# Long QT Syndrome: A Comprehensive Review of the Literature and Current Evidence

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**Abstract: Long QT syndrome (LQT) represents a heterogeneous family of cardiac electrophysiologic disorders characterized by QT prolongation and T-wave abnormalities on the electrocardiogram. It is commonly associated with syncope, however, sudden cardiac death can occur due to torsades de pointes. LQT is a clinical diagnosis and should be suspected in individuals on the basis of clinical presentation, family history and ECG characteristics. Management is focused on the prevention of syncope and ultimately sudden death. Complete cessation of symptoms is the goal. Life-style modification, beta blockers and ICD implantation are the most important therapeutic modalities in proper management of patients with LQT. Awareness should be raised regarding possible circumstances that could increase the risk of QT prolongation. Advanced age, hypokalemia, a history of heart failure, and structural heart disease are often mentioned in this context. Prudent consideration is needed before making a decision to recommend an ICD implantation in a young, active patient. Medical and/or device therapy still represent important therapeutic modalities in the management of patients with LQT with careful clinical judgement for the substrate of patients who will benefit. Insights from benchside to bedside have facilitated progress toward better**

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**therapeutic strategies, there also remains a need for tailoring management toward individuals in a mechanism-specific manner to optimize care. In addition, continued progress toward fundamental understanding of mechanisms of ion channel function and drug-channel interaction will guide the development of more effective, mechanism-based molecular agents in the treatment of LQT. (Curr Probl Cardiol 2019;44:92–106.)**

## Introduction

Long QT syndrome (LQT) represents a heterogeneous family of cardiac electrophysiologic disorders characterized by QT prolongation and T-wave abnormalities on the electrocardiogram (ECG). It is commonly associated with syncope, however, sudden cardiac death can occur due to torsades de pointes. The QT interval signifies the duration of action potential. When this duration is prolonged over a certain number, the disease process becomes known as LQT. The latest European Society of Cardiology guideline suggests upper limits of 480 ms on the ECG strip, for both males and females.[1] The chances of developing LQT is commonly associated with multiple factors including age, electrolyte abnormalities, drugs, medical conditions such as diabetes mellitus and epilepsy.[2–7] Furthermore, LQT can arise congenitally from ion channel mutations, or can have acquired causes. In this article, we review the current evidence for acquired LQT treatment strategies along with prognosis, summarizing recent advances into the management of LQT.

## Diagnosis

LQT is a clinical diagnosis and should be suspected in individuals on the basis of clinical presentation, family history and ECG characteristics. Most commonly, patients present with syncope and dizziness.[2] Other symptoms include palpitations and seizures.[3-4] Syncope is typically without warning and is abrupt without any warning signs, thus differing from vasovagal and orthostatic forms of syncope in which presyncope and other warning symptoms occur. Furthermore, absence of aura, urinary incontinence, tongue biting and postictal findings help differentiate LQT-associated syncope from seizures. Besides, vigorous exercise, cocaine abuse and prolonged sneezing, which may cause coronary vasospasm, are

all thought to cause LQT in rare cases. Certain neurologic conditions, including subarachnoid bleed, and structural heart diseases also increase the QT interval thereby increasing the chances of developing LQT later in life. Furthermore, a known family history of syncope or sudden death in a child or young adult supports the diagnosis of LQT.

The ECG in LQT is crucial for the diagnosis. Specific findings include a prolonged QT interval measured in lead II of a 12-lead ECG from the onset of the QRS complex to the end of the T wave. The QTc (corrected for HR) can also be calculated (QTc = QT interval + square root of the RR interval). The QTc interval can also help us diagnose LQT. A QTc is prolonged if exceeding 0.47 seconds in women and 0.45 seconds in men.[8] Hence, with appropriate ECG findings coupling with a detailed history and clinical symptoms, diagnosis for LQT can be made.

A 2009 study estimated LQT prevalence in approximately 1:2,500 births.[8] Three major genes are responsible for 80% of total genotyped patients with LQT.[9] By contrast, acquired causes of LQT are much more common than genetic causes. Most common cause of acquired LQT was electrolyte imbalances, most frequently hypokalemia. Recently, a hypokalemia mouse model has been used to study the pathophysiology behind LQT, demonstrating several consequences of action potential prolongation. Firstly, it increases the $Ca^{2+}$ current available $Na^{+}$ channel reactivation during the repolarizing phase, leading to the development of early afterdepolarizations and subsequent triggered activity.[10] Secondly, action potential prolongation preferentially occurs at the epicardium compared to the endocardium, resulting in an increase in the transmural dispersion of repolarization, thereby increasing the likelihood of reentrant arrhythmias. Continued progress towards fundamental understanding of mechanisms of ion channel function will guide the development of more effective, mechanism-based molecular agents which could be used for diagnostic purposes of the disease in the near future.

## Management/Treatment

Management is focused on the prevention of syncope and ultimately sudden death. Complete cessation of symptoms is the goal. To establish the extent of the disease, main focus in the management of individuals with LQT is to identify the subset of individuals at high risk for cardiac events. For this risk stratification specific evaluations are recommended. This includes evaluating the ECG in detail: Individuals with a QTc interval $>500$ ms are at higher risk for an event; individuals with QTc interval $>600$ ms are at extremely high risk.[11] Overt T-wave alternans is also

associated with a higher risk for cardiac events.[11] Alternatively, individuals who have a normal QTc interval are at low risk.[11] Below we look at some of the treatment strategies used commonly for managing patients with LQT:

## Lifestyle Modification

A healthy lifestyle is very important in the management of patients with LQT. Strenous exercises, including swimming and water sports, should be avoided.[12] Exposure to loud noises (example an alarm clock) should be reduced. Furthermore, avoidance of drugs that prolong the QT interval, should be done as much as possible.[12-14]

The 36th Bethesda Conference guidelines limited LQT patients to Class 1A sports such as brisk walking.[15] It also recommended asymptomatic patients to avoid swimming, however, other competitive sports were allowed.[15] Alternatively, the European Society of Cardiology guidelines are more strict and restrictive suggesting all LQT patients should be disqualified from all competitive sports based on the QTc cutoff (>440 ms in males, >460 ms in females), whether symptomatic or asymptomatic.[16]

Currently, there is an ongoing debate regarding participation in competitive sports among experts, especially in aymptomatic patients. Some experts think that these guideline-based recommendations for disqualification are excessive and patients may participate in competitive sports safely.[17] Recently revised recommendations allow some consideration of competitive sports after ensuring that effective treatment and appropriate precautionary measures such as automatic external defibrillators are available, especially among asymptomatic patients.[17-18] Data suggests that patients with implantable cardioverter defibrillator (ICDs) can engage in vigorous competitive sports without any significant of sudden cardiac death.[19] Interestingly, data also suggests that recommendation for exercise in asymptomatic patients is also influenced by physicians' personal exercise habits; less-active physicians are more likely to restrict exercise.[20] Besides vigorous exercise regime, the risk of sudden cardiac death or syncope during sexual activity seems to be extremely low as well.[21]

Data suggests that sudden emotional stress or sudden exposure to auditory stimuli, such as noise from telephones, increases the risk of developing cardiac events, hence, should be avoided.[13,22] Emotional stress and sleep disturbance can be worsened during the time of conception: data suggests that the 9-month post-partum period has a 2.7-fold increased risk of cardiac events when compared with the preconception period.[13,23] It is recommended that other family members should take care of infants

at nighttime without disturbing the mothers.[24] Furthermore, electrolyte abnormalities, especially potassium levels, should be closely monitored during this period.[24]

Some patients with LQT also suffer from asthma. Asthma comorbidity in LQT patients is associated with increased risk of cardiac events, which is diminished after initiation of beta-blocker therapy.[25] Alternatively, the beta-agonist therapy in asthmatics increases the risk of cardiac events.[26] Consequently, Intravenous aminophylline and salbutamol should be avoided and inhaled anticholinergic medication, corticosteroids and leukotriene receptor antagonists may be considered as alternatives.[27-28]

Also, patients should avoid exposure to QT prolonging drugs. Awareness regarding specific commonly used drugs among patients and family members is very important. The list of such drugs is easily available and it should be given to the patient and their family members. Additionally, herbal medicines like grapefruit and liquorice should also be avoided.[29-30] Remotely, the effect of oral contraceptives seems to be neutral.[31-32]

## *Beta Blockers*

Beta blockers are the primary therapy since the mid-1970s.[33-34] They are the mainstay of therapy for LQT including asymptomatic individuals with prolonged QT intervals. A recent study showed that beta-blockers were still the first-line therapy in 76% of European centers.[35] They are associated with a significant reduction in cardiac events in LQT patients.[33] Unfortunately, cardiac events cannot be completely stopped in these patients despite taking beta-blockers: 32% of symptomatic patients will have a cardiac event over 5 years, and 14% of patients with a prior cardiac arrest will have a recurrence within 5 years.[33] Besides, data suggests that beta blockers are only effective in preventing ventricular arrhythmias in approximately 70% of the patients.[33-35] The remaining 30% still remain susceptible to arrhythmias.[33-35] As beta-blockers are somewhat effective in LQT patients, noncompliance and use of QT prolonging drugs are responsible for almost all life-threatening 'beta-blocker failures'.[13, 36] Thus, the differentiation between medication 'non-compliance' and medication 'failure' is important in the management of symptomatic patients.[13, 37] Hence, patients should be made aware of the life-threatening consequences to their medication non-compliance.

Beta-blockers are very effective in preventing stress-triggered cardiac events, including vigorous exercise.[38-39] However, beta blockers do not have any significant effect on sleep-triggered cardiac events.[38-39] Nevertheless, beta blockers should still be administered since subsequent exercise-triggered events may still occur in this population.[38]

Side effect profile of low-dosing beta blockers are minimal. Common side effects include fatigue, weight gain and aggravation of asthma.[36] However, bronchial asthma is no longer considered an absolute contraindication to beta blockers.[40] Beta blocker-induced symptomatic bradycardia is an extremely rare event if the dosage is gradually increased.[36] Beta blockers are also associated with the development of clinically important hypoglycemia in young adults.[41,42] Hence, care should be taken in prescribing these medications in these set of patients.

For symptomatic LQT patients, long acting beta blockers in maximally tolerated doses are recommended and abrupt discontinuation should be avoided.[33] Recently, some experts suggested that not all beta blockers are equally effective in preventing cardiac events, although clear evidences supporting this issue seem to be limited.[43-46] Data suggests that propranolol and nadolol are definitely more effective than metoprolol and atenolol.[43–46] However, another large study showed that atenolol, metoprolol, propranolol, and nadolol were equally effective in reducing the risk of a first cardiac event in LQT.[47] Data also suggests that the efficacy may vary from one drug to another: Nadolol being the most effective and Propranolol being the least effective drug in the high-risk group of patients who experienced cardiac events.[47] The cause of this discrepancy is not clear. Probably the differences in clinical characteristics of the patients and both dosage and dosing intervals of each beta blocker may have caused this discrepancy.[47]

In conclusion, beta blockers remain the first line of drugs for the treatment and management of both asymptomatic and symptomatic LQT. Side effects of beta blockers can be avoided by administering beta blockers daily and have strategies in place in case of missed doses. Furthermore, long-acting agents, like nadolol, preferentially increases compliance (and hence, should be used more often) as compared to short-acting agents, like metoprolol, although the evidence is limited. Furthermore, avoiding inadequate beta blocker dosing by regular adjustments with evaluation of the efficacy of dose by assessment of the exercise ECG/ambulatory ECG should be done regularly. Also, administration of QT-prolonging drugs should only be done after careful consideration of risks versus benefits by the individual and physician.

## ICD implantation

ICD placement is an important management option for patients with LQT. Specifically, symptomatic patients with syncope despite being on beta blocker therapy and patients considered as high risk with a very long QTc interval (>550 ms), or signs of electrical instability such as T-wave alternans.[48-49] Patients with a relative contraindication for beta blocker therapy (like severe life-threatening asthma) can also be considered for an ICD implantation treatment. The recent guidelines do not recommend ICD implantation in asymptomatic LQT patients who have not been tried on beta blocker therapy.[12] However, the current guidelines do not recommend ICD implantation in patients with acquired LQT if an underlying cause can be identified.[49] Nevertheless, studies have shown that ICD placement can be helpful in patients with acquired LQT in the long run.[50]

ICD implantation comes with side effects. Most common ones include inappropriate shocks, lead problems, vascular occlusion, infection, psychological adjustment, and social discrimination.[51–53] These side effects may affect the quality of life of young and active patients. However, the diagnosis of a symptomatic LQT usually leads to an ICD implantation.[44] A recent European study showed that appropriate drugs and ICD implantation was the first-line treatment of LQT in 19% of participating centers.[35] Recommending ICD implantation in a symptomatic LQT patient is much easier than not recommending implantation of an ICD in this era of defensive medicine. The ICD implantation rate seems to be as high as 75% in some centers.[54] One recent study with 157 patients showed a trend that the majority of patients had Class II and Class III indications for ICD implantation.[51] The greatest rate of ICD implantation occurred among LQT patients who were women and were assessed to be at high risk.[54] The largest study on ICD showed that female (77%) patients had a disproportionately high probability of being implanted with an ICD.[48] Follow-up studies have shown that after about a period of 5 years, adverse events occurred in 25% of the patients. Interestingly, greater than 50% of these patients had not suffered a cardiac arrest.[48] Some patients were even asymptomatic.[48]

A new scoring clinical system for ICD placement has been suggested for selecting appropriate patients.[48] Studies in multiple big centers have suggested that majority of LQT patients can be treated and managed without an ICD and that LQT-triggered death did not occur in the >500 LQTS patients managed without an ICD.[46,54] This was followed by experts suggesting that even patients who suffered a cardiac arrest without previous beta blocker therapy, can be managed without ICD implantation. They

think that beta blockers may suffice in such cases.[52] Recent evidence suggests that unnecessary ICD placement should be avoided to prevent inappropriate side effects, however, thoughtful programming is necessary, and it usually requires a ventricular fibrillation only zone, with a cutoff rate >220 beats per minute.[12]

In conclusion, ICD placement is an option if the first line treatment (beta blocker-therapy) fails. However, there are some complications which need to be addressed as well. Furthermore, selecting appropriate patients for ICD placement is still a challenge. With continued research, we can expect more cost- effective and patient-friendly drug therapies and ICD placement techniques to be developed in the near future.

## *Left Cardiac Sympathetic Denervation*

Left Cardiac Sympathetic Denervation (LCSD) is a rarely performed procedure but it is quite effective.[35] It is used in patients in whom ICD therapy is refused or contraindicated or in people in whom beta blockers are nor tolerated or effective.[55-57] Studies have shown that they are equally as effective as ICD.[55] One study showed comorbidities associated with LCSD were lower as compared to ICD implantation alone.[46] LCSD usually works by reducing norepinephrine release at the ventricles, therefore, increasing the threshold for ventricular fibrillation, without reducing the heart rate or contractility.[58-60] The usual procedure involves high thoracic left sympathectomy and involves ablation of the lower half of the stellate ganglion along with T2 to T4. This relatively new technique could play a huge role in reducing the gap between beta blocker medication only and additional ICD implantation.

The largest study done on LCSD patients who were at a high risk of cardiac events with an extremely prolonged QT showed a 91% risk reduction in cardiac events.[56] Nowadays, LCSD is usually used in very-high risk patients as a bridge to ICD. Since the technique is relatively new, the results of the procedure depend heavily on the experience of the surgeon: a complete resection of the lower half of the left stellate ganglion is critical.[55-57] Data suggests that recent advances, including videoscopic LCSD, is associated with a short hospital stay and less morbidity. This procedure is quite similar to sympathectomy for hyperhidrosis. The surgical time is usually less than 1 hour, and the patient can be discharged within a few days in experienced centers.[56]

Prophylactic LCSD in selected patients may improve the quality of life resulting from medication-related side effects.[56] Unfortunately, approximately 50% of high risk patients have experienced more than one cardiac

event after LCSD.[57-59] Hence, LCSD must not be viewed as curative or as an ICD-alternative for high risk patients. The most common side effects of LCSD are dry left arm and face and profuse sweating on the right side.[61] Complications such as Horner's syndrome or droopy eyelid is very rare and mostly transient.[57] A recently published study showed that most of the patients or their parents were satisfied with LCSD and would recommend LCSD to another patient.[61] Furthermore, whenever cardiac events recur in patients on beta blockers, LCSD should be strongly considered. LCSD is especially effective in patients with beta blocker noncompliance and intolerance.[57,60]

In conclusion, LCSD use should be used as an alternative to beta blocker therapy and ICD placement. It is especially useful in patients with cardiac events during adequate beta blocker therapy or very young patients who are considered technically inappropriate for ICD implantation.[56]

## Prognosis

Limited data is available regarding the prognosis of these patients, however, most affected individuals live normal lifestyles. Education of adult individuals and the parents of affected children, especially about beta blocker compliance, is an important aspect of management. Prolongation of cardiac repolarization is a severe complication caused by many substances including commonly used drugs. Increasing awareness and ongoing research have raised suspicion regarding several pharmacological agents. However, the clinical significance of single reports and in-vitro experiments is not always clear. While advances in technologies have helped elucidate many aspects of these diseases, many mysteries still remain. With continued research, we can expect more cost- effective and patient-friendly drug therapies to be developed in the near future.

## Conclusion

In conclusion, life-style modification, beta blockers and ICD implantation are the most important therapeutic modalities in proper management of patients with LQT. Awareness should be raised regarding possible circumstances that could increase the risk of QT prolongation. Advanced age, hypokalemia, a history of heart failure, and structural heart disease are often mentioned in this context. Prudent consideration is needed before making a decision to recommend an ICD implantation in a young and otherwise active patient. Medical and/or device therapy still represent important therapeutic modalities in the management of patients with

LQT, LCSD has a significant role in minimising the arrhythmia load in LQT patients, but not obliterating it altogether, with minimal acute and long term complications. Careful clinical judgement for the substrate of patients who will benefit from LCSD is of the utmost significance. As the potential for complications is increased, a discussion of proficiency training and guidelines for best practices for procedures like LCSD are crucial to reducing risk in cases where these procedures are necessary. Furthermore, when the possible benefits of therapy outweigh the associated risks, slow dose titration and ECG monitoring are recommended.

Ion channels represent the molecular entities that give rise to the cardiac action potential, the fundamental cellular electrical event in the heart. The concerted function of these channels leads to normal cyclical excitation and resultant contraction of cardiac muscle. Research into cardiac ion channel regulation that underlie disease pathogenesis has greatly enhanced our knowledge of the causes and clinical management of cardiac arrhythmia. It is likely that a systems physiology approach will play a large role in studying the complex spatial and temporal properties of cardiac dynamics. Its application will no doubt transform arrhythmia management by identifying agents that have lower toxicity and toxic side effects of currently available drugs. Besides, insights from benchside to bedside have facilitated progress toward better therapeutic strategies, there also remains a need for tailoring management toward individuals in a mechanism-specific manner to optimize care. In addition, continued progress toward fundamental understanding of mechanisms of ion channel function and drug-channel interaction will guide the development of more effective, mechanism-based molecular agents in the treatment of LQT.

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The long QT syndrome (LQTS) is a disorder of myocardial repolarization characterized by a prolonged QT interval on the electrocardiogram.

Several perspectives can be taken from this review of long QT syndrome manuscript.

First, advanced age, hypokalemia, a history of heart failure, and structural heart disease are possible risk factors that could increase the risk of QT prolongation.

Second, life-style modification, beta blockers and ICD implantation are the most important therapeutic modalities in proper management of patients with LQT. Left Cardiac Sympathetic Denervation has a significant role to decrease the arrhythmia load in LQT patients with minimal acute and long-term complications.

Finally, continued progress toward understanding of mechanisms of ion channel function and drug-channel interaction will guide the development of more effective, mechanism-based molecular agents in the treatment of LQT.

I want to thank the authors for this interesting manuscript and I hope our readers will appreciate this review of long QT syndrome.