Importance of Knowing the Genotype and the Specific Mutation When Managing Patients With Long-QT Syndrome

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Long-QT syndrome (LQTS) is an inherited disorder with prolonged ventricular repolarization and an increased propensity to ventricular tachyarrhythmias of the torsade de pointes type that are responsible for arrhythmogenic syncope and sudden cardiac death.1 During the past 13 years, 10 different genotype forms of LQTS have been identified (LQT1–LQT10), with the most frequent clinical types (LQT1–LQT3) categorized as ion channelopathies.2 The remaining 7 infrequently occurring forms of LQTS (LQT4–LQT10) also affect myocellular ion channel currents either directly or indirectly, but LQT4–LQT10 make up less than 5% of the genotype-identified LQTS. To date, approximately 500 different LQTS mutations have been identified in the 10 LQTS genes, and cellular expression studies of these mutations have elucidated basic electrophysiological mechanisms responsible for the delayed repolarization and the manifest QT prolongation. Different LQTS genes affect different ion current mechanisms, and the clinical course of patients with LQT1–LQT3 genotypes have been shown to be quite different.3 In addition, different mutations on the same LQTS gene may produce different electrophysiological effects. For example, mutations involving the LQT1 gene are all associated with reduction in the repolarizing $I_{Kr}$ current, but the magnitude of the reduction in this current can vary considerably among the different LQT1 mutations.4 This variability in the electrophysiological effects of different mutations contributes to the variability in the risk of life-threatening cardiac events that are independent of the manifest QTc interval on the ECG.

Thus, knowledge of the LQTS genotype and the associated specific mutations are useful in risk-stratifying individual patients for the selection of appropriate therapy for patient-specific risk-reduction.

Response by Vincent see p 226

Because of the extensive literature that currently exists in LQTS, we will focus on the 3 common forms of LQTS (LQT1–LQT3) and related mutations to make our point that this information is useful in managing patients with LQTS.

Risk by Genotype

By 1995, the 3 major LQT1–LQT3 genetic loci were identified, and shortly thereafter, it was appreciated that the ECG manifestations and the clinical course of LQTS were different among the 3 common genotypes. Each of the 3 LQTS genotypes was associated with somewhat distinctive ECG repolarization features.5 Among affected individuals, the QT onset-c was unusually prolonged in those individuals with LQT3 mutations (lead II QT onset-c: LQT1, 243±73 ms; LQT2, 290±56 ms; LQT3, 341±42 ms; P<0.001); $T_{amplitude}$ was generally quite small in the LQT2 genotype (lead II $T_{amplitude}$, mV: LQT1, 0.37±0.17; LQT2, 0.13±0.07; LQT3, 0.36±0.14; P<0.001); and $T_{duration}$ was particularly long in LQT1 genotype (lead II $T_{duration}$, ms: LQT1, 262±65; LQT2, 191±51; LQT3, 187±33; P<0.001).

Life-threatening cardiac events tend to occur under specific circumstances in a gene-specific manner (Figure 1).5 LQT1

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219
patients were shown to experience 68% of their lethal events during exercise, whereas most LQT2 and LQT3 patients experience lethal events during rest or sleep, respectively. The triggering role of sympathetic activation in LQT1 patients has important therapeutic implications, because it suggests that protection could be expected by the use of antiadrenergic 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 because LQT2 patients are particularly sensitive to startling and sudden noises, such as a telephone or alarm clock ring (Figure 1).

In the 246 genotyped patients reported by Zareba et al the frequency of cardiac events was significantly higher among subjects with mutations at the LQT1 locus (63%) or the LQT2 locus (46%) than among subjects with mutations at the LQT3 locus (18%) as shown in Figure 2. However, the likelihood of dying during a cardiac event was significantly higher among families with mutations at the LQT3 locus (20%) than among those with mutations at the LQT1 locus (4%) or the LQT2 locus (4%).

The genotypic risk is also influenced by age and sex of the patient. Priori et al showed that the genotype of the causative mutation affects the clinical course of the LQTS and modulates the effects of the QTc and sex on clinical manifestations. Goldenberg et al reported in children aged 1 to 12 years that the 3 major LQTS genotypes were associated with similar risks for life-threatening cardiac events after adjustment for clinical factors (LQT1 versus LQT2: hazard ratio =1.61, \( P=0.56 \); LQT3 versus LQT2: hazard ratio =2.37; \( P=0.49 \)). Similar risk results were observed for the 3 genotypes during adolescence. However, in adults aged 18 to 40 years, patients with the LQT2 genotype had a significantly higher cardiac event rate than patients with the other 2 genotypes, and this was especially so in women. The risk by genotype was also examined in female patients during their childbearing years. Compared with a time period before a woman’s first conception, the pregnancy time was associated with a reduced risk of cardiac events (hazard ratio 0.28, \( P=0.01 \)), whereas the 9-month postpartum time had an increased risk (hazard ratio 2.7, \( P<0.001 \)). Genotype analysis showed that women with the LQT2 genotype were more likely to experience a postpartum cardiac event than women with the LQT1 or LQT3 genotype (Figure 3). In the only study looking at the clinical course of patients older than 40 years, Goldenberg et al showed that LQT3 genotype carriers exhibited the highest cumulative lethal event rate (35%) compared with LQT2, LQT1, and genotype negative subjects (24%, 14%, and 10%, respectively; \( P=0.001 \)).

Figure 1. Triggers for lethal cardiac events according to 3 genotypes. Numbers in parentheses indicate the number of triggers and not the number of patients (reproduced with permission from ref. 6). LQT indicates long QT.

Figure 2. Kaplan-Meier estimate of the cumulative probability of a long-QT (LQT) syndrome-related cardiac event in LQT1, LQT2, and LQT3 genotyped patients (reproduced with permission from ref. 3).

Figure 3. Annualized a long-QT (LQT) syndrome-related cardiac event rates by genotype in LQT1, LQT2, and LQT3 genotyped patients for defined pregnancy-related time periods. None of the 12 LQT3 women had a cardiac event during the postpartum period (reproduced and modified with permission from ref. 11).
A summary of the risk of cardiac events by the LQT1–LQT3 genotypes for 4 different age groups is presented in Table 1. The risk for cardiac events is augmented in female LQT2 patients aged 21 to 40 years and in LQT3 patients more than 40 years of age.

Risk by Mutation Location and Function
There are 2 proposed molecular mechanisms that may account for reduced potassium currents in patients with KCNQ1 and HERG mutations13,14: (1) coassembly or trafficking abnormalities, in which mutant subunits either do not coassemble with normal subunits or if they do are not transported to the cell membrane, resulting in a net effect of ≤50% reduction in the number of functional channels (haplotype insufficiency); and (2) formation of defective channels involving mutant subunits, with the altered channel protein transported to the cell membrane, resulting in a >50% reduction in channel function (dominant-negative effect). Knowledge of the functional effects of the mutation and its location have been demonstrated to provide incremental prognostic information to clinical risk factors and the genotype,4 which may be used for improved risk stratification and a more focused management of higher-risk LQTS patients.

Mutations in the KCNQ1 Gene
Prior studies that assessed the functional role of LQT1 mutations have yielded conflicting results, possibly because of sample size limitations.15,16 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.4 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 loss of function (haploinsufficiency; Figure 4A). After multivariable adjustment for clinical covariates, subjects with mutations having dominant-negative functional effects exhibited a 2-fold increase in the risk for cardiac events (P<0.001) compared with those with haploinsufficiency mutations. The study further demonstrated that the frequency 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 (Figure 4B), and those with missense mutations had a significantly higher event rate than those with nonmissense mutations (Figure 4C).4 It is possible that $I_{\text{Ks}}$ channels with transmembrane mutations might have reduced responsiveness to the regulator $\beta$-adrenergic signaling of the ion conduction pathway with
Hereditary long QT syndrome (LQTS), a genetic condition associated with a prolongation of the QT interval on electrocardiogram (ECG), increases the risk of life-threatening cardiac events, including sudden cardiac death. This condition is caused by mutations in key genes, most notably HERG (KCNH2), SCN5A, and KCNQ1. Different mutations can lead to distinct clinical outcomes and response to therapy.

**Mutations in the HERG Gene**

The pore region of the HERG channel provides the potassium conductance pathway. Most mutations involving this region are missense mutations with dominant-negative effects on I\textsubscript{Kr}, whereas most mutations in the nonpore regions of HERG are associated with coassembly or trafficking abnormalities resulting in haplotype insufficiency. 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 of arrhythmia-related cardiac events, occurring at an earlier age than did subjects with nonpore mutations (Figure 5). 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 implicate the Per-Arnt-Sim (PAS) domain within the N-terminus and the cyclic nucleotide binding domain (cNBD) of the C-terminus as important regulators of the biophysical properties of HERG. 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.

**Mutations in the SCN5A Gene**

LQT3 mutations in the SCN5A gene produce a gain of function, through faster recovery from inactivation and/or increase in residual current. These mechanisms produce a small but functionally important enhancement of inward sodium plateau current sufficient to delay repolarization and increase vulnerability of the heart to arrhythmias. Preliminary data from the US portion of the International LQTS Registry indicate that the biophysical function and location of the LQT3 location are also important determinants of outcome in this population. These recent findings suggest that the ΔKPQ mutation, which is located in the intracellular loops and operates through both faster recovery from inactivation and an increase in residual sodium current, is associated with a significantly higher risk for cardiac events than the C-terminus D1790G mutation that has distinct biophysical function effects on steady-state inactivation and intracellular calcium homeostasis. The US, Japanese, and Netherlands LQTS Registries are currently cooperating in a combined assessment of the risk associated with the location, function, and coding type of LQT3 mutations.

**Risk by Specific Mutation**

Several individual mutations in the LQTS genotypes have been demonstrated to be associated with a more severe clinical course and reduced response to therapy that is not fully explained by the biophysical properties of the mutation. In a cohort study involving individuals from South Africa harboring the same A341V mutation in the KCNQ1 gene, mutation carriers were shown to experience an unusual, severe clinical course, independent of the origin of the families, and to be at higher risk for cardiac events compared with a more general LQT1 population. Importantly, patients who harbored the A341V mutation experienced a higher frequency of recurrent cardiac events despite β-blocker therapy. Furthermore, a recent study, comprising 78 A341V mutation carriers from 21 families and 8 countries, showed that A341V is associated with a significantly higher arrhythmic risk compared with non-A341V LQT1 mutations with a dominant-negative effect or other LQT1 transmembrane mutations despite the fact that A341V was shown to exert only a relatively mild dominant-negative effect. Individual mutations may also contribute independently to risk in LQT2 patients. Rossenbacker et al have identified a novel nonpore missense mutation (K28E) in the KCNH2 polymorphism. These findings suggest that cellular electrophysiological studies cannot always predict the clinical phenotype and that data regarding individual LQTS mutations and associated polymorphisms in modifier genes may be used to identify high-risk patients with this genetic disorder who may have attenuated response to medical therapy.

**Therapy by Genotype and Mutation**

The main therapeutic modalities for the prevention of life-threatening cardiac events include β-blockers, left cervicothoracic sympathetic denervation (LCSD), and the implantable cardioverter defibrillator (ICD). In nongenotyped
patients, β-blockers comprise the mainstay therapy, whereas LCSD and implantation of an ICD are therapeutic options in high-risk LQTS patients who experience recurrent cardiac events despite β-blocker therapy. Genetic data can be used to provide an improved therapeutic management plan that is individualized by knowledge of genotype-specific and mutation-specific risk factors, prevention measures, and therapies. A proposed therapeutic regimen for each of the 3 major LQTS genotypes is considered separately below and is summarized in Table 2.28

**LQT1 Patients**

Life-threatening events occur during sympathetic activation in patients with this genotype and, therefore, this patient subset benefits from appropriate lifestyle modifications and are effectively protected by the use of antiadrenergic interventions. 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 patients with this genotype.29 Patients who are identified as carriers of the LQT1 genotype should be treated with β-blockers. Priori et al30 observed in a group of 187 LQT1 patients who were treated with β-blockers a very low rate of life-threatening cardiac events (1.2%) during a median-term follow-up period of 4.7 years. Implantation of an ICD and/or LCSD should be considered in high-risk LQT1 patients, especially those harboring dominant negative and/or transmembrane mutations who exhibit phenotypic QT prolongation and recent syncope despite β-blocker therapy. Because LQT1 patients are most sensitive to sympathetic stimulation, LCSD is expected to be most effective in this population. In a study of 147 patients who underwent LCSD, Schwartz et al31 showed that the procedure was associated with a significant long-term reduction in the frequency of aborted cardiac arrest and syncope but was not entirely effective in preventing sudden death. However, LQT1 patients in the study were shown to experience a very low rate of life-threatening cardiac events after LCSD (1 event per 100 person-years). Recent data from the LQTS-ICD Registry demonstrate the efficacy and safety of the implantable defibrillator in combination with β-blockers in LQT1 patients: in a subset of 69 (36%) patients, from the LQTS-ICD Registry, who were genotyped, none of the LQT1 patients who received combined ICD and β-blocker therapy died or experienced appropriate ICD therapy during a median follow-up of 6 years, whereas the rate of appropriate ICD therapy among LQT2 patients during the same time period was 24%.32,33

**LQT2 Patients**

Preventive measures in LQT2 patients include avoidance of unexpected auditory stimuli in the bedroom that can cause a startle reaction because these may be associated with lethal events, especially during rest or sleep. The efficacy of β-blocker therapy in LQT2 patients is lower than in patients with the LQT1 genotype. In the study of Priori et al30 27 of 120 (23%) LQT2 patients experienced a cardiac event during follow-up, and the adjusted risk of cardiac events among LQT2 patients was significantly higher (HR = 2.91; P = 0.001) as compared with LQT1 patients. Similarly, the benefit of LCSD in this population may be more limited: Schwartz et al31 reported that the combined incidence of aborted cardiac arrest of sudden cardiac death after LCSD was 3-fold higher among LQT2 patients as compared with LQT1 patients. Thus, high-risk LQT2 patients (eg, those with pore mutations with concomitant phenotypic QT prolongation and recent syncope and symptomatic adult females) should be considered for early ICD implantation.

LQT2 patients are especially vulnerable when their potassium levels are low because Ik is sensitive to extracellular potassium level. Experimental wedge studies suggested that

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**Table 2. Risk Mechanisms and Genotype-Specific Therapy Based on Clinical and Experimental Data in LQT1, LQT2, and LQT3 Forms of Long QT (LQT) Syndrome**

<table>
<thead>
<tr>
<th>LQTS Form</th>
<th>LQT1</th>
<th>LQT2</th>
<th>LQT3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity to sympathetic stimulation</td>
<td>Yes</td>
<td>To some degree</td>
<td>No</td>
</tr>
<tr>
<td>Torsade de pointes</td>
<td>Exercise related</td>
<td>Startle</td>
<td>Sleep/rest</td>
</tr>
<tr>
<td>Specific triggers/occurrence</td>
<td>Swimming</td>
<td>Telephone, alarm clock, postpartum</td>
<td>Inactivity</td>
</tr>
<tr>
<td>Risk by mutation</td>
<td>Dominant neg., transmembrane location, A341V</td>
<td>Pore location, K2BE</td>
<td>ΔKPQ</td>
</tr>
<tr>
<td>Exercise restriction</td>
<td>+++</td>
<td>++</td>
<td>?</td>
</tr>
<tr>
<td>β-blockers</td>
<td>+++</td>
<td>++</td>
<td>?</td>
</tr>
<tr>
<td>Potassium supplement</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Flecainide</td>
<td>No data</td>
<td>No data</td>
<td>+++ (ΔKPQ, D1790G)</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>No data</td>
<td>No data</td>
<td>+++ (ΔKPQ)</td>
</tr>
<tr>
<td>LCSD in high-risk patients</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>ICD in high-risk patients</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

The number of plus signs indicates the relative benefit of therapy in minimal (+), moderate (++) and marked (+++) effectiveness categories. ? indicates uncertain data. LCSD, left cervicothoracic sympathetic denervation; ICD, implantable cardioverter-defibrillator.

Reproduced and modified with permission from ref. 28.
an increase in extracellular potassium can limit the development of an arrhythmogenic substrate under long-QT conditions. Furthermore, in clinical practice, exogenously administered potassium was reported to correct repolarization abnormalities in patients with \( f_\text{Na} \) defects, and long-term oral potassium administration was recently shown to improve repolarization abnormalities in LQT2 patients. Therefore, efforts should be made to maintain a serum potassium level >4 mEq/L in patients with this genotype.

**LQT3 Patients**

Data regarding management of LQT3 patients are more limited. Patients harboring this genotype have excessive further prolongation of the QT intervals at slow heart rates, and the QTc was shown to prolong even further during the night when heart rate decreases. Thus, a reduction in heart rate with \( \beta \)-blockers may pose a therapeutic problem in this population. Accordingly, \( \beta \)-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 is lower in LQT3 patients compared with those with the other 2 main LQTS genotypes. In the study of Priori et al, 9 of 28 (32%) LQT3 patients experienced a cardiac event while on \( \beta \)-blocker therapy and the adjusted risk for a cardiac event among LQT3 patients was 4-fold higher than among LQT1 patients.

As 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 was shown to shorten the QT interval by an average of 90 ms. However, the response to mexiletine was not consistent and was shown to be mutation specific. Similarly, the effectiveness of flecainide, a class IC sodium channel blocker, in this population was also demonstrated to be mutation specific. Benhorin et al demonstrated that administration of flecainide abbreviated the QT interval in LQT3 patients with the D1790G mutation in SCN5A, and Windle et al showed that oral flecainide shortened the QTc interval and normalized the repolarization T-wave pattern patients with SCN5A-\( \Delta \text{KPQ} \) mutation. The antiarrhythmic agent ranolazine reduces late sodium channel current, shortens the action potential duration, and suppresses early afterdepolarization-triggered arrhythmias in animal models of LQT3 with sustained inward sodium current. In a recent study, we have shown that therapeutic concentrations of ranolazine were associated with a dose-dependent shortening of QTc interval and improved diastolic relaxation in patients with the LQTS-\( \Delta \text{KPQ} \) 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 or ranolazine and to initiate medical therapy in combination with a \( \beta \)-blocker in patients who respond with QTc shortening of \( \geq 50 \) ms. It should be noted, however, that data regarding the clinical efficacy of sodium channel blockers and ranolazine in LQT3 patients are limited, and an electrocardiographic response may not correlate with clinical response in LQT3 carriers. Thus, because of limited long-term clinical data regarding the benefit of medical therapy in LQT3 patients, together with the fact that the lethality among carriers of this genotype is higher than in LQT1 and LQT2 patients, early ICD implantation should be encouraged more aggressively in symptomatic LQT3 patients than among patients with the LQT1 or LQT2 genotypes.

**Conclusion**

Patients with LQTS are at increased risk for sudden cardiac death, with the risk probability influenced by a number of phenotypic and genotypic factors. Optimal drug and/or device therapy to reduce the probability of a fatal event should be tailored to the magnitude of the perceived risk and to amelioration of the risk mechanisms involved in life-threatening ventricular tachyarrhythmias. During the past decade, various genetic and mutation-related risk mechanisms have been identified, and the available studies indicate that this genotype-specific information should be used in the selection of therapy to reduce morbidity and mortality in patients with LQTS.

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**Disclosures**

Dr Moss received an honorarium when he served in the past year as member of an advisory group for Cardiovascular Therapeutics, Inc.

**References**


I appreciate the fine article by Drs Moss and Goldenberg. In addition to their many outstanding contributions, their article has confirmed my conclusions that, at present, there is no genotype-specific therapy in LQTS and that genotyping plays a minor role in selecting therapy for LQTS patients. Table 2 shows the confirmation. Both the ICD and LCSD treatments are represented as effective and to the same degree in all three genotypes. β-Blockers are represented as very effective in LQT1 and quite effective in LQT2, so they are not genotype specific either; however, these two genotypes cause roughly 95% of LQT1–3 LQTS, so β-blockers are effective and safe therapy in the majority of LQTS patients. Potassium, mexiletine, flecainide, and ranolazine have not been shown to prevent sudden death or cardiac arrest, so we cannot assume that they are effective or genotype-specific therapy nor should we accept that they are appropriate for primary therapy. Drs. Moss and Goldenberg primarily focus their excellent discussion on data showing that the genotype, the mutation location and function, and the specific mutation involved influence the risk of cardiac events in populations of LQTS patients. Be that as it may, there is no data to show that “therapy by genotype or mutation” improves outcome over nonspecific therapy in patients with the “higher risk” genetic findings. At present, the tremendous variability of expression of symptoms in patients with the same genotype and mutation type, as shown in my discussion, indicates that these findings are unlikely to be useful for selecting therapy in individual patients. Furthermore, the risk of sudden death or cardiac arrest is low in the most recent reports. Importantly, these data are essentially the natural history for many of the patients in these studies, because only about 30% received β-blockers, some may not have taken the β-blocker regularly or at all, and just a small percent received ICDs or LCSD. Any consistent application of the known effective therapies will reduce the rate of events even further, particularly if applied to presymptomatic patients and during the high-risk years.
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