REVIEW ARTICLE

The Risk of Cardiac Events and Genotype-Based Management of LQTS Patients

Grażyna Markiewicz-Łoskot, M.D., Ph.D.,*† Ewa Moric-Janiszewska, Ph.D.,‡ and Urszula Mazurek, Ph.D.§

From the *Department of Pediatric Cardiology, Medical University of Silesia, Katowice, Poland; †Department of Nursing and Social Medical Problems, Medical University of Silesia, Katowice, Poland; ‡Department of Biochemistry, and §Department of Molecular Biology, Medical University of Silesia, Sosnowiec, Poland

This review discusses the risk of cardiac events and genotype-based management of LQTS. We describe here the genetic background of long QT syndrome and the eleven different genes for ion-channels and a structural anchoring protein associated with that disorder. Clinical Background section discusses the risk of cardiac events associated with different LQTS types. Management and Prevention section describes in turn gene-specific therapy, which was based on the identification of the gene defect and the dysfunction of the associated transmembrane ion channel. In patients affected by LQTS, genetic analysis is useful for risk stratification and for making therapeutic decisions. A recent study reported a quite novel pathogenic mechanism for LQTS and suggested that treatments aimed at scaffolding proteins rather than specific ion channels may be an alternative to antiarrhythmic strategy in the future.

Ann Noninvasive Electrocardiol 2009;14(1):86–92

congenital long QT syndrome; ion channel; genotype–phenotype correlation; arrhythmias; beta-blocker therapy

GENETIC BACKGROUND

Congenital long QT syndrome (LQTS) is a familial disorder with an autosomal dominant (Romano-Ward syndrome and Timothy syndrome) or recessive trait of inheritance (Jervell and Lange-Nielsen syndrome). LQTS is associated with prolonged QT interval in the electrocardiogram, abnormal T-wave morphology, and a propensity to recurrent syncope, which are caused by polymorphic ventricular tachyarrhythmia known as torsade de pointes (TdP).^{1,2}

LQTS is a primary electrical disease caused by mutations in eleven different genes for ion channels and a structural anchoring protein, located on chromosomes 3, 4, 6, 7, 11, 17, and 21 (Table 1).^{3–11} Mutations in KCNQ1 (LQTS1) and KCNE1 (LQTS5) are responsible for defects in the slowly activating

component of the delayed rectifier potassium current (I_{Ks}). The mutations in HERG (LQTS2) and KCNE2 (LQTS6) are, in turn, responsible for defects in the rapidly activating component of the delayed rectifier potassium current (I_{Kr}). Mutations in SCN5A alter the function of the sodium channel (I_{Na}) and are responsible for LQTS3.³

Five out of eleven genes encode for cardiac potassium channels; one codes for cardiac sodium channels (SCN5A) and one for the Ankyrin B (ANKB) protein, which is involved in anchoring of ion channels to the cellular membrane (LQTS4).⁵ Abnormalities of T-wave morphology and QT interval prolongation have also been reported in patients with Andersen's syndrome (LQTS7), an hereditary periodic paralysis disorder caused by reduction in the inwardly rectifying potassium current ($I_{Kir2.1}$).⁶

Address for reprints: Ewa Moric-Janiszewska, Ph.D., Department of Biochemistry, Narcyzów 1, 41-200 Sosnowiec, Poland. Fax: +48-32-364-1074; E-mail: ejaniszewska@sum.edu.pl

This study was supported by a grant from the Polish Ministry of Science and Higher Education (MNiSW) No. N 404 038 31/2150.

©2009, Copyright the Authors
Journal compilation ©2009, Wiley Periodicals, Inc.

Table 1. LQTS Subtypes

Phenotype	Subtype	Locus	Gene	Ion Channel
Romano-Ward syndrome; Jervell and Lange-Nielsen syndrome	LQTS1	11p15.5	<i>KCNQ1 (K_vLQT1)</i>	↓I _{Ks} alpha subunit
	LQTS2	7q35-36	<i>KCNH2 (HERG)</i>	↓I _{Kr} alpha subunit
	LQTS3	3p21-24	<i>SCN5A (Na_v1.5)</i>	↑I _{Na} alpha subunit
	LQTS4	4q25-27	<i>ANK2 (ANKB)</i>	Targeting protein
	LQTS5	21p22.1-22.2	<i>KCNE1 (minK)</i>	↓I _{Ks} beta subunit
	LQTS6	21p22.1-22.2	<i>KCNE2 (MiRP1)</i>	↓I _{Kr} beta subunit
Andersen-Tawil syndrome	LQTS7	17q23	<i>KCNJ2 (Kir2.1)</i>	↓I _{K1} (I _{Kir2.1})
	LQTS8	6q8A	<i>CACNA1C (Ca_v1.2)</i>	I _{Ca-L} alpha subunit
	LQTS9	3p25	<i>CAV3</i>	Caveolin 3
	LQTS10	11q23	<i>SCN4B</i>	Na _v beta-4 subunit
	LQTS11	7q21-q22	<i>AKAP9</i>	A-kinase anchoring protein 9

Perturbed inactivation of Ca²⁺ channel activity known as Timothy syndrome (LQTS8) has been caused by mutations in Ca_v1.2 gene, which encodes for an alpha subunit of the calcium channel I_{Ca-L}.⁷⁻⁹ Timothy syndrome is characterized by lethal ventricular arrhythmias with prolonged QT interval in the electrocardiogram, autism, hypoglycemia, immune deficiency, and multiorgan dysfunction (congenital heart disease, webbing of the fingers and toes).⁷

Recent studies reported the mutations in caveolin-3 (LQTS9) as well as a mutation in A-kinase anchoring protein (LQTS11), which may underlie novel pathogenetic mechanisms of LQTS.^{10,11} Mutations in SCN4B is also a novel LQTS-susceptibility gene (LQTS10), which encodes for beta-4 subunit of the cardiac sodium channel.¹²

Approximately 500 different mutations have already been associated with LQTS, but most identified mutations occur in LQTS1, LQTS2, and LQTS3 genes. It is anticipated that many more mutations in these genes and in new LQTS candidate genes will be identified in the future.^{4,13}

CLINICAL BACKGROUND

Sympathetic stimulation, such as exercise, strong emotion, and loud noise, has been associated with playing a role in the genesis of QT prolongation and TdP in some forms of LQTS.¹⁴⁻¹⁷ These adrenergic conditions give rise to early after depolarizations and triggered activity, and produce a marked dispersion of ventricular repolarization, particularly in LQTS1 and LQTS2 genotypes.^{18,19}

The highest rate of cardiac events such as syncope episodes, aborted cardiac arrest, or sudden

cardiac death (SCD) was shown to occur during adolescence in the LQTS subjects.²⁰⁻²³

The recent data suggest that female gender, corrected QT interval (QTc ≥ 500 ms), LQT2 genotype, and frequency of cardiac events before age 18 years were associated with increased risk of having any cardiac events between the ages of 18 and 40 years.²⁴ The LQTS3 genotype and the recent syncope (<2 years in the past) were shown to be significant risk factors after age 40 years.²⁵

LQT1 syndrome has been reported both experimentally and clinically as well as to be more sensitive to sympathetic stimulation (physical or emotional stress) and more responsive to beta-blockers than either LQT2 or LQT3 of syndrome.^{14,26-32}

Exercise-related events, especially swimming, dominate the clinical picture in patients with LQTS1.^{15,16,33} A sudden startle in the form of an auditory stimulus (alarm clock) is the predominant trigger of cardiac events in LQT2 syndrome, whereas cardiac events also occur during rest or emotion.¹⁵ LQTS3 patients are susceptible to cardiac events occurring at rest and during sleep.^{19,34}

Sixty-five percent of the patients with a given genotype are more likely to experience cardiac events under conditions similar to their first classified event. But the greater probability of becoming symptomatic under one condition does not exclude the possibility of a cardiac events occurring under different circumstances.¹⁴ Use of clinical information in determining genetic screening for LQTS was reported.³⁵

The cumulative survival curves demonstrate that the age at which LQTS becomes clinically manifest is also gene specific. LQTS1 patients

are the youngest to experience cardiac events; 86% of them have their first episode by age 20. In contrast, symptomatic LQTS2 and LQTS3 patients are also at risk of the onset of cardiac events later in life.¹⁴ However, 48% cumulative probability of cardiac events concerns LQTS2 females between ages 16 and 40; only LQTS1 and LQTS3 males show a higher risk of cardiac events. This observation emphasizes the need to carefully follow and treat LQTS patients (particularly females) who remain at high risk of cardiac events despite asymptomatic course in childhood and adolescence.^{36,37}

The lethality of cardiac events (the risk of death during a cardiac event), which is significantly higher in the LQTS3 patients than in the LQTS1 and or LQTS2 patients, may also suggest the need for more aggressive treatment of LQTS3 patients.³⁴ QT interval duration was identified as the strongest predictor of risk for cardiac events in LQTS1 and LQTS2 patients. QTc exceeding 500 ms identifies patients with the highest risk of becoming symptomatic by the age of 40.^{15,38,39} Males with LQTS3 may represent a group at higher risk, irrespective of QT interval duration.^{34,39} A normal QT interval in family member without identifying mutations portends a good prognosis.^{40,41}

Patients with the LQTS associated with syndactyly (Timothy syndrome) and with congenital deafness (Jervell and Lange-Nielsen syndrome) are at higher risk of cardiac events.^{7,42} Patients with Andersen's syndrome seem to have bidirectional ventricular arrhythmias but not a high incidence of cardiac arrest.⁶

The recent data indicate that the type of biophysical ion channel dysfunction and location of LQTS1 and LQTS2 mutations may have important influence on the phenotypic manifestations and clinical course of patients with these disorders.^{43,44}

Patients with mutations in the pore region of the HERG gene had more severe clinical manifestations of the genetic disorder and experienced a higher frequency of arrhythmia-related cardiac events occurring at earlier age compared with patients with nonpore mutation.⁴³

Another genotype-phenotype study indicates that in type 1 LQTS, mutations located in the transmembrane portion of the ion channel protein and the degree of ion channel dysfunction caused by the mutations are important independent risk factors influencing the clinical course of this disorder.⁴⁴

MANAGEMENT AND PREVENTION

There were three classical modalities of treating LQTS: beta-adrenergic blocking agents (beta-blockers),^{2,14,45–50} elective pacing (pacemakers),^{49–52} and left cervicothoracic sympathetic ganglionectomy.^{53–55}

Beta-blockers have been used as standard therapeutic and preventive measures in patients with clinical diagnosis of LQTS.^{2,14,45–48} The mechanism of beta-blocker action is to prevent the increase in repolarization dispersion induced by sympathetic stimulation.^{26,27}

Beta-blocker treatment is effective in about 60–70% of LQTS patients in all age groups.^{23–25,47} Beta-blockers effectively reduce but do not completely eliminate the risk of fatal or near-fatal cardiac events in high-risk patients with LQTS.^{23–25}

Beta-blocker therapy does not improve magnesium (Mg) deficiency; the latter may become a triggering mechanism of life-threatening arrhythmias. Management with intravenous magnesium sulfate may be a possible therapeutic option for an acute episode of TdP, but not for chronic treatment.⁵⁶

The evidence of pause or bradycardia-dependent arrhythmias and symptomatic bradycardia induced by beta-blocker therapy should be considered an indication for use of cardiac pacing as an adjunct to beta-blockers.^{49–52} The cardiac pacing prevents pauses and shortens the QTc interval by enhancing the repolarizing potassium currents as the result of increased heart rates. Beta-blocker therapy with pacemakers does not prevent sudden death in LQTS patients.^{50,51}

Left cardiac sympathetic neural denervation is considered for LQTS patients, with syncope, TdP, or cardiac arrest, who do not respond to beta-blockers.^{53–55} It is an effective method of surgical antiadrenergic therapy, especially during early childhood, in which cardioverter-defibrillator implantation may be technically more difficult.^{54,55}

The implantable cardioverter-defibrillators (ICDs) have been used successfully in cases TdP persist despite therapy with the classical modalities.^{57,58} The ICDs will not prevent the precipitation of torsades but will prevent sudden cardiac death when torsades are prolonged or generate to ventricular fibrillation. The use of beta-adrenergic blocking agent should be continued because emotional distress associated with

the unnecessary shocks from the cardioverter-defibrillator may cause adrenergic stimulation and torsades. Implantation of an ICD with continued use of beta-blockers can be effective in reducing SCD in LQTS patients with previous cardiac arrest and in patients with experiencing syncope and/or VT.^{57,58}

The identification of specific ion current abnormalities in genetically diagnosed LQTS patients has provided understanding of electrophysiologic mechanisms underlying LQTS, but more importantly it opened new therapeutic options.⁵⁹

The role of I_{Ks} impairment in facilitating adrenergic-dependent arrhythmias has been documented to have implications for beta-blocker therapy in LQTS1 patients.^{14,27,29,31,47} Eighty percent of them remained free from recurrences with a total mortality rate of 4%. Only a few LQTS1 patients required therapy other than antiadrenergic intervention.¹⁴

The use of potassium channel openers is another attractive therapeutic option in LQTS1 patients with potassium channel abnormalities.^{60–62} Experimental administration of nicorandil, the ATP-sensitive potassium channel opener, contributed to a decrease in QT interval duration, monophasic action potential duration and dispersion, as well as eliminated early afterdepolarizations in LQTS1 patients.⁶¹ Currently, these agents may be considered only as adjuncts to the standard therapy.

Gene-specific management for LQTS2 is more problematic. The efficacy of beta-blockers in LQTS2 patients was already demonstrated.^{1,26} The experimental prevention with beta-blocker therapy for life-threatening arrhythmias triggered by a loud noise suggests their effectiveness also for LQTS2 patients at risk under this specific condition.¹⁵ But Priori et al. have found a high rate of cardiac events in patients with LQTS2 and LQTS3 genotypes treated with beta-blockers. These observations suggest that cardioverter-defibrillator may be a reasonable alternative in high-risk LQTS2 and LQTS3 patients.⁶³

It is known that elevated levels of serum potassium increase outward potassium currents in patients with potassium current abnormalities.¹⁴ In LQTS2 patients with mutation in HERG gene and with defects in the rapidly activating component of the delayed rectifier potassium current (I_{Kr}), extracellular potassium levels are increased following intravenous potassium chloride injection and

oral spironolactone administration (I_{Kr}), which results in raised channel activity and improved repolarization.⁶⁴ Preliminary clinical observations indicate that long-term oral potassium supplementation and/or administration of spironolactones in LQTS2 patients decrease QT interval duration and QT dispersion.^{65,66} However, renal potassium homeostasis causes difficulties in achieving high potassium with chronic oral therapy.⁶⁵

LQTS3 patients are at higher risk of longer cycle lengths and they did not tolerate very well with use of beta-blocker therapy, which can reduce heart rate. LQTS3 patients may benefit from pacemakers, which would also allow safe use of beta-blockers, because their QT interval tends to shorten significantly at faster heart rates.¹⁴ Since this mutation causes the inward flow of sodium ions during repolarization, administration of sodium channel blockers, especially class Ib drugs, is the right choice for potential genetically driven therapy.²⁸

Schwartz et al. were the first to use mexiletine in patients with mutations in the sodium channel SCN5A gene.⁶⁷ Mexiletine, lidocaine, and tocainide in low doses were found to block abnormal inward current, normalizing sodium channel inactivation.^{28,67,68} Under clinical conditions, intravenous lidocaine or oral mexiletine may be considered in patients who present LQTS3 and TdP. These agents yielded in few LQTS3 patients a very significant QT interval shortening.^{67,68} This spectacular electrocardiographic effect does not mean that class Ib antiarrhythmic drugs will prove effective in preventing cardiac events in LQTS3 patients. Effective chronic therapy results with class Ic antiarrhythmic drug flecainide, a late sodium current blocker, were reported for LQTS3 deltaKPO mutant.^{69–73}

Even though the data regarding therapy for LQTS3 patients remain numerically limited, their high mortality rate despite therapy and particularly at the first episode suggests considering internal cardioverter-defibrillator implantation with use of beta-blockers for prophylaxis of SCD.

Little is known about risk stratification and management of patients with Andersen's syndrome. The benefit of prophylactic treatment with beta-blockers has not been defined in these patients. The beneficial role of calcium channel blockers and flecainide has also been proposed on the basis of bidirectional ventricular arrhythmias suppression observed in a few patients.^{74–76}

Table 2. Lifestyle Modifications Recommendations for LQTS Patients on the Basis of Genotype

Recommendations	LQTS1	LQTS2	LQTS3
Avoid competitive sport activity	+++	++	+
Avoid swimming without supervision	+++	+	
Avoid emotional stress	+++	+++	+
Avoid exposure to acoustic stimuli mostly during sleep	+	+++	++
Avoid drugs that may prolong QT interval	++	+++	++
Avoid drugs that may deplete potassium/magnesium	++	+++	++

Lifestyle modification is recommended for patients with clinical and/or molecular LQTS diagnosis (see Table 2).^{14,77,78}

Genetic analyses are very important for identifying all mutation carriers within an LQTS family. Although genetic analysis is not yet widely available, it is advisable to try to make it accessible to LQTS patients. In patients affected by LQTS, genetic analysis is useful for risk stratification and for making therapeutic decisions.⁷⁹ Asymptomatic gene carriers could be advised to avoid stressful conditions and competitive sport as well as drugs known to prolong the QT interval. Depending on the malignancy of the disease in the family, beta-blockers can be started for prophylaxis of life-threatening arrhythmias.^{14,77,78}

Conversely, family members identified as "non-gene carriers" can be assured that they can conduct a completely normal life.⁸⁰ Furthermore, silent mutation carriers should receive genetic counseling to learn about the risk of transmitting LQTS to offspring. With rare exceptions, LQTS is an autosomal dominant disease, and these silent gene carriers should be informed that 50% of their offspring may be expected to carry the same mutations.⁸¹ Molecular diagnosis, therefore, has to be scheduled for their newborn infants unless they have obvious QT prolongations.^{82–84}

The discovery in 1995 of cardiac channel mutations causing "cardiac channelopathy" opened new therapeutic options for LQTS patients. However, a recent study reported a quite novel pathogenic mechanism for LQTS.^{10,11} The LQTS-associated mutations in the scaffolding protein caveolin-3

alter the properties of the caveolar-localized cardiac sodium channel and confer a gain-of-function phenotype to the structurally intact sodium channel.¹⁰ The latter study suggests that treatments aimed at scaffolding proteins rather than specific ion channels may be an alternative to antiarrhythmic strategy in the future.

REFERENCES

- Schwartz PJ, Moss AJ, Vincent GM, et al. Diagnostic criteria for the long QT syndrome. An update. *Circulation* 1993;88:782–784.
- Moss AJ, Schwartz PJ, Crampton RS, et al. The long QT syndrome. Prospective longitudinal study of 328 families. *Circulation* 1991;84:1136–1144.
- Splawski I, Shen J, Timothy KW, et al. Genomic structure of three long QT syndrome genes: KVLQT1, HERG, and KCNE1. *Genomics* 1998;51:86–97.
- Splawski I, Shen J, Timothy KW, et al. Spectrum of mutations in long-QT syndrome genes KVLQT1, HERG, SCN5A, KCNE1 and KCNE2. *Circulation* 2000;102:1178–1185.
- Mohler PJ, Schott JJ, Gramolini AO, et al. Ankyrin-B mutation causes type 4 long-QT cardiac arrhythmia and sudden cardiac death. *Nature* 2003;421:634–639.
- Plaster MN, Tawil R, Tristani-Firouzi M, et al. Mutations in Kir2.1 cause the developmental and episodic electrical phenotypes of Andersen's syndrome. *Cell* 2001;105:511–519.
- Splawski I, Timothy KW, Sharpe IM, et al. Ca(V)1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. *Cell* 2004;119:19–31.
- Barrett CF, Tsien RW. The Timothy syndrome mutation differentially affects voltage- and calcium-dependent inactivation of Cav1.2 L-type calcium channels. *PNAS* 2008;6:2157–2162.
- Erxleben CH, Liao Y, Gentile S, et al. Cyclosporin and Timothy syndrome increase mode 2 gating of CaV1.2 calcium channels through aberrant phosphorylation of S6 helices. *PNAS* 2006;103:3932–3937.
- Vatta M, Ackerman MJ, Ye B, et al. Mutant caveolin-3 induces persistent late sodium current and is associated with long-QT syndrome. *Circulation* 2006;114:2104–2112.
- Chen L, Marquardt ML, Tester DJ, et al. Mutation of an A-kinase-anchoring protein causes long QT syndrome. *PNAS* 2007;52:20990–20995.
- Medeiros-Domingo A, Kaku T, Tester DJ, et al. SCN4B encoded sodium channel 4 subunit in congenital long QT syndrome. *Circulation* 2007;116:134–142.
- Moss AJ. T-Wave patterns associated with the hereditary long QT syndrome. *CEPR* 2002;6:311–315.
- Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001;103:89–95.
- Moss AJ, Robinson JL, Gessman L, et al. Comparison of clinical and genetic variables of cardiac events associated with loud noise versus swimming among subjects with the long QT syndrome. *Am J Cardiol* 1999;84:876–879.
- Ackerman MJ, Tester DJ, Porter CJ. Swimming, a gene-specific arrhythmogenic trigger for inherited long QT syndrome. *Mayo Clin Proc* 1999;74:1088–1094.
- Wilde AAM, Jongbloed RJE, Doevendans PA, et al. Auditory stimuli as a trigger for arrhythmic events differentiate HERG-related (LQTS2) patients from KVLQT1-related patients (LQTS1). *J Am Coll Cardiol* 1999;33:327–332.

18. Antzelevitch C, Oliva A. Amplification of spatial dispersion of repolarization underlies sudden cardiac death associated with catecholaminergic polymorphic VT, long QT and Brugada syndromes. *J Intern Med* 2006;259:48–58.
19. Roden DM, Spooner PM, et al. Inherited long QT syndromes: A paradigm for understanding arrhythmogenesis. *J Cardiovasc Electrophysiol* 2000;10:1664–1683.
20. Moss AJ, Schwartz PJ, Crampton RS, et al. The long QT syndrome: A prospective international study. *Circulation* 1985;71:17–21.
21. Moss AJ. Prolonged QT syndrome. *JAMA* 1986;256:2985–2987.
22. Goldenberg I, Moss AJ, Peterson DR, et al. Risk factors for aborted cardiac arrest and sudden cardiac death in children with the congenital long-QT syndrome. *Circulation* 2008;117:2184–2191.
23. Hobbs JB, Peterson DR, Moss AJ, et al. Risk of aborted cardiac arrest or sudden cardiac death during adolescence in the long-QT syndrome. *JAMA* 2006;296:1249–1254.
24. Sauer AJ, Moss AJ, McNitt S, et al. Long QT syndrome in adults. *J Am Coll Cardiol* 2007;49:329–337.
25. Goldenberg I, Moss AJ, Bradley J, et al. Long-QT syndrome after age 40. *Circulation* 2008;117:2192–2201.
26. Shimizu W, Antzelevitch C. Cellular basis for the electrocardiographic features of the LQTS1 form of the long QT syndrome: Effects of beta-adrenergic agonists, antagonists and sodium channel blockers on transmural dispersion of repolarization and torsade de pointes. *Circulation* 1998;98:2314–2322.
27. Shimizu W, Antzelevitch C. Differential effects of beta-adrenergic agonists and antagonists in LQTS1, LQTS2, and LQTS3 models of the long QT syndrome. *J Am Coll Cardiol* 2000;35:778–786.
28. Shimizu W, Antzelevitch C. Sodium channel block with mexiletine is effective in reducing dispersion of repolarization and preventing torsade de pointes in LQT2 and LQT3 models of the long QT syndrome. *Circulation* 1997;96:2038–2047.
29. Shimizu W, Tanabe Y, Aiba T, et al. Differential effects of beta-blockade on dispersion of repolarization in the absence and presence of sympathetic stimulation between the LQT1 and LQT2 forms of congenital long QT syndrome. *J Am Coll Cardiol* 2002;39:1894–1896.
30. Tanabe Y, Inagaki M, Kurita T, et al. Sympathetic stimulation produces a greater increase in both transmural and special dispersion of repolarization in LQT1 than LQT2 forms of congenital long QT syndrome. *J Am Coll Cardiol* 2001;37:911–919.
31. Khositseth A, Nemec J, Hejlik J, et al. Effect of phenylephrine provocation on dispersion of repolarization in congenital long QT syndrome. *ANE* 2003;8:208–214.
32. Conrath CE, Wilde AAM, Jongbloed RJE, et al. Gender differences in the long QT syndrome: Effects of B-adrenoceptor blockade. *Cardiovasc Res* 2002;53:770–776.
33. Batra AS, Silka MJ. Mechanism of sudden cardiac arrest while swimming in a child with the prolonged QT syndrome. *J Pediatr* 2002;141:283–284.
34. Zareba W, Moss AJ, Schwartz PJ, et al. Influence of the genotype on the clinical course of the long-QT syndrome. *N Engl J Med* 1998;339:960–965.
35. Van Langen IM, Birnie E, Alders M, et al. The use of genotype-phenotype correlations in mutations analysis for the long QT syndrome. *J Med Genet* 2003;40:141–145.
36. Zareba W, Moss AJ. Long QT syndrome in children. *J Electrocardiol* 2001;34(Suppl.):167–171.
37. Zareba W, Moss AJ, Locati EH, et al. Modulating effects of age and gender on the clinical course of long QT syndrome by genotype. *J Am Coll Cardiol* 2003;42:103–109.
38. Goldenberg I, Mathew J, Moss AJ, et al. Corrected QT variability in serial electrocardiograms in long QT. *J Am Coll Cardiol* 2006;48:1047–1052.
39. Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. *N Engl J Med* 2003;348:1866–1874.
40. Hofman N, Wilde AA, Kaab S, et al. Diagnostic criteria for congenital long QT syndrome in the era of molecular genetics: Do we need a scoring system? *Eur Heart J* 2007;28:575–580.
41. Kimbrough J, Moss AJ, Zareba W, et al. Clinical implications for affected parents and siblings of probands with the long-QT syndrome. *Circulation* 2001;104:557–562.
42. 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;17:1161–1168.
43. Moss AJ, Zareba W, Kaufman ES, et al. Increased risk of arrhythmic events in long-QT syndrome with mutations in the pore region of the human ether-a-go-go-related gene potassium channel. *Circulation* 2002;105:794–799.
44. 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;115:2481–2489.
45. Schwartz PJ, Locati E. Idiopathic long QT syndrome: Pathogenic mechanism and therapy. *Eur Heart J* 1985;6:103–114.
46. Moss AJ. Management of patients with the hereditary long QT syndrome. *J Cardiovasc Electrophysiol* 1998;9:668–674.
47. Moss AJ, Zareba W, Hall WJ, et al. Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome. *Circulation* 2000;101:616–623.
48. Viskin S, Fish R. Prevention of ventricular arrhythmias in the congenital long QT syndrome. *Curr Cardiol Rep* 2000;2:492–497.
49. Eldar M, Griffin JC, Van Hare GF, et al. Combined use of beta-adrenergic blocking agents and long-term cardiac pacing for patients with the long QT syndrome. *J Am Coll Cardiol* 1992;3:830–837.
50. Dorostkar PC, Eldar M, Belhassen B, et al. Long-term follow-up of patients with long QT syndrome treated with beta-blockers and continuous pacing. *Circulation* 1999;100:2431–2436.
51. Moss AJ, Liu JE, Gottlieb S, et al. Efficacy of permanent pacing in the management of high-risk patients with long-QT syndrome. *Circulation* 1991;84:1524–1529.
52. Viskin S. Cardiac pacing in the long QT syndrome: Review of available data and practical recommendations. *J Cardiovasc Electrophysiol* 2000;11:593–600.
53. Moss AJ, McDonald J. Unilateral cervicothoracic sympathetic ganglionectomy for the treatment of long QT interval syndrome. *N Engl J Med* 1970;285:903–904.
54. Schwartz PJ, Locati E, Moss AJ, et al. Left cardiac sympathetic denervation in the therapy of the congenital long QT syndrome: A worldwide report. *Circulation* 1991;84:503–511.
55. Schwartz PJ, Priori SG, Cerrone M, et al. Left cardiac sympathetic denervation in the management of high-risk patients affected by the long QT syndrome. *Circulation* 2004;109:1826–1833.
56. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death-executive summary. A report if the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines. Developed in collaboration with the European

- Heart Rhythm Association and the Heart Rhythm Society. *Eur Heart J* 2006;27:2009–2140.
57. Zareba W, Moss AJ, Daubert JP, et al. Implantable cardioverter defibrillator in high-risk long QT syndrome patients. *J Cardiovasc Electrophysiol* 2003;14:337–341.
58. Etheridge SP, Sanatani S, Cohen MI, et al. Long QT syndrome in children in the era of implantable defibrillators. *J Am Coll Cardiol* 2007;50:1335–1340.
59. Moric-Janiszewska E, Markiewicz-Łoskot G, Łoskot M, et al. Challenges of diagnosis of long QT syndrome in children. *PACE* 2007;30:1168–1170.
60. Carlsson L, Abrahamsson C, Drews L, et al. Antiarrhythmic effects of potassium channel openers in rhythm abnormalities related to delayed repolarization. *Circulation* 1992;85:1491–1500.
61. Shimizu W, Curita T, Matsuo K, et al. Improvement of repolarization abnormalities by K⁺ channel opener in the LQT1 form of congenital long QT syndrome. *Circulation* 1998;97:1581–1588.
62. Aizawa Y, Uchiyama H, Yamamura M, et al. Effect of the ATP-sensitive K channel opener nicorandil on the QT interval and the effective refractory period in patients with congenital long QT syndrome. *J Electrocardiol* 1998;31:117–123.
63. Priori SG, Napolitano C, Schwartz PJ, et al. Association of long QT syndrome loci and cardiac events among patients treated with beta-blockers. *JAMA* 2004;292:1341–1344.
64. Compton SJ, Lux RL, Ramsey MR, et al. Genetically defined therapy of inherited long QT-syndrome. Correction of abnormal repolarization by potassium. *Circulation* 1996;94:1018–1022.
65. Tan HL, Alings M, Van Olden RW, et al. Long-term (sub-acute) potassium treatment in congenital HERG-related long QT syndrome (LQTS2). *Cardiovasc. Electrophysiol* 1999;10:229–233.
66. Etheridge SP, Compton JS, Tristani-Firouzi M, et al. A new oral therapy for long QT syndrome. Long-term oral potassium improves repolarization in patients with HERG mutations. *J Am Coll Cardiol* 2003;42:1777–1782.
67. Schwartz PJ, Priori SG, Locati EH, et al. Long QT syndrome patients with mutations on the SCN5A and HERG genes have differential responses to Na⁺ channel blockade and to increases in heart rate: Implications for gene-specific therapy. *Circulation* 1995;92:3381–3386.
68. Rosero SZ, Zareba W, Robinson JL, et al. Gene specific therapy for long QT syndrome: QT shortening with lidocaine and tocainide in patients with mutation of the sodium channel gene. *ANEC* 1997;2:274–278.
69. Ruan Y, Liu N, Bloise R, et al. Gating properties of SCN5A mutations and the response to mexiletine in syndrome type 3 patients. *Circulation* 2007;116:1137–1144.
70. Benhorin J, Taub R, Goldmit M, et al. Effect of flecainide in patients with new SCN5A mutation: Mutation specific therapy for long QT syndrome? *Circulation* 2000;101:1698–1706.
71. Windle JR, Geletka RC, Moss AJ, et al. Normalization of ventricular repolarization with flecainide in long QT syndrome patients with SCN5a: deltaKPQ mutation. *Ann Non-invasive Electrocardiol* 2001;6:153–158.
72. Nagatomo T, January CT, Makielski JC. Preferential block of late sodium current in the LQT3 deltaKPQ mutant by the class I(C) antiarrhythmic flecainide. *Mol Pharmacol* 2005;57:101–107.
73. Moss AJ, Windle JR, Hall WJ, et al. Safety and efficacy of flecainide in subject with long QT-3 syndrome (delta KPQ mutation): A randomized, double-blind, placebo-controlled clinical trial. *Ann Noninvasive Electrocardiol* 2005;10:59–66.
74. Kannankeril PJ, Roden DM, Fish FA. Suppression of bidirectional ventricular tachycardia and unmasking of prolonged QT interval with verapamil in Andersen's syndrome. *J Cardiovasc Electrophysiol* 2004;15:119.
75. Bokenkamp R, Wilde AA, Schali J, et al. Flecainide for recurrent malignant ventricular arrhythmias in two siblings with Andersen-Tawil syndrome. *Heart Rhythm* 2007;4:508–511.
76. Pellizzon OA, Kalaizich L, Ptacek LJ, et al. Flecainide suppresses bidirectional ventricular tachycardia and reverses tachycardia-induced cardiomyopathy in Andersen-Tawil syndrome. *J Cardiovasc Electrophysiol* 2008;19:95–97.
77. Pelliccia A, Fagard R, Bjornstad HH, et al. Recommendations for competitive sports participation in athletes with cardiovascular disease. A consensus document from the Study Group of Sports Cardiology of the Working Group Cardiac Rehabilitation and Exercise Psychology and the Working Group of Myocardial and Pericardial Disease of the European Society of Cardiology. *Eur Heart J* 2005;26:1422–1445.
78. Corrado D, Pelliccia A, Bjornstad HH, et al. Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: Proposal for a common European protocol. Consensus Statement of the Study Group of Sports Cardiology of the Working Group Cardiac Rehabilitation and Exercise Psychology and the Working Group of Myocardial and Pericardial Disease of the European Society of Cardiology. *Eur Heart J* 2005;26:516–524.
79. Napolitano C, Priori SG, Schwartz PJ, et al. Genetic testing in the long QT syndrome: Development and validation of an efficient approach to genotyping in clinical practice. *JAMA* 2005;294:2975–2980.
80. Priori SG. Long QT syndrome: Entering the era of molecular diagnosis. *Heart* 1997;77:5–6.
81. Priori SG, Napolitano C, Schwartz PJ. Low penetrance in the long QT syndrome. Clinical impact. *Circulation* 1999;99:529–533.
82. Weese-Mayer DE, Ackerman MJ, Marazita ML, et al. Sudden infant death syndrome: Review of implicated genetic factors. *Am J Med Genet A* 2007;143:771–788.
83. Arnestad M, Crotti L, Rognum TO, et al. Prevalence of long-QT syndrome gene variants in sudden infant death. *Circulation* 2007;115:361–367.
84. Wang DW, Desai RR, Crotti L, et al. Cardiac sodium channel dysfunction in sudden infant death syndrome. *Circulation* 2007;115:368–376.