive management, including LCSD and implantation of an ICD, should be considered. Ongoing and future studies are also evaluating innovative therapeutic strategies involving mutation-specific medications and possibly gene therapy for LQTS patients.

Melvin M. Scheinman: We are indebted to the authors for an amazingly detailed, comprehensive description of all aspects of the LQTS. The authors (who are among the pioneers in this area) have lucidly described the complex biological and genetic underpinnings and beautifully related these abnormalities to the clinical realm. The strength of this essay lies in its clarity to relate to both the clinical cardiologist as well as the electrophysiology specialist. I have long been interested in this topic and wish to thank the authors for assembling this important contribution.

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