Long QT Syndrome

Prevenzione Morte Improvvisa secondo LG ACC- AHA-ESC 2006

Recommendations

Class I

1. <u>Lifestyle modification</u> is recommended for patients with an LQTS diagnosis (clinical and/or molecular). *(Level of Evidence: B)*

2. <u>Beta blockers</u> are recommended for patients with an LQTS clinical diagnosis (i.e., in the presence of prolonged QT interval). *(Level of Evidence: B)*

3. <u>Implantation of an ICD along with use of beta blockers is recommended for LQTS patients with previous cardiac arrest</u> and who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: A)*

Class IIa

1. Beta blockers can be effective to reduce SCD in patients with a molecular LQTS analysis and normal QT interval. *(Level of Evidence: B)*

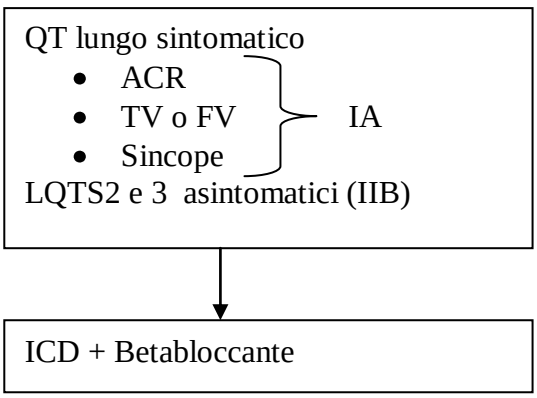
2. <u>Implantation of an ICD with continued use of beta blockers can be effective to reduce SCD in LQTS patients experiencing syncope and/or VT</u> while receiving beta blockers and who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: B)*

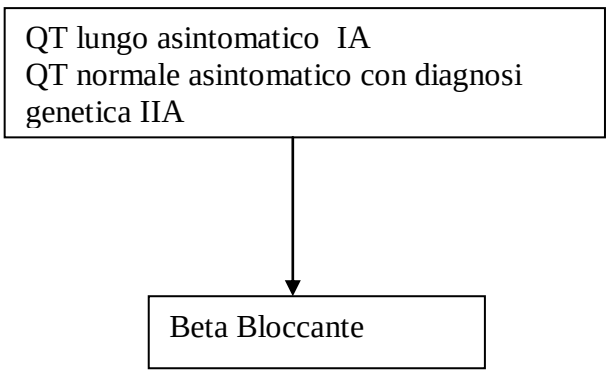
Class IIb

1. Left cardiac sympathetic neural denervation may be considered for LQTS patients with syncope, torsades de pointes, or cardiac arrest while receiving beta blockers. *(Level of Evidence: B)*

2. Implantation of an ICD with the use of beta blockers may be considered for prophylaxis of SCD for patients in categories possibly associated with higher risk of cardiac arrest such as LQT2 and LQT3 and who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: B)*

	I	*IIA*	*IIB*
Prevenzione primaria	**Beta blockers** are recommended for patients with an **LQTS clinical diagnosis (i.e., in the presence of prolonged QT interval)**. *(Level of Evidence: B)*	**Beta blockers** can be effective to reduce SCD in patients **with a molecular LQTS analysis and normal QT interval.** *(Level of Evidence: B)*	**Implantation of an ICD with the use of beta blockers may be considered for prophylaxis of SCD for patients in categories possibly associated with higher risk of cardiac arrest such as LQT2 and LQT3** and who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: B)*
Prevenzione Secondaria	**Implantation of an ICD along with use of beta blockers is recommended for LQTS patients with previous cardiac arrest** and who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: A)*	**Implantation of an ICD with continued use of beta blockers can be effective to reduce SCD in LQTS patients experiencing syncope and/or VT** while receiving beta blockers and who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: B)*	





Causes and Risk Factors

The LQTS is an inherited disease characterized by prolonged ventricular repolarization (QT interval) and by ventricular tachyarrhythmias that may manifest as syncopal events. Cardiac arrhythmias are often elicited by stress and emotion, although in some cases they may also occur at rest or during sleep . Two patterns of inheritance have been identified: the more common autosomal dominant **Romano-Ward** and Timothy syndromes and the much rarer autosomalrecessive cases. The latter are usually more severe, often but not always involving consanguineous marriages, and are often associated with congenital deafness (the **Jervell Lange-Nielsen** syndrome). Mutations in 8 genes have been identified: 7 of them encode cardiac ion channel subunits and 1 encodes an anchoring protein that has been implicated in controlling ion channel targeting specific membrane sites .The distinguishing features of some of the genetic variants of the disease have been identified and incorporated in risk stratification algorithms.

Risk Stratification

Even before the identification of the genetic subtypes, QT interval duration was identified as the strongest predictor of risk for cardiac events (syncope, SCD) in LQTS, and it remains so. A normal QT interval in anungenotyped family member portends a good prognosis. A **QTc exceeding 500 ms (corresponding to the upper QTc quartile among affected genotyped individuals) identifies patients with the highest risk** of becoming symptomatic by age 40. Patients with the Jervell Lange- Nielsen and other homozygous syndromes and patients with LQTS associated with syndactyly are at higher risk. A family history of SCD has not proved to be a risk factor for SCD .

Genetic testing is often useful in probands with a clinical diagnosis of LQTS to provide more accurate risk stratification and to guide therapeutic strategies.

Symptoms in LQTS range from SCD to syncope and near syncope. Patients resuscitated from SCD have an especially ominous prognosis, with a relative risk of 12.9 of experiencing another cardiac arrest. In addition, affected patients may be identified because of QT prolongation detected incidentally or because they are relatives of affected individuals and are found to be mutation carriers in genetic screening; prognosis in such family members tends to be better than that for the proband. **Risk is increased during the immediate postpartum period** . It has been shown that the interplay between genetic defect, QT duration, and gender may provide an algorithm for risk stratification . Patients with the highest risk of becoming symptomatic are LQT1 and LQT2 patients with a QTc greater than 500 ms and males with LQT3 irrespective of QT interval duration. LQT3 patients may represent a group at higher risk. Among LQT2 patients, those with a mutation resulting in a change in the pore region of the protein appear to be at higher risk of cardiac events than are those with mutations in other regions of the gene. **Beta blockers are highly effective in LQT1, whereas they offer incomplete protection in LQT2 and LQT3** .

Ventricular Arrhythmias

Syncope in LQTS patients is usually attributed to severe ventricular arrhythmias (although other causes can occur). Syncopal events are usually associated with stress, emotion, or exercise; however, gene-specific triggers for cardiac events have been identified in the 3 most common genetic variants of the disease. Individuals affected by the **LQT1** form of the disease (mutations in the *KCNQ1* or *KvLQT1* gene encoding the ion channel that conducts the potassium current IKs) are **more susceptible to cardiac events occurring during exercise** and particularly during swimming . **LQT2** patients harbor mutations in the *KCNH2* (or *HERG*) gene encoding the channel conducting the potassium current IKr are susceptible

to cardiac events occurring during **rest or emotion, and characteristically with acoustic stimuli** . Finally**, LQT3 patients carrying mutations in the *SCN5A* gene encoding the cardiac sodium channel are susceptible to cardiac events occurring at rest and during sleep** .

A description of the long QT subtypes is given in Table

Long QT Syndrome Subtypes

Variant	Gene	Chromosome	Function	evento
LQT1	*KCNQ1*	11p15.5 IKs	alpha subunit	ACR da sforzo
LQT2	*KCNH2*	7q35-35 IKr	alpha subunit	ACR riposo, stress rumore
LQT3	*SCN5A*	3p21-23 INa	alpha subunit	ACR nel sonno
LQT4	*ANK2*	4q25-2	Targeting protein	
LQT5	*KCNE1*	21p22.1-22-2	IKs beta subunit	
LQT6	*KCNE2*	21p22.1-22-2	IKr beta subunit	
LQT7	*KCNJ2*	17p23.1-24.2	IK1	
LQT8	*CACNA1C*	12p13.3	ICa alpha subunit	
JLN1	*KCNQ1*	11p15.5 IK	s alpha subunit	
JLN2	*KCNE1*	21p22.1-22-2	IKr beta subunit	

The mean age for first manifestation of the disease is 12 y, but there is a wide range from the first year of life to as late as the fifth through sixth decades. Documentation of the arrhythmia during cardiac events is relatively uncommon in LQTS: when arrhythmias are recorded, the characteristic polymorphic VT, “torsades de pointes,” is identified ; SCD may be the first manifestation of the disease.

Lifestyle Changes

It is recommended that all patients affected by LQTS avoid competitive sports activity . For LQT1 patients, swimming should be specifically limited or performed under supervision. LQT2 patients should avoid exposure to acoustic stimuli especially during sleep (avoidance of telephone and alarm clock on the night stand). All patients with LQTS should avoid drugs known to prolong the QT interval and those that deplete potassium and magnesium.

Tabella 4. Farmaci potenzialmente a rischio di prolungare il tratto QT.

Farmaci cardiovascolari	***Farmaci SNC***	Olanzapina	***Farmaci respiratorio***	***Farmaci antivirali***	***Farmaci decongestionanti nasali e antistaminici***
Amiodarone	Aloperidolo	Paroxetina	Salbutamolo	Amantidina	Fenilefrina
Chinidina	Amitriptilina	Quetiapina	Salmeterolo	Foscarnet	Fenilpropanolamina
Disopiramide	Citalopram	Risperidone	Terbutalina		Pseudoefedrina
Dobutamina	Cloralio idrato	Sertindolo		***Farmaci antiparassitari***	Terfenadina
Dopamina	Clorpromazina	Sertralina	***Farmaci antibatterici***	Clorochina	
Efedrina	Clomipramina	Tioridazina	Azitromicina	Meflochina	***Altri farmaci***
Epinefrina	Droperidolo	Tizanidina	Ciprofloxacina	Pentamidina	Alfuzosina
Flecainide	Felbamato	Trimipramina	Claritromicina		Octreotide
Ibutilide	Fluoxetina	Venlafaxina	Eritromicina	***Farmaci antimicotici***	Sibutramina
Indapamide	Galantamina		Levofloxacina	Fluconazolo	Tacrolimus
Isradipina	Imipramina	***Farmaci GI***	Moxifloxacina	Itraconazolo	Tamoxifene
Midodrina	Levomepromazina	Dolasetron	Ofloxacina	Ketoconazolo	Vardenafil
Norepinefrina	Litio	Domperidone	Cotrimossazolo	Voriconazolo	
Sotalolo	Metadone	Granisetron			
	Metilfenidato	Ondansetron			
	Nortriptilina				