2015 춘계통합학술대회

Management for a Girl With LQTS and Sinus Bradycardia

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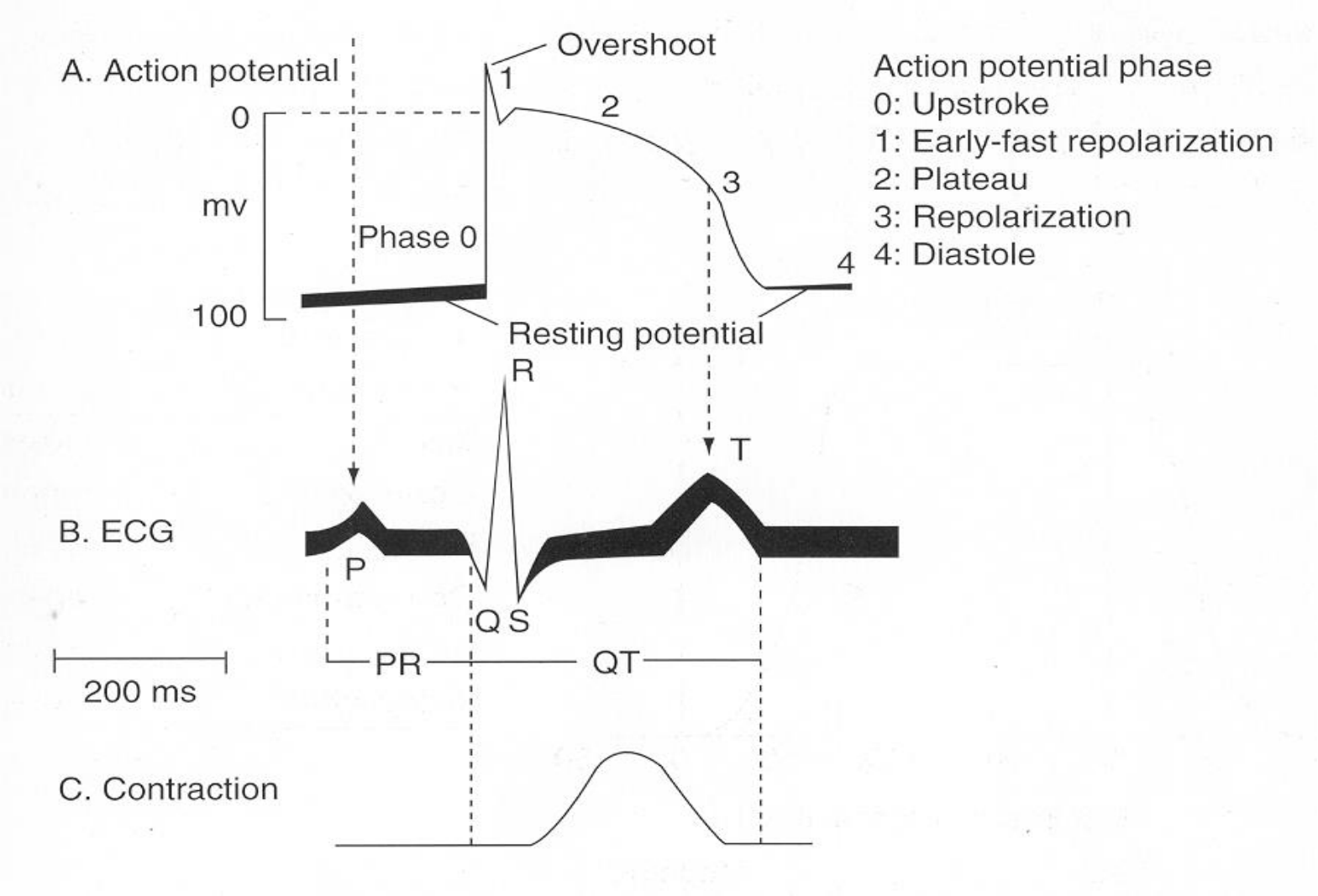
Management for a Girl With Long QT syndrome (LQTS) and Sinus Bradycardia

Management for a Girl With LQTS and Sinus Bradycardia

Action Potential and Electrocardiogram



Normal Values for Durations of ECG Waves and Intervals in Adults

Wave, Interval	Duration (msec)
P wave duration	<120
PR interval	120-200
QRS duration	<110-120*
QT interval (corrected)	≤440-460*

Braunwald's Heart Disease, 8th

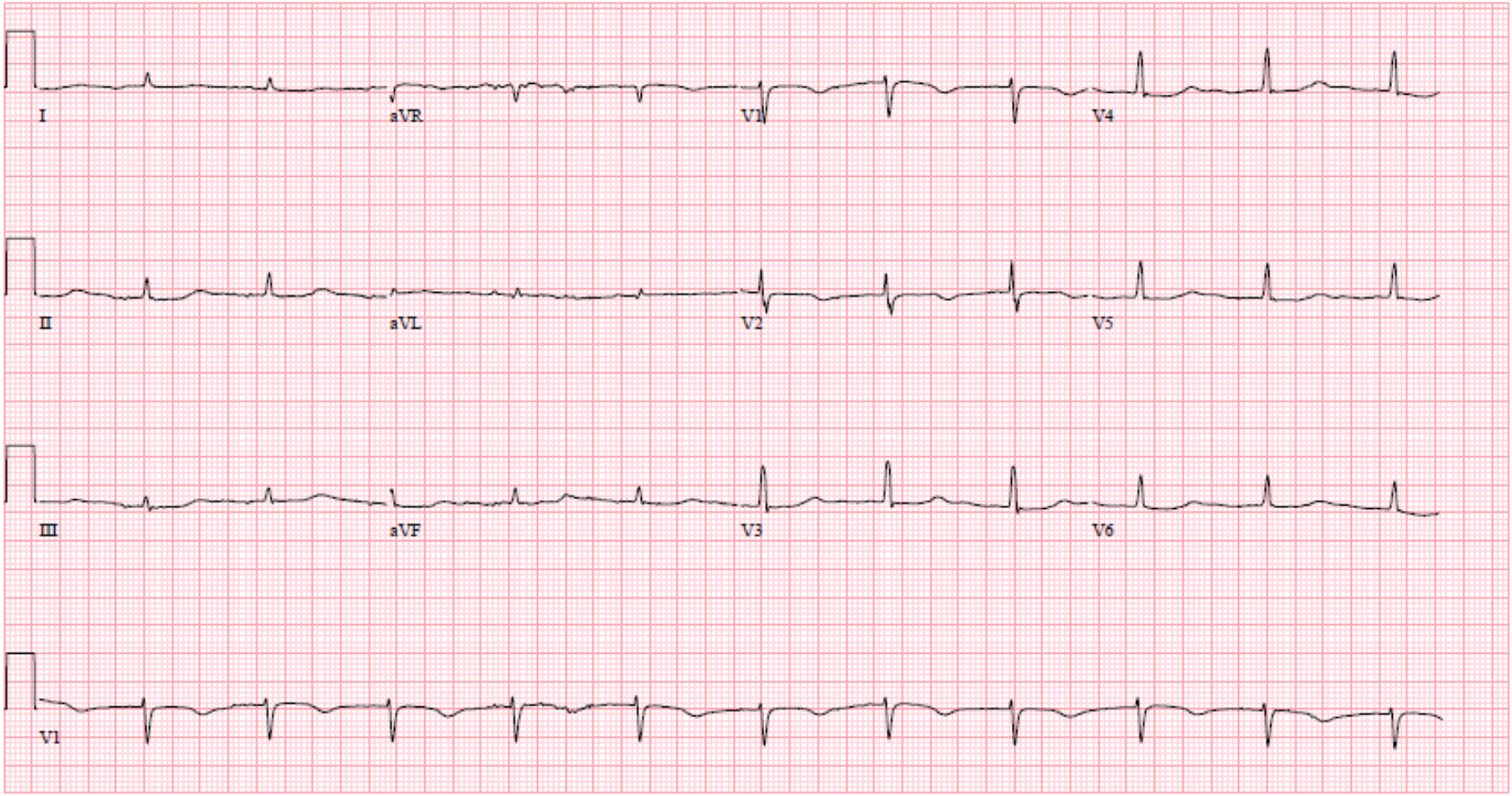
The corrected QT interval (QTc)=
QT interval/√RR (Bazett's formula)

	Vent. rate	68	BPM	Accelerated Junctional rhythm
	PR interval	*	ms	Low voltage QRS
	QRS duration	88	ms	Nonspecific T wave abnormality
Room:	QT/QTc	504/535	ms	Prolonged QT
Loc:7	P-R-T axes	* 53	102	Abnormal ECG

Technician:
Test ind:

Referred by:

Confirmed By: HWANG GYO SEUNG



Congenital LQTS

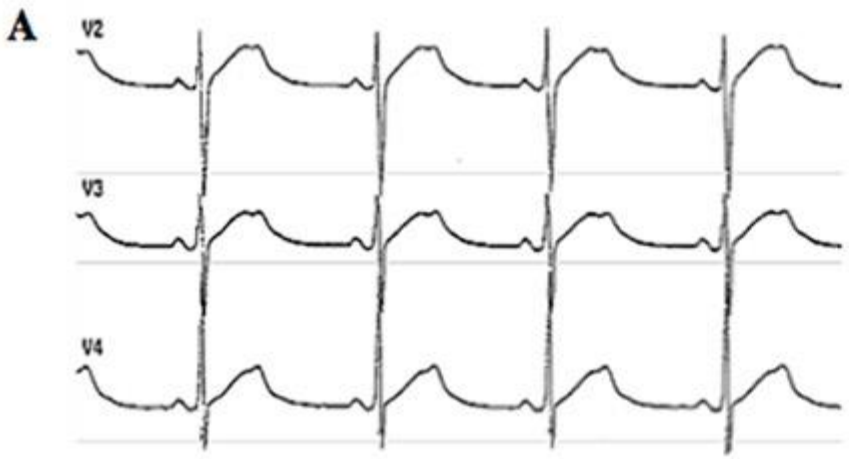
Historical features
- Syncope
- Congenital deafness
- Family history of long QT syndrome
- Unexplained sudden death in family member b age 30

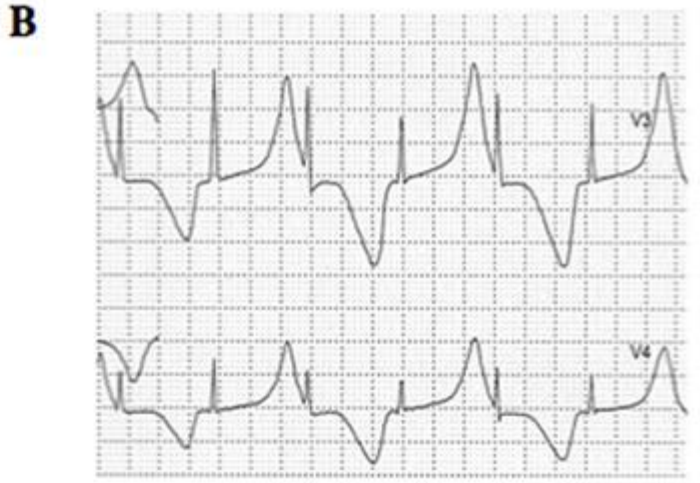
ECG features
- Prolonged QTc interval
- Torsades de pointes
- T-wave alternans
- Notched T-waves in 3 or more leads
- Bradycardia

* The best example of genotype-phenotype correlation

Notched T Waves

T Wave Alternans





Eur Heart J. 2013

Molecular Basis of LQTS

Gene	Locus	Protein
LONG QT SYNDROME		
Major LQTS Genes		
KCNQ1 (LQT1)	11p15.5	I_{Ks} potassium channel alpha subunit (KVLQT1, $K_V7.1$)
KCNH2 (LQT2)	7q35-36	I_{Kr} potassium channel alpha subunit (HERG, $K_V11.1$)
SCN5A (LQT3)	3p21-p24	Cardiac sodium channel alpha subunit ($Na_V1.5$)
Minor LQTS Genes (listed alphabetically)		
AKAP9	7q21-q22	Yotiao
CACNA1C	12p13.3	Voltage gated L-type calcium channel ($Ca_V1.2$)
CALM1	14q32.11	Calmodulin 1
CALM2	2p21.3-p21.1	Calmodulin 2
CAV3	3p25	Caveolin-3
KCNE1	21q22.1	Potassium channel beta subunit (MinK)
KCNE2	21q22.1	Potassium channel beta subunit (MiRP1)
KCNJ5	11q24.3	Kir3.4 subunit of I_{KACH} channel
SCN4B	11q23.3	Sodium channel beta 4 subunit
SNTA1	20q11.2	Syntrophin-alpha 1

J Am Coll Cardiol. 2013 July 16; 62(3): 169–180

TABLE 2. 1993 LQTS Diagnostic Criteria

		Points
ECG findings*		
A.	QT_c†	
	≥480 $msec^{1/2}$	3
	460-470 $msec^{1/2}$	2
	450 $msec^{1/2}$ (in males)	1
B.	Torsade de pointes‡	2
C.	T-Wave alternans	1
D.	Notched T wave in three leads	1
E.	Low heart rate for age§	0.5
Clinical history		
A.	Syncope‡	
	With stress	2
	Without stress	1
B.	Congenital deafness	0.5
Family history‖		
A.	Family members with definite LQTS#	1
B.	Unexplained sudden cardiac death below age 30 among immediate family members	0.5

P J Schwartz Circulation. 1993;88:782-784

Table 1 1993–2012 long QT syndrome diagnostic criteria

			Points
Electrocardiographic findings[a]			
A	QTc[b]	≥480 ms	3
		460–479 ms	2
		450–459 (male) ms	1
B	QTc[b] 4th minute of recovery from exercise stress test ≥480 ms		1
C	Torsade de pointes[c]		2
D	T-wave alternans		1
E	Notched T-wave in three leads		1
F	Low heart rate for age[d]		0.5
Clinical history			
A	Syncope[c]	With stress	2
		Without stress	1
B	Congenital deafness		0.5
Family history			
A	Family members with definite LQTS[e]		1
B	Unexplained sudden cardiac death below age 30 among immediate family members[e]		0.5

European Heart Journal (2013) 34, 3109–3116

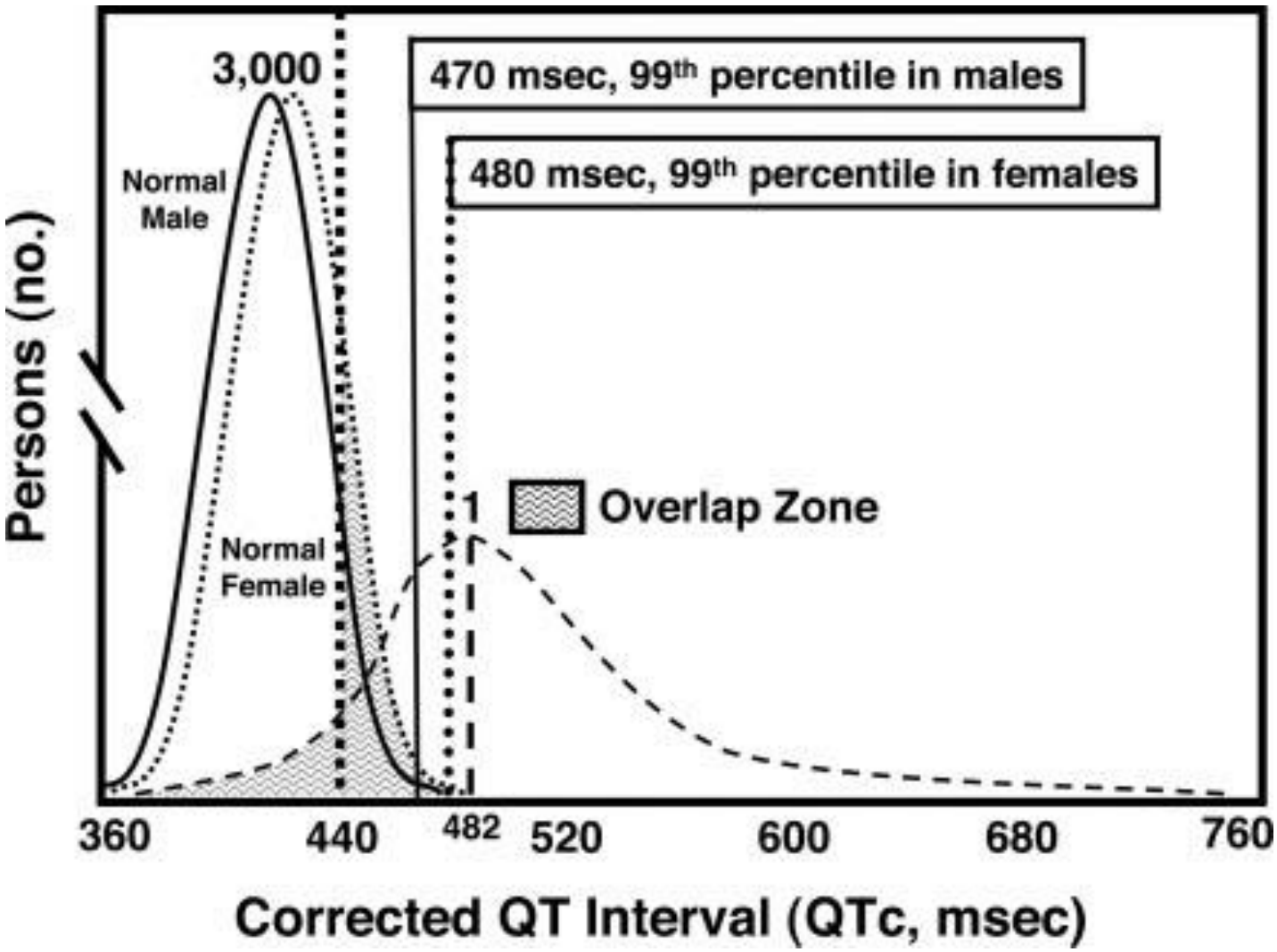
LQTS Diagnosis

Expert Consensus Recommendations on ***LQTS Diagnosis***

1. LQTS is diagnosed:
   a. In the presence of an LQTS risk score ≥ 3.5 in the absence of a secondary cause for QT prolongation *and/or*
   b. In the presence of an unequivocally pathogenic mutation in one of the LQTS genes *or*
   c. In the presence of a corrected QT interval for heart rate using Bazett's formula (QTc) ≥ 500 ms in repeated 12- lead electrocardiogram (ECG) and in the absence of a secondary cause for QT prolongation.
2. LQTS can be diagnosed in the presence of a QTc between 480 and 499 ms in repeated 12-lead ECGs in a patient with unexplained syncope in the absence of a secondary cause for QT prolongation and in the absence of a pathogenic mutation.

Europace (2013) 15, 1389–1406

Distribution of QTc Values Among Individuals With and without LQTS



Circulation. 2007;115:2613-2620

Epinephrine QT Stress Test

* 25% to 50% of patients with LQT1, LQT2, or LQT3: nondiagnostic resting QTc

Circulation. 2006;113:1385-1392

* One-third of patients with LQTS: normal QT interval on at least one ECG

Circulation 2007;115:2613

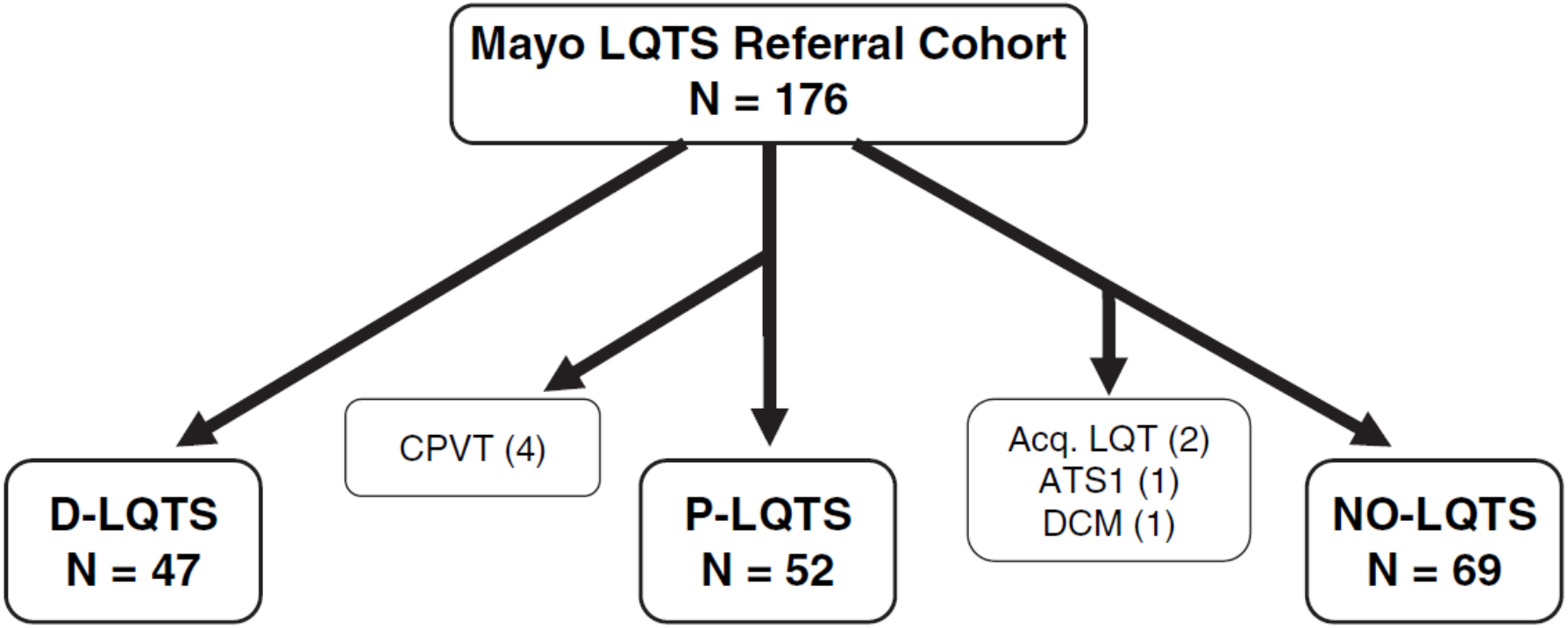
1. A 25-minute infusion protocol (0.025 to 0.3 g · kg1 · min1).

Circulation. 2006;113:1385-1392

2. A bolus injection of epinephrine (0.1 g/kg)--- continuous infusion (0.1 g/kg/min)

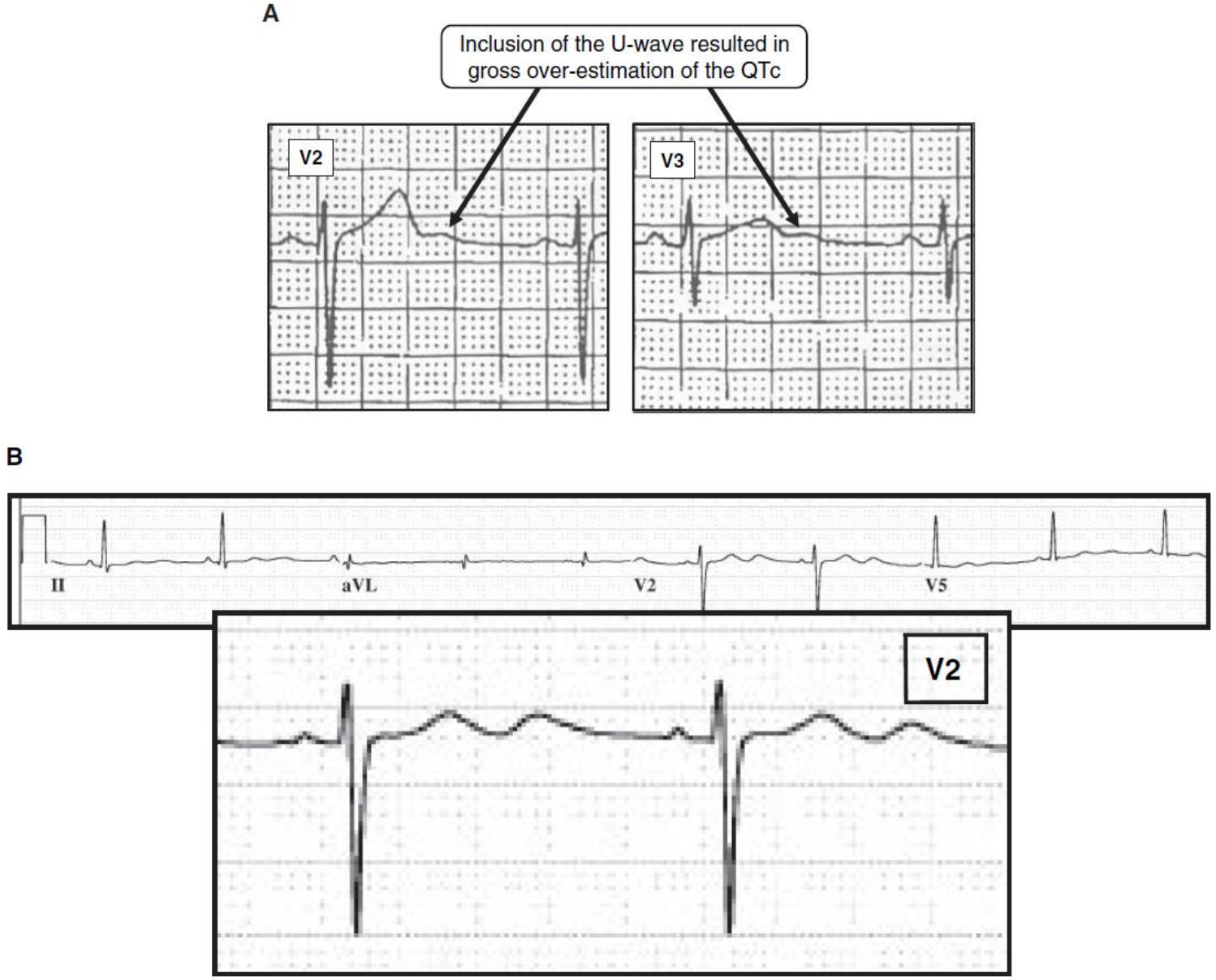
Heart Rhythm (2004) 3, 276–283

Diagnostic Outcome of LQTS Referral Cohort



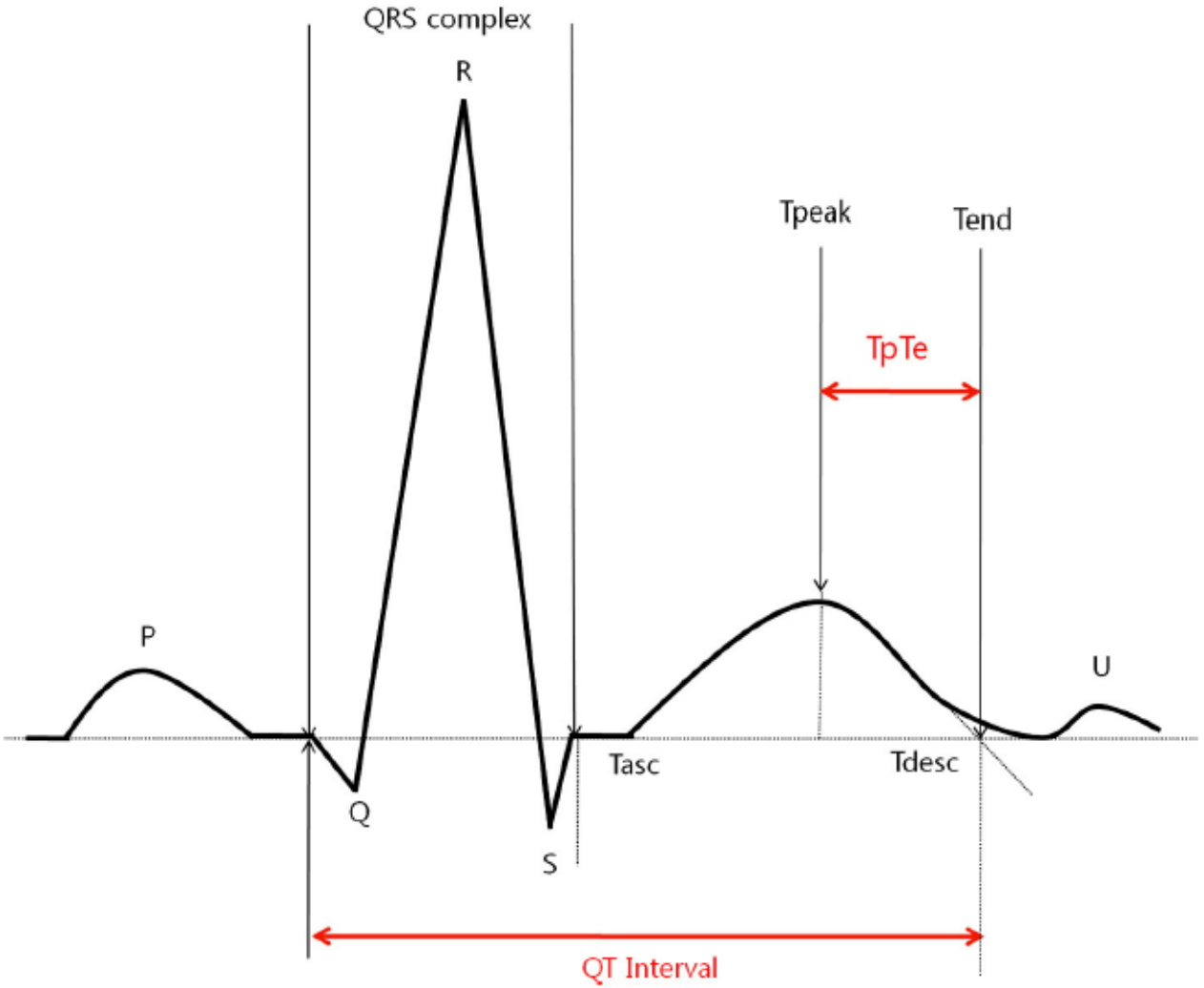
Circulation. 2007;115:2613-2620

Erroneous U-wave Inclusion in the QTc Calculation



Circulation. 2007;115:2613-2620

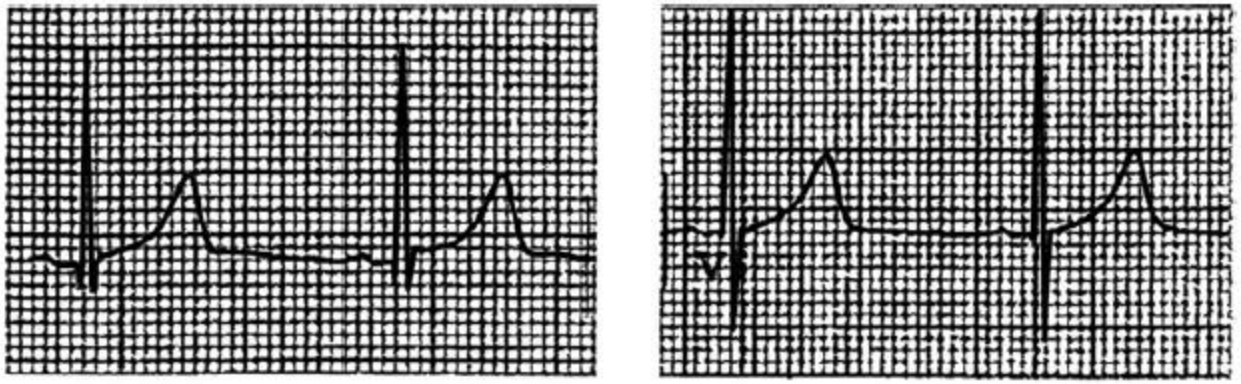
QT interval



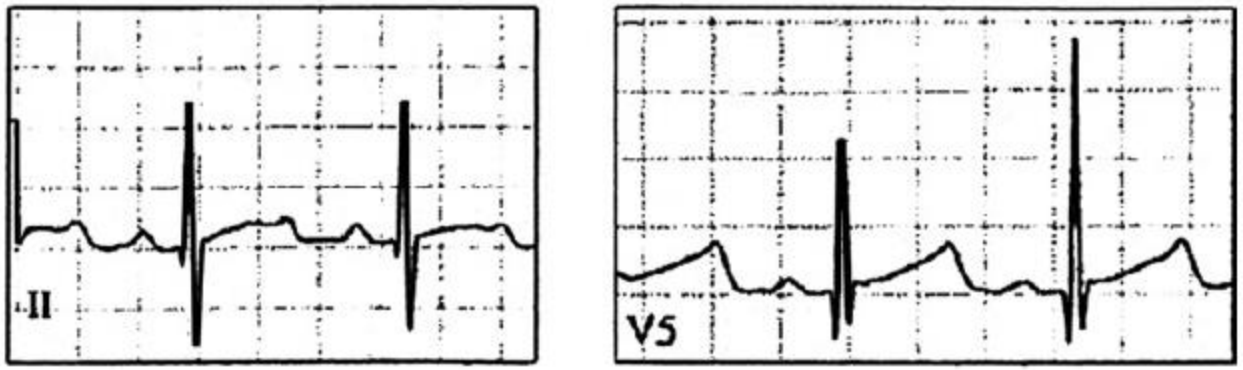
Kim SM, Hwang GS. J Electrocardiol. 2014 Jan-Feb;47(1):84-92

Congenital Long QT Syndrome

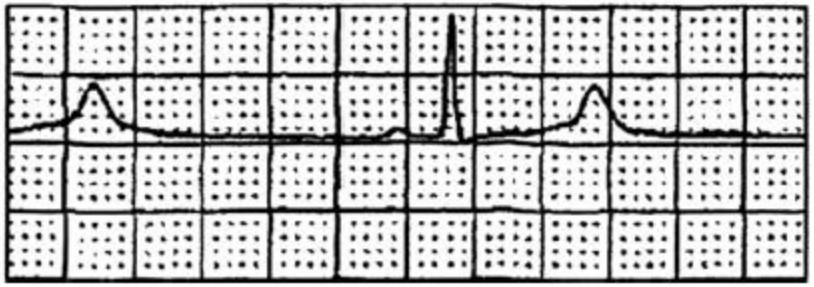
LQT 1
($\downarrow I_{Ks}$)



LQT 2
($\downarrow I_{Kr}$)

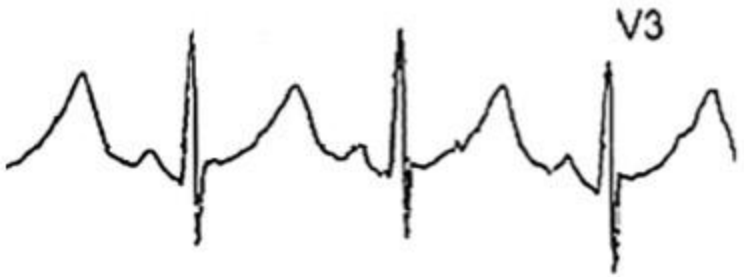


LQT 3
($\uparrow I_{Na}$)

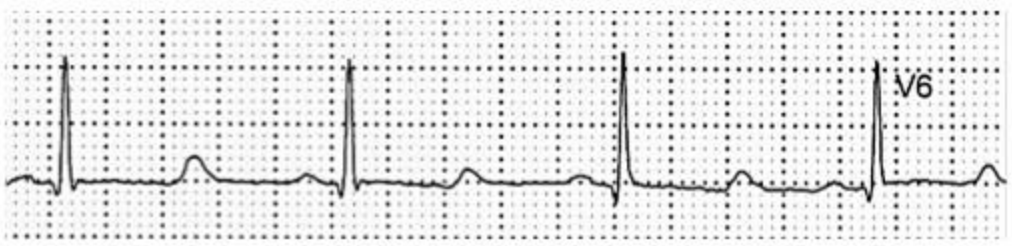


Curr Probl Cardiol, August 2012

ECG Tracings of LQT1 and LQT3 Patients



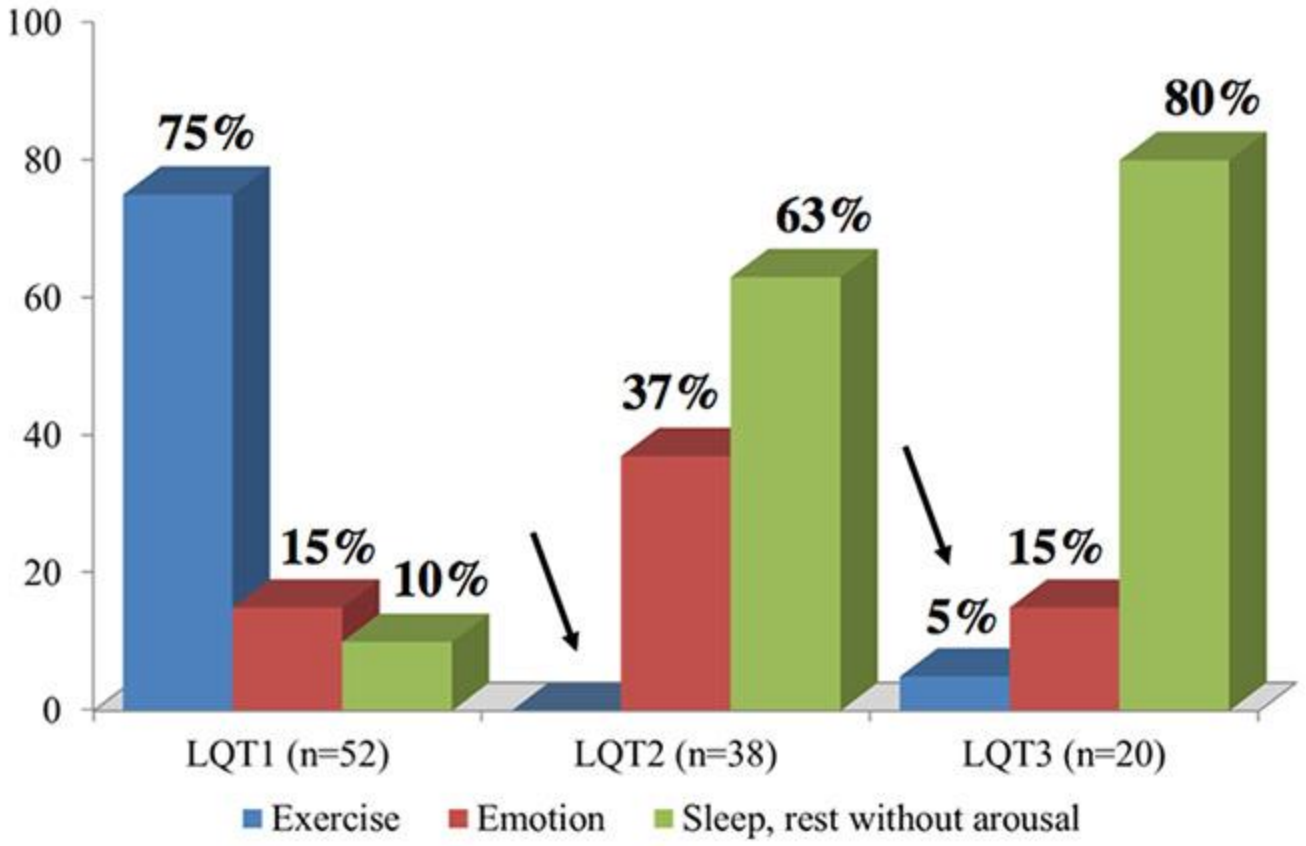
LQT1



LQT3

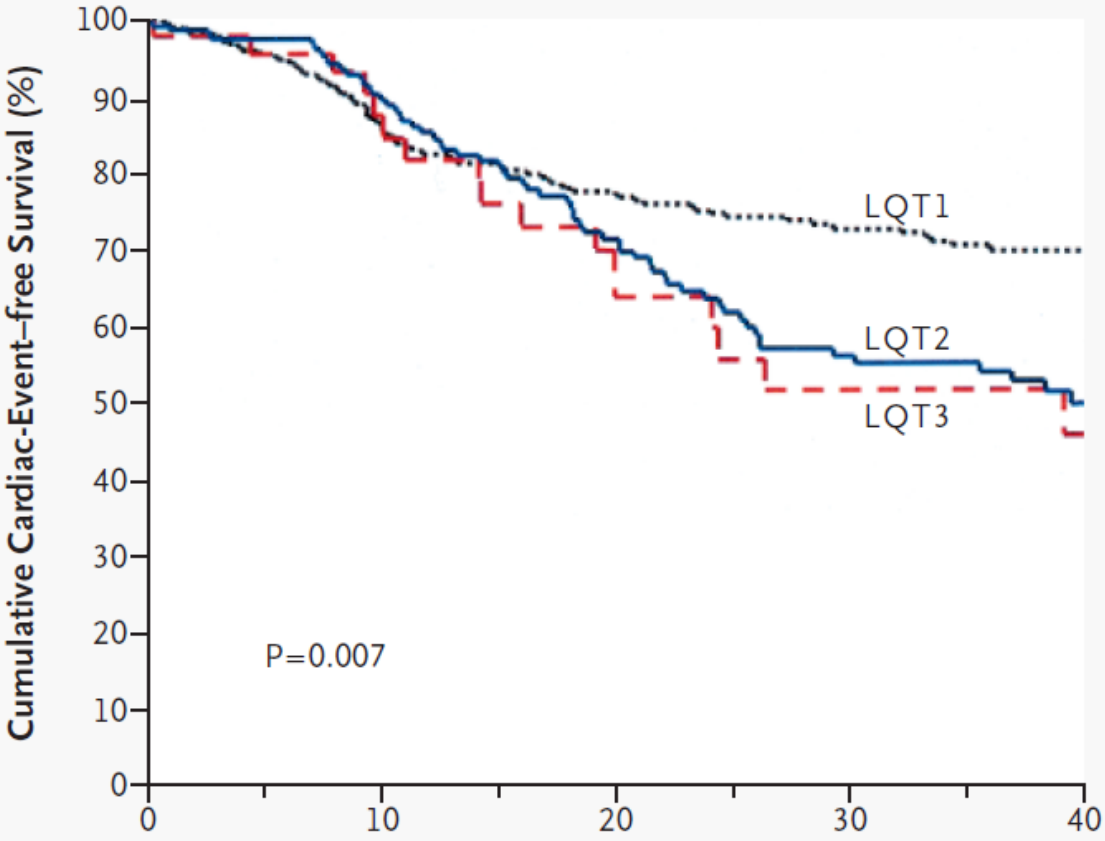
Swiss Med Wkly. 2013;143:w13843

Triggers for Lethal Cardiac Events in LQT1, LQT2 and LQT3 Patients



Circulation. 2001;103:89–95

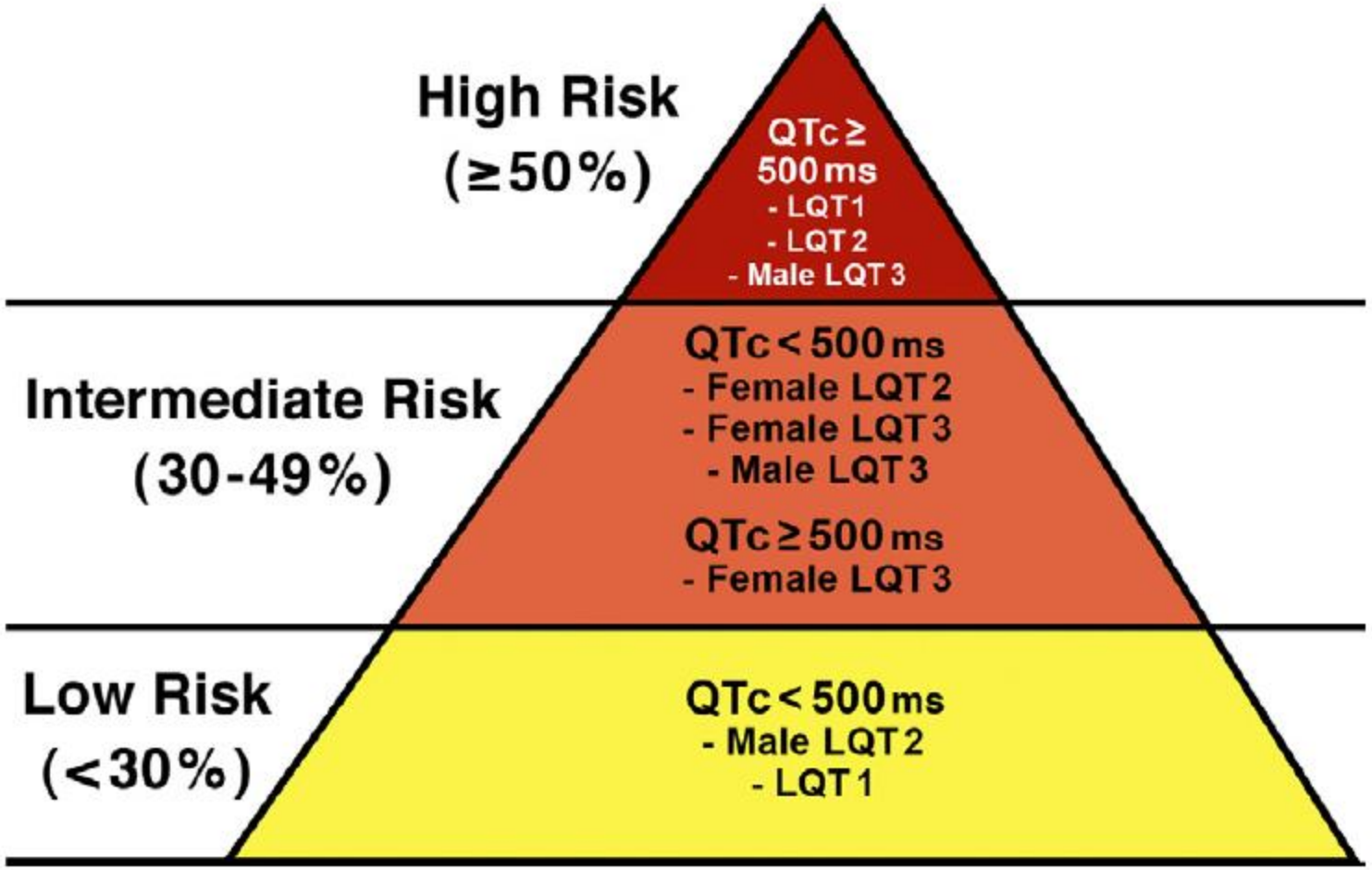
LQTS in the Risk-Stratification Analysis



No. at Risk					
LQT1	355	249	192	146	100
LQT2	176	130	187	57	34
LQT3	49	30	20	9	7

Circulation. 2001;103:89–95

Risk Stratification in the Long-QT Syndrome



N Engl J Med 2003;348:1866.

The key Elements of Management of LQTS Patients

- The mortality rate among untreated symptomatic LQTS patients
  : 60%–65%

Am Heart J. 1975; 89:378–90

- Symptomatic patients without therapy
  : high mortality rate, 21% within 1 year from the first syncope

Am Heart J. 1985;109:399–41

- With proper treatment:
  : mortality ≈1% during a 15-year follow-up

Philadelphia, PA: Elsevier/Saunders; 2009:731–744

The key Elements of Management of LQTS Patients

- β-adrenergic blocking agents
- left cardiac sympathetic denervation (LCSD)
- ICD

β-blockers

- Propranolol: 2 to 3 mg/kg/day

  : blocking effect more on the late noninactivating Na+ current than on the peak Na+ current

- Nadolol: 1 to 1.5 mg/kg/day

  : preferred for teenagers

Biophysical Properties of the Channel

- Propranolol and nadolol
  : the membrane-stabilizing effect by peak Na+ current blockade

- Propranolol
  : late noninactivating Na+ current blocking ability
  ---shortening of the APD and QTc

J Mol Cell Cardiol. 2010; 48:246–53

- Metoprolol has no effect on either the peak or late Na+ current

J Cardiovasc Pharmacol. 2012; 59:249–53

β-blockers

- In a study of 869 LQTS patients of unknown genotype

  * overall mortality on β-blocker therapy: 2%,

Circulation. 2000;101:616–23

- Life-threatening events with β-blockers

  LQT1 patients: 0.5%

  LQT2 patients: 6–7%

  LQT3 patients: 10-15%

JAMA. 2004;292:1341–4
Circulation. 2009;119:215–21
Circulation. 2001;103:89–95

β-blockers

- Beta-blockers are associated with a significant reduction in cardiac events in LQTS patients

- Syncope, aborted cardiac arrest, and LQTS-related death continue to occur while patients are on prescribed beta-blockers, particularly in those who were symptomatic before starting this therapy: 15-30%

Circulation. 2000; 101:616–23

JAMA. 2004; 292:1341–44

Circulation. 1991; 84:1136–44

The key Elements of Management of LQTS Patients

- B-adrenergic blocking agents
- left cardiac sympathetic denervation (LCSD)
- ICD

Left Cardiac Sympathetic Denervation (LCSD)

- Removal of the first four thoracic ganglia (T1–T4)

- Striking antifibrillatory effect:
  a major reduction in noradrenaline release at the ventricular level

  - without post-denervation supersensitivity

  - with no reduction in heart rate

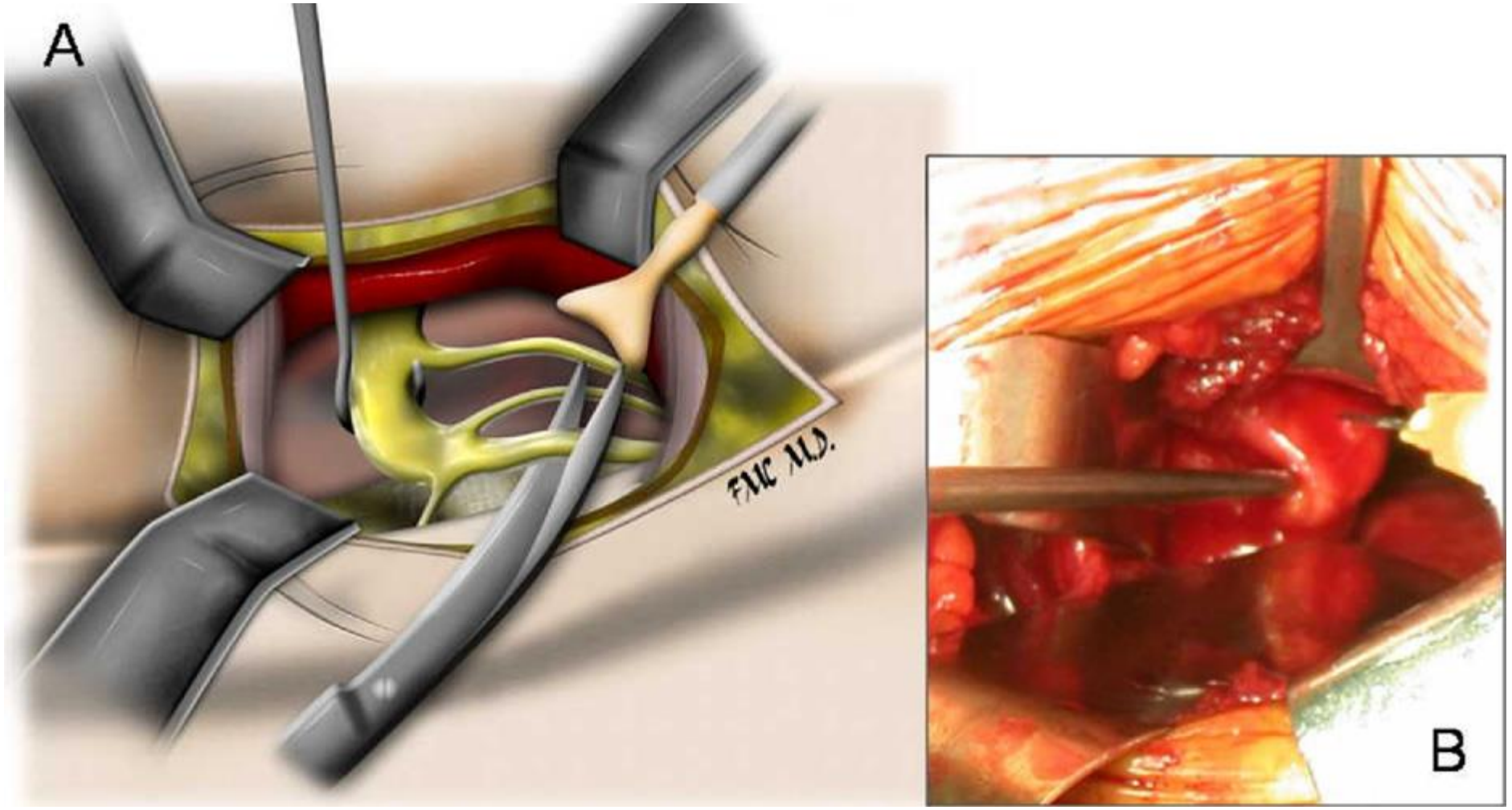
Heart Rhythm. 2009;6:752–9

Am J Cardiol. 1982;49:1185–90

Circ Res. 1979;44:637–45

Left Cardiac Sympathetic Denervation (LCSD)

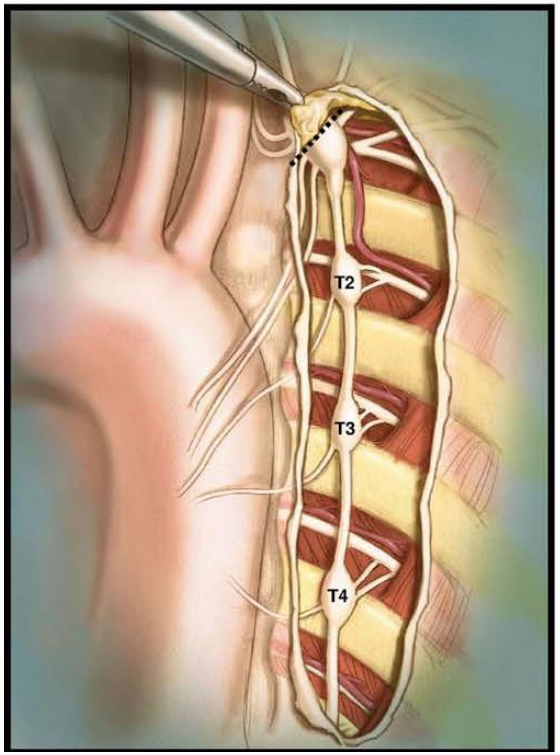
Extrapleural approach

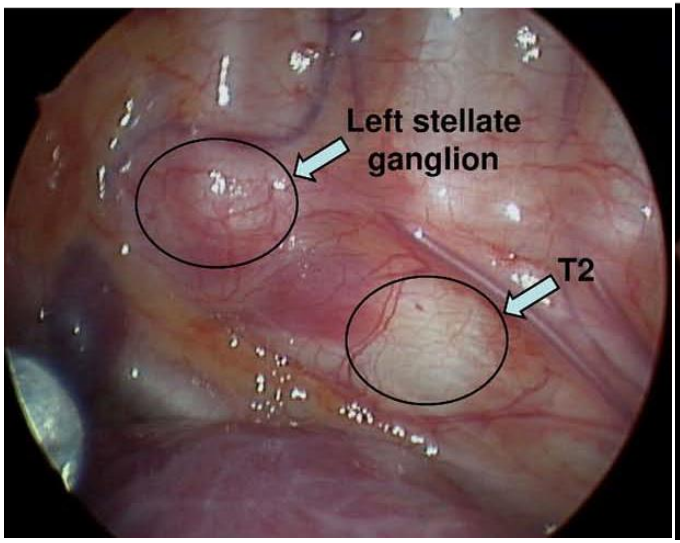


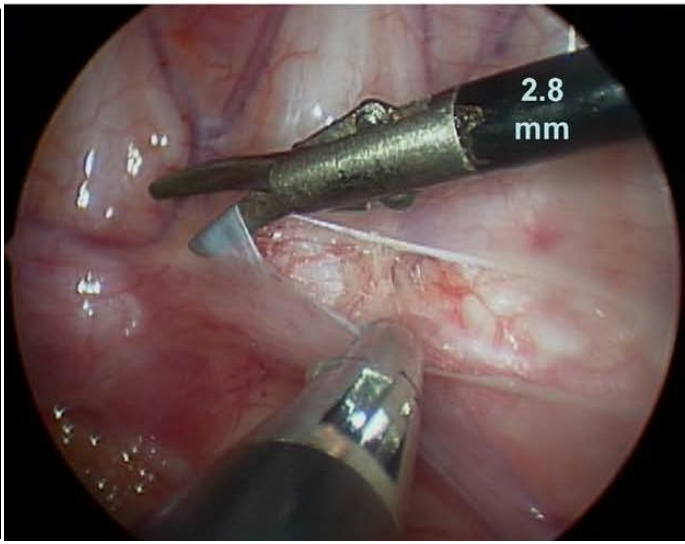
Heart Rhythm. 2010;7:1161–5

Left Cardiac Sympathetic Denervation (LCSD)

Thoracoscopy







Heart Rhythm. 2009;6:752–9

Left Cardiac Sympathetic Denervation (LCSD)

Indications for denervation

(1) patients with appropriate VF terminating ICD shocks

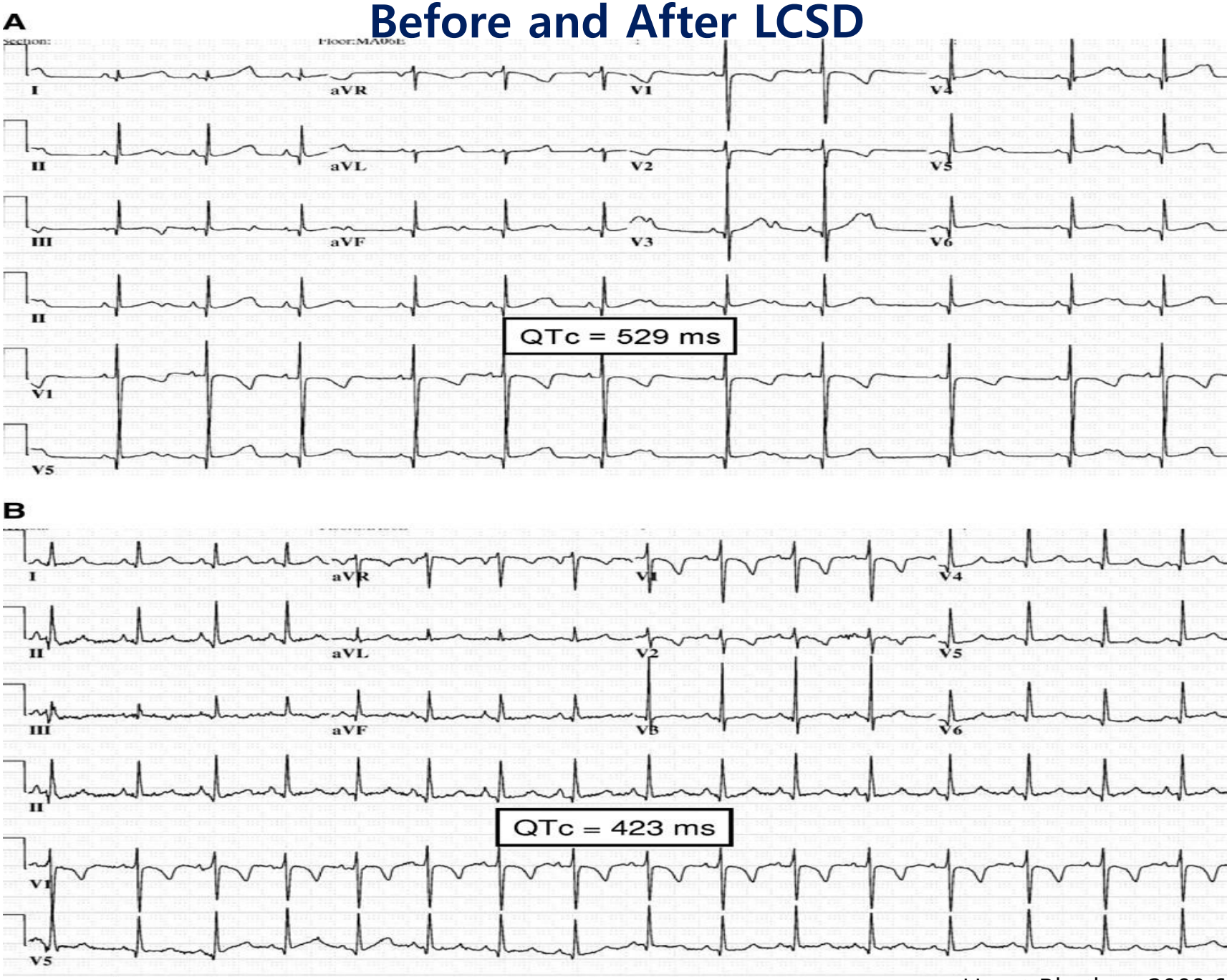
(2) patients with LQTS-triggered breakthrough cardiac events while on adequate drug therapy

(3) patients with failure to tolerate β-blocker therapy because of unacceptable side effects or because of asthma

(4) high-risk, very young patients where primary drug therapy may not be sufficiently protective and where there are hopes of LCSD serving as a "bridge to an ICD"

Swiss Med Wkly. 2013;143:w13843

Before and After LCSD

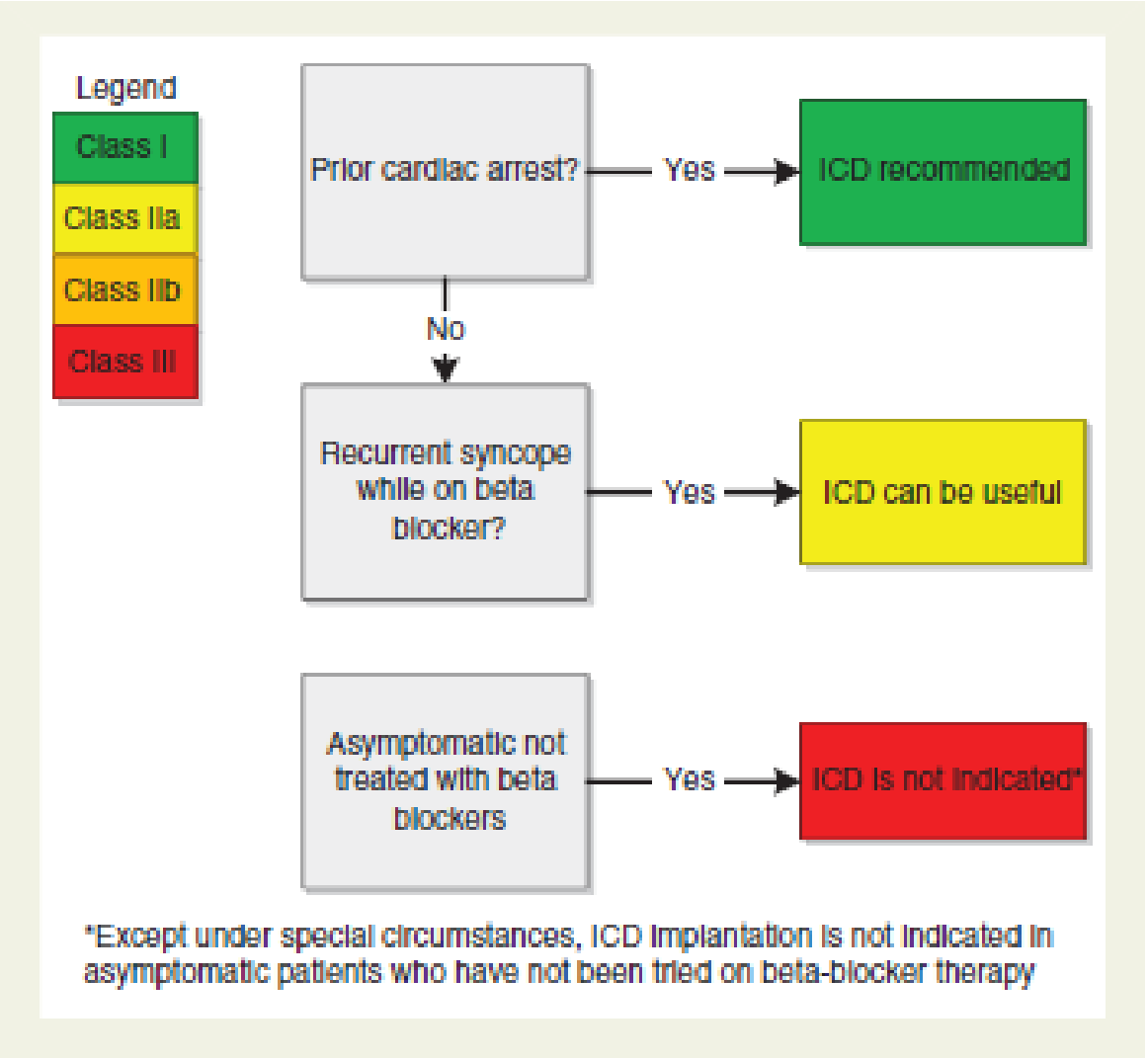


Heart Rhythm. 2009;6:752–9

The key Elements of Management of LQTS Patients

- β-adrenergic blocking agents
- left cardiac sympathetic denervation (LCSD)
- ICD

Consensus Recommendations for ICDs in Patients Diagnosed With Long QT Syndrome



Europace (2013) 15, 1389–1406

Implantation of an ICD

(1) all patients who survived a cardiac arrest while compliant on adequate drug Therapy

(2) most of those who survived a cardiac arrest except those with a reversible/preventable cause, and possibly some of those with previously undiagnosed and therefore untreated LQT1

(3) those with LQTS-triggered syncope despite a full dose of β-blocker, whenever the option of LCSD is either not available or discarded after discussion with the patient

(4) all patients with syncope despite a full dose of β-blocker and LCSD

(5) exceptionally, asymptomatic postpubertal LQT2 women with a QTc ≥550 ms and asymptomatic patients with a QTc >550 ms who also manifest signs of high electrical instability (e.g. T wave alternans) or other evidence of being at high risk despite β-blockade and LCSD (e.g. long sinus pauses followed by abnormal T-wave morphologies)

Circulation. 2010;122:1272–82

LQTS Therapeutic Interventions

Expert Consensus Recommendations on ***LQTS Therapeutic Interventions***

Class I	1. The following lifestyle changes ***are recommended*** in all patients with a diagnosis of LQTS: a. Avoidance of QT-prolonging drugs (www.qtdrugs.org) b. Identification and correction of electrolyte abnormalities that may occur during diarrhea, vomiting, metabolic conditions, or imbalanced diets for weight loss 2. Beta-blockers ***are recommended*** in patients with a diagnosis of LQTS who are: a. Asymptomatic with QTc ≥470 ms *and/or* b. Symptomatic for syncope or documented ventricular tachycardia/ventricular fibrillation (VT/VF).

Continued

Europace (2013) 15, 1389–1406

LQTS Therapeutic Interventions

Europace (2013) 15, 1389–1406

Continued

Expert Consensus Recommendations on ***LQTS Therapeutic Interventions***

	3. Left cardiac sympathetic denervation (LCSD) ***is recommended*** in high-risk patients with a diagnosis of LQTS in whom: a. Implantable cardioverter-defibrillator (ICD) therapy is contraindicated or refused *and/or* b. Beta-blockers are either not effective in preventing syncope/arrhythmias, not tolerated, not accepted or contraindicated.
	4. ICD implantation ***is recommended*** in patients with a diagnosis of LQTS who are survivors of a cardiac arrest.
	5. All LQTS patients who wish to engage in competitive sports ***should be*** referred to a clinical expert for the evaluation of risk.
Class IIa	6. Beta-blockers ***can be useful*** in patients with a diagnosis of LQTS who are asymptomatic with QTc ≤470 ms.
	7. ICD implantation ***can be useful*** in patients with a diagnosis of LQTS who experience recurrent syncopal events while on beta-blocker therapy.
	8. LCSD ***can be useful*** in patients with a diagnosis of LQTS who experience breakthrough events while on therapy with beta-blockers/ICD.
	9. Sodium channel blockers ***can be useful***, as add-on therapy, for LQT3 patients with a QTc 4500 ms who shorten their QTc by 440 ms following an acute oral drug test with one of these compounds.
Class III	10. Except under special circumstances, ICD implantation ***is not indicated*** in asymptomatic LQTS patients who have not been tried on beta-blocker therapy.

Sinus Bradycardia and Long QT Syndrome

TABLE 2. 1993 LQTS Diagnostic Criteria

		Points
ECG findings*		
A.	QT_c†	
	≥480 $msec^{1/2}$	3
	460-470 $msec^{1/2}$	2
	450 $msec^{1/2}$ (in males)	1
B.	Torsade de pointes‡	2
C.	T-Wave alternans	1
D.	Notched T wave in three leads	1
E.	Low heart rate for age§	0.5
Clinical history		
A.	Syncope‡	
	With stress	2
	Without stress	1
B.	Congenital deafness	0.5
Family history‖		
A.	Family members with definite LQTS#	1
B.	Unexplained sudden cardiac death below age 30 among immediate family members	0.5

P J Schwartz Circulation. 1993;88:782-784

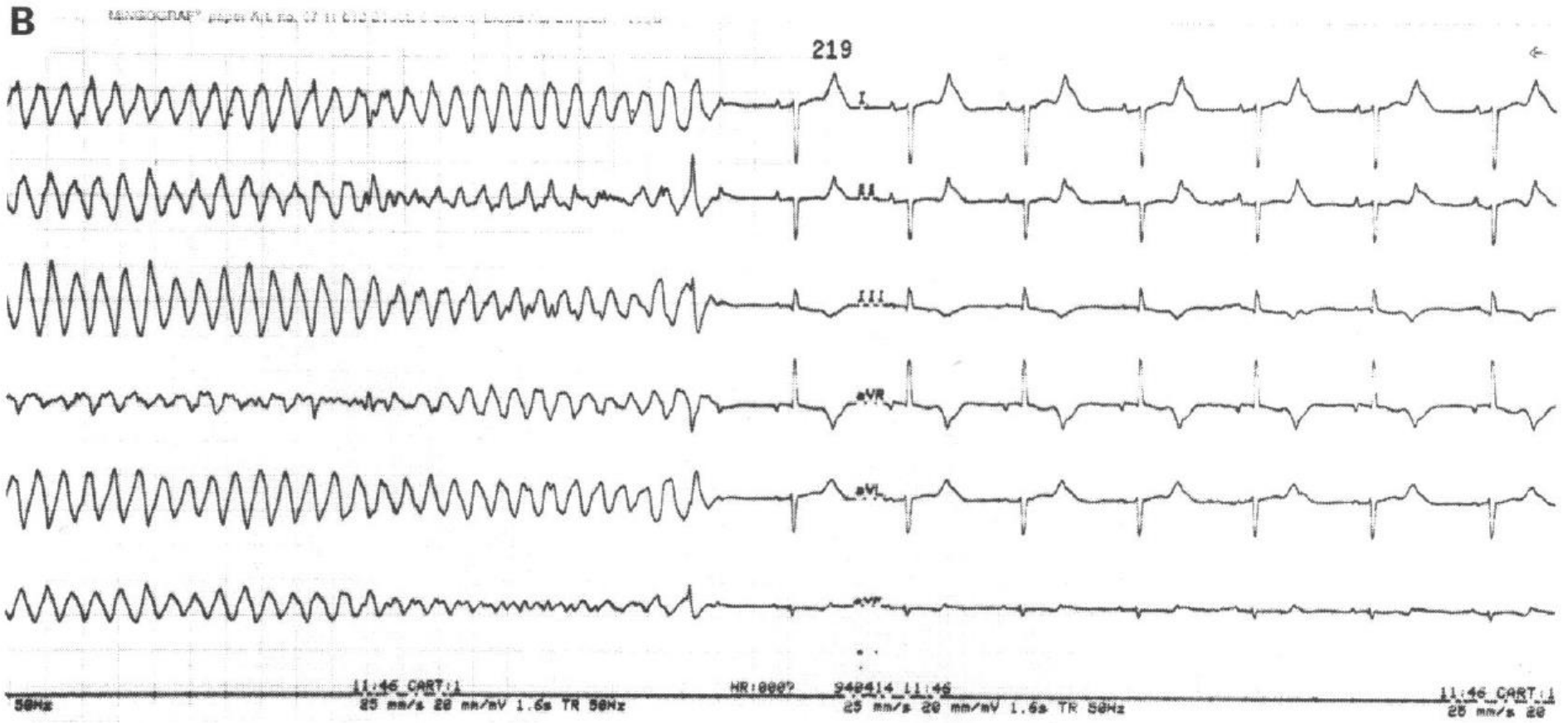
Table 1 1993–2012 long QT syndrome diagnostic criteria

			Points
Electrocardiographic findings[a]			
A	QTc[b]	≥480 ms	3
		460–479 ms	2
		450–459 (male) ms	1
B	QTc[b] 4th minute of recovery from exercise stress test ≥480 ms		1
C	Torsade de pointes[c]		2
D	T-wave alternans		1
E	Notched T-wave in three leads		1
F	Low heart rate for age[d]		0.5
Clinical history			
A	Syncope[c]	With stress	2
		Without stress	1
B	Congenital deafness		0.5
Family history			
A	Family members with definite LQTS[e]		1
B	Unexplained sudden cardiac death below age 30 among immediate family members[e]		0.5

European Heart Journal (2013) 34, 3109–3116

Sinus Bradycardia and Long QT Syndrome

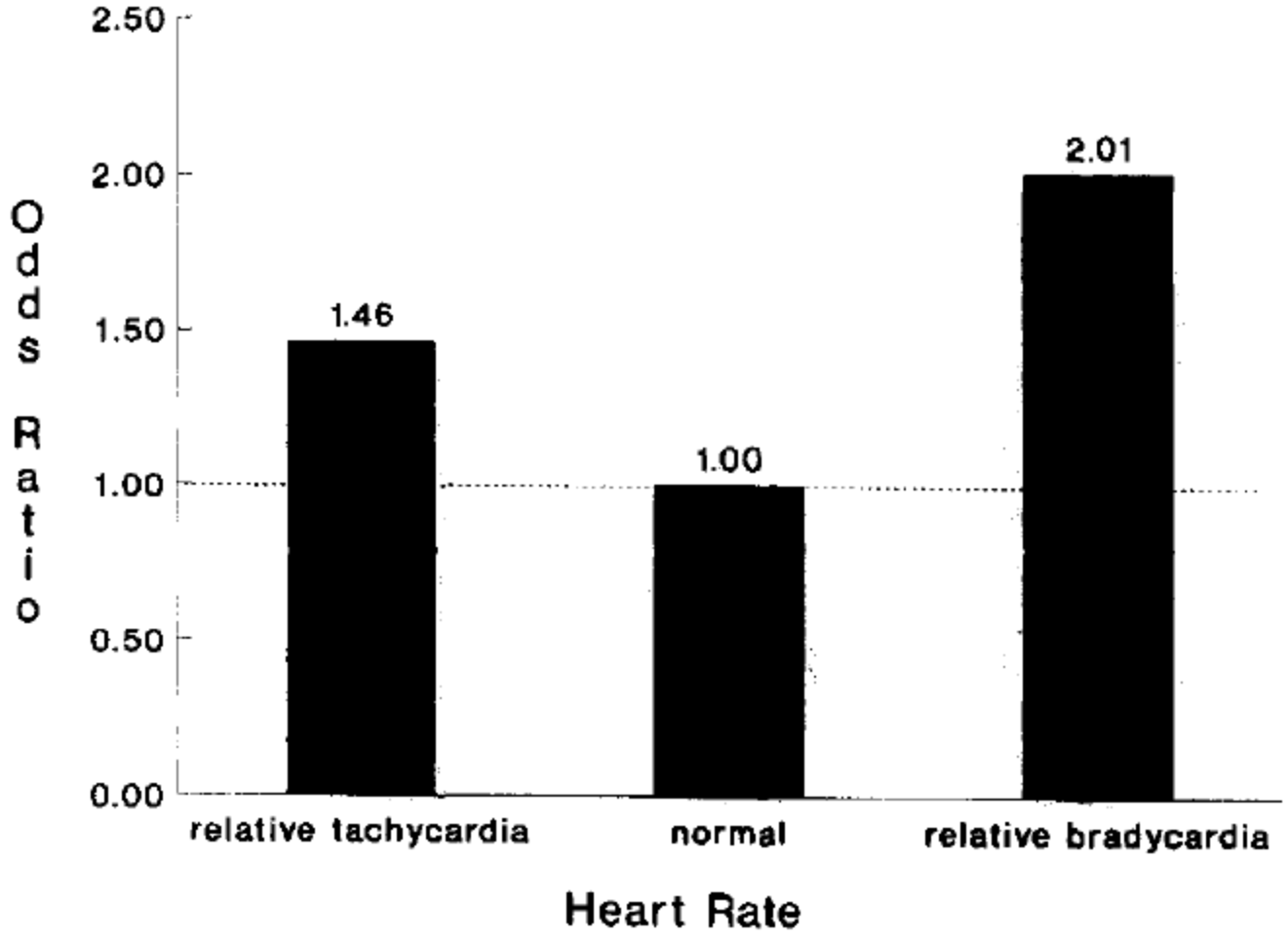
*** Sinus bradycardia in normal fetus may be a symptom of long QT syndrome**



Heart. 1997; 77:198–204

Sinus Bradycardia and Long QT Syndrome

*** Sinus bradycardia is a risk factor for cardiac events in family members of LQTS patients**



J Am Coll Cardiol. 1995; 26:1685–1691

LQTS Genes

Gene	Syndrome	Frequency	Locus	Protein (Functional Effect)
KCNQ1 (LQT1)	RWS, JLNS	40–55	11p15.5	Kv7.1 (↓)
KCNH2 (LQT2)	RWS	30–45	7q35–36	Kv11.1 (↓)
SCN5A (LQT3)	RWS	5–10	3p21–p24	NaV1.5 (↑)
ANKB (LQT4)	RWS	<1%	4q25–q27	Ankyrin B (↓)
KCNE1 (LQT5)	RWS, JLNS	<1%	21q22.1	MinK (↓)
KCNE2 (LQT6)	RWS	<1%	21q22.1	MiRP1 (↓)
KCNJ2 (LQT7)	AS	<1%	17q23	Kir2.1 (↓)
CACNA1C (LQT8)	TS	<1%	12p13.3	L-type calcium channel (↑)
CAV3 (LQT9)	RWS	<1%	3p25	Caveolin 3 (↓)
SCN4B (LQT10)	RWS	<1%	11q23.3	Sodium channel-β4 (↓)
AKAP9 (LQT11)	RWS	<1%	7q21–q22	Yotiao (↓)
SNTA1 (LQT12)	RWS	<1%	20q11.2	Syntrophin α1 (↓)
KCNJ5 (LQT13)	RWS	<1%	11q24	Kir3.4 (↓)

Circ Arrhythm Electrophysiol. 2012;5:868-877

Sinus Bradycardia and Long QT Syndrome

• LQT1 (KVLQT1 gene): diminished chronotropic response and exaggerated prolongation of QT interval after exercise

• LQT2 (HERG Gene): marked QT interval shortening and normal heart rate response to exercise.

J Am Coll Cardiol 1999;34: 823–9

• LQT3 (SCN5A): association with sinus node dysfunction including SSS

Progress in Biophysics and Molecular Biology 98 (2008) 171–178

• Sinus pauses: warning signal especially in patients with S*CN5A mutations*

Heart Rhythm. 2009;6:113–120

• LQTS6 (M54T MiRP1): sinus bradycardia through effects on both hERG and HCN currents

J Cardiovasc Electrophysiol. 2013 September ; 24(9): 1021–1027

Risk Factors for Torsade de Pointes in Hospitalized Patients

- Clinically recognizable risk factors[61–65]
  - QTc >500 ms[71–74]
    - LQT2-type repolarization: notching, long T_{peak}–T_{end}[11,12]
  - Use of QT-prolonging drugs[75–77]
    - Concurrent use of more than 1 QT-prolonging drug[78–80]
    - Rapid infusion by intravenous route[59]
  - Heart disease[64,73,75,76]
    - Congestive heart failure[39]
    - Myocardial infarction[39,73]
  - Advanced age[75,77,86]
  - Female sex[64,72,73,75–77,79,81–85]
  - Hypokalemia[46,74,87–90]
  - Hypomagnesemia[89,91–94]
  - Hypocalcemia[95,96]
  - Treatment with diuretics[72,74,97]
  - Impaired hepatic drug metabolism (hepatic dysfunction or drug-drug interactions)[76,79]
  - Bradycardia[65,87]
    - Sinus bradycardia, heart block, incomplete heart block with pauses[98,99]
    - Premature complexes leading to short-long-short cycles[65,72]
  - Multiple clinically recognizable risk factors[64,65,76,79,84]
- Clinically silent risk factors
  - Occult (latent) congenital LQTS[23,64]
  - Genetic polymorphisms (reduced repolarization reserve)[26,27,31,66–69]

Circulation. 2010; 121:1047–1060

Sinus Bradycardia and Long QT Syndrome

- Bradycardia remains an important risk factor for sudden cardiac events in patients with LQTS

J Cardiovasc Electrophysiol. 2013 September ; 24(9): 1021–1027

Case

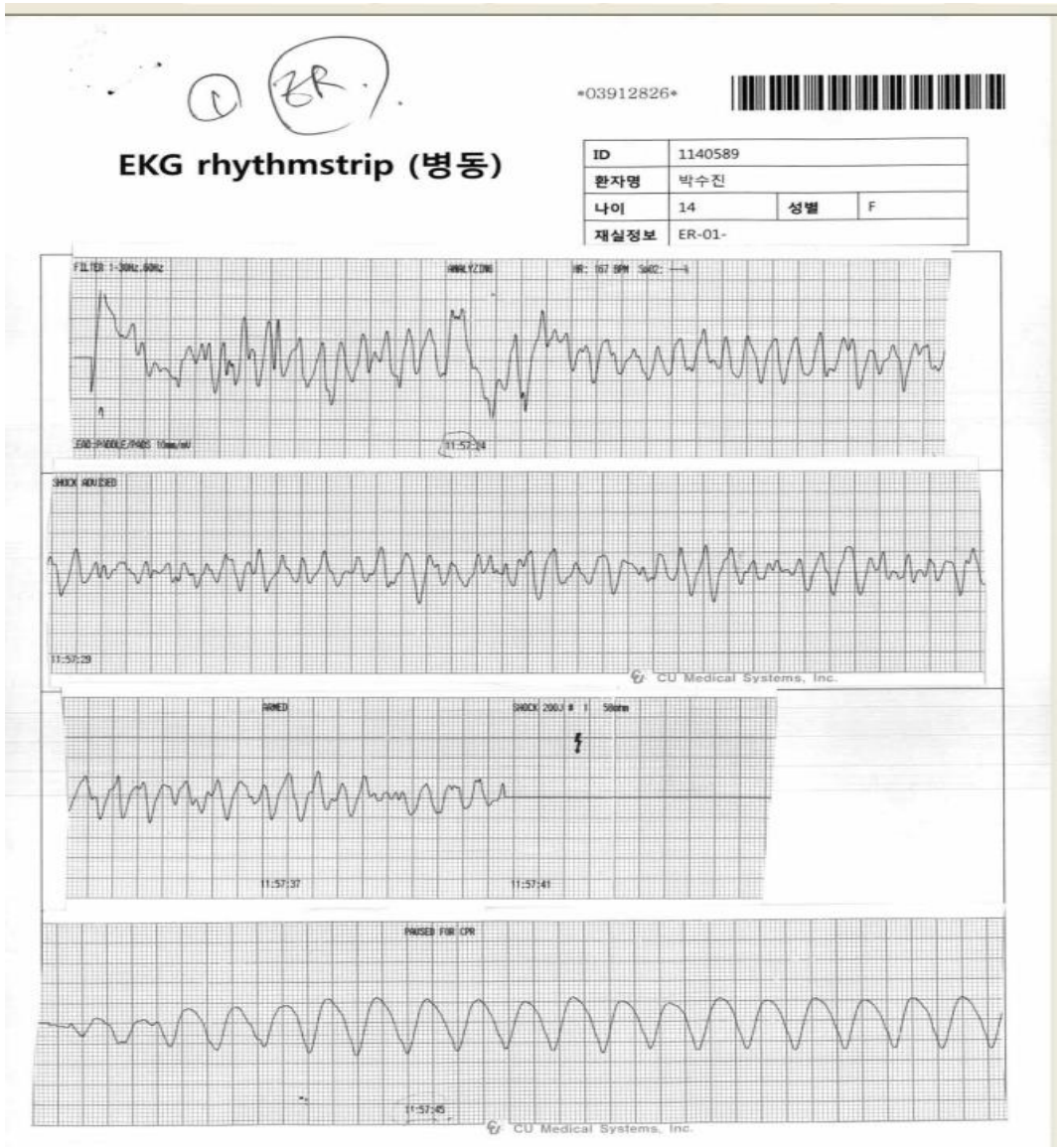
- F/ 14

- C/C: Aborted SCD

- PI: 특이병력 없던 환자로 금일 오전 11시 47분 경 학교에서 뛰다가 갑자기 쓰러졌으며 1~2분가량 seizure like movement 있었다고 함, 쓰러지고 4~5분 뒤 119 도착 시 arrest 상황으로 CPR 시행하였고 (중간 심실세동 발생하여 200J 제세동) 5분 뒤 ROSC 된 상태로 local 병원 들렀다가 전원옴
이전에도 운동 중 실신이 수 차례 있었다고 함
심정지 목격 일시 2013-08-27 11:47

- FHx: 1) 환아 부: 2010. 11. expire d/t suicide
  2) 환아 모: 2005. expire d/t cancer
  3) 환아 첫째언니(35세): 초등학교 교사, 기혼, 남편과 5세된 딸이 있음. 언니가 환아와 환아 오빠의 보호자 역할을 하고 있음. 주된 의사결정권자임
  4) 고모: 심장병 약 복용 중, 심장에 기구 삽입함 (stent? Valve placement?)
  5) 큰아버지: 심장마비로 사망

Electrocardiogram I



Electrocardiogram II

*** PID / NAME MISMATCH ***
14 yr
Female

Room:
Loc:26

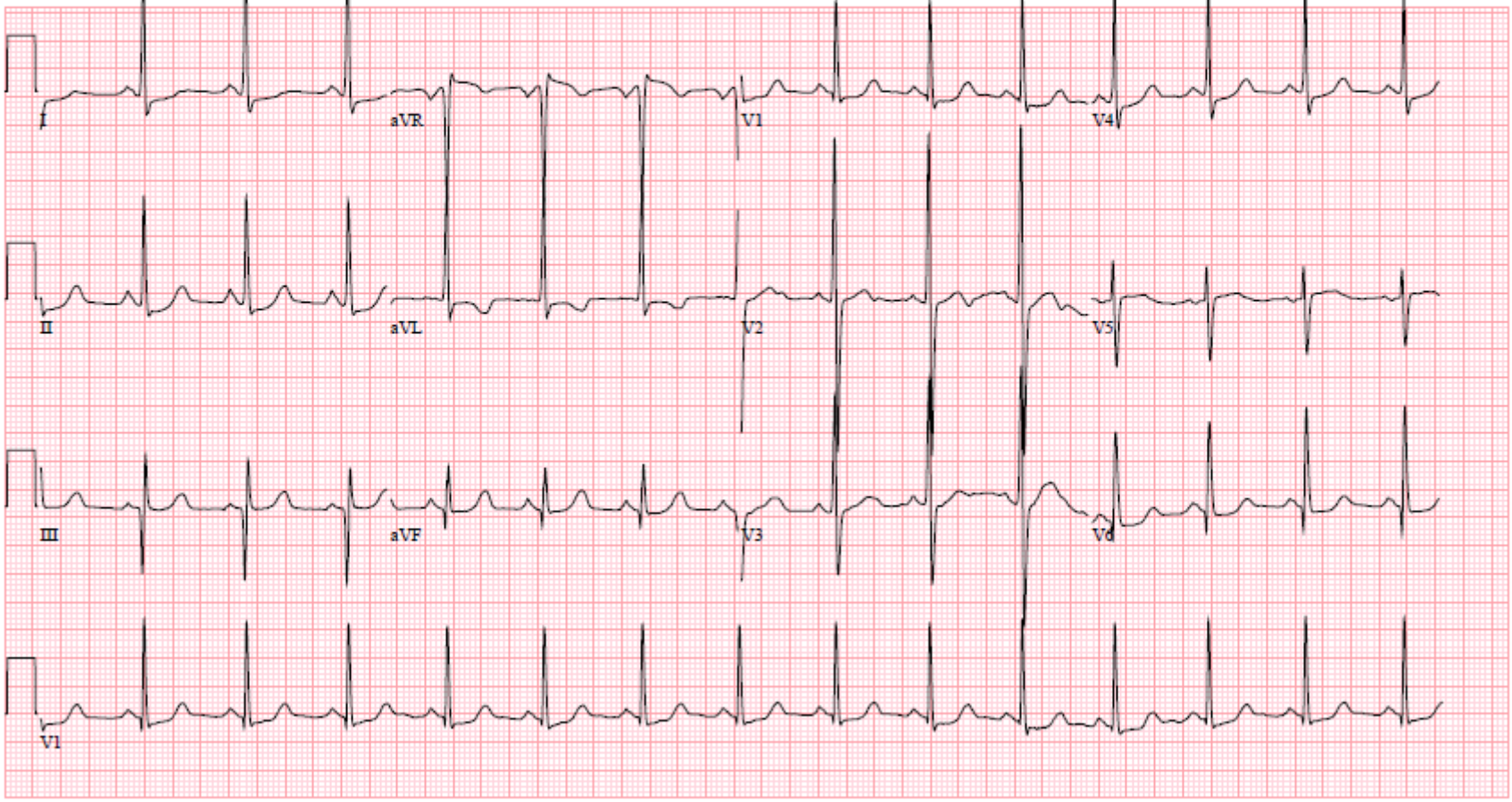
Vent. rate	87	BPM
PR interval	140	ms
QRS duration	86	ms
QT/QTc	396/476	ms
P-R-T axes	52 21	84

** ** ** ** * Pediatric ECG Analysis * ** ** ** **
Normal sinus rhythm
Biatrial enlargement
Right ventricular hypertrophy
Possible Biventricular hypertrophy
Nonspecific ST and T wave abnormality
Borderline Prolonged QT , may be secondary to QRS abnormality

Technician:
Test ind:

Referred by:

Unconfirmed



25mm/s 10mm/mV 40Hz 8.0.1 12SL 237 CID: 1

EID: EDT: ORDER:

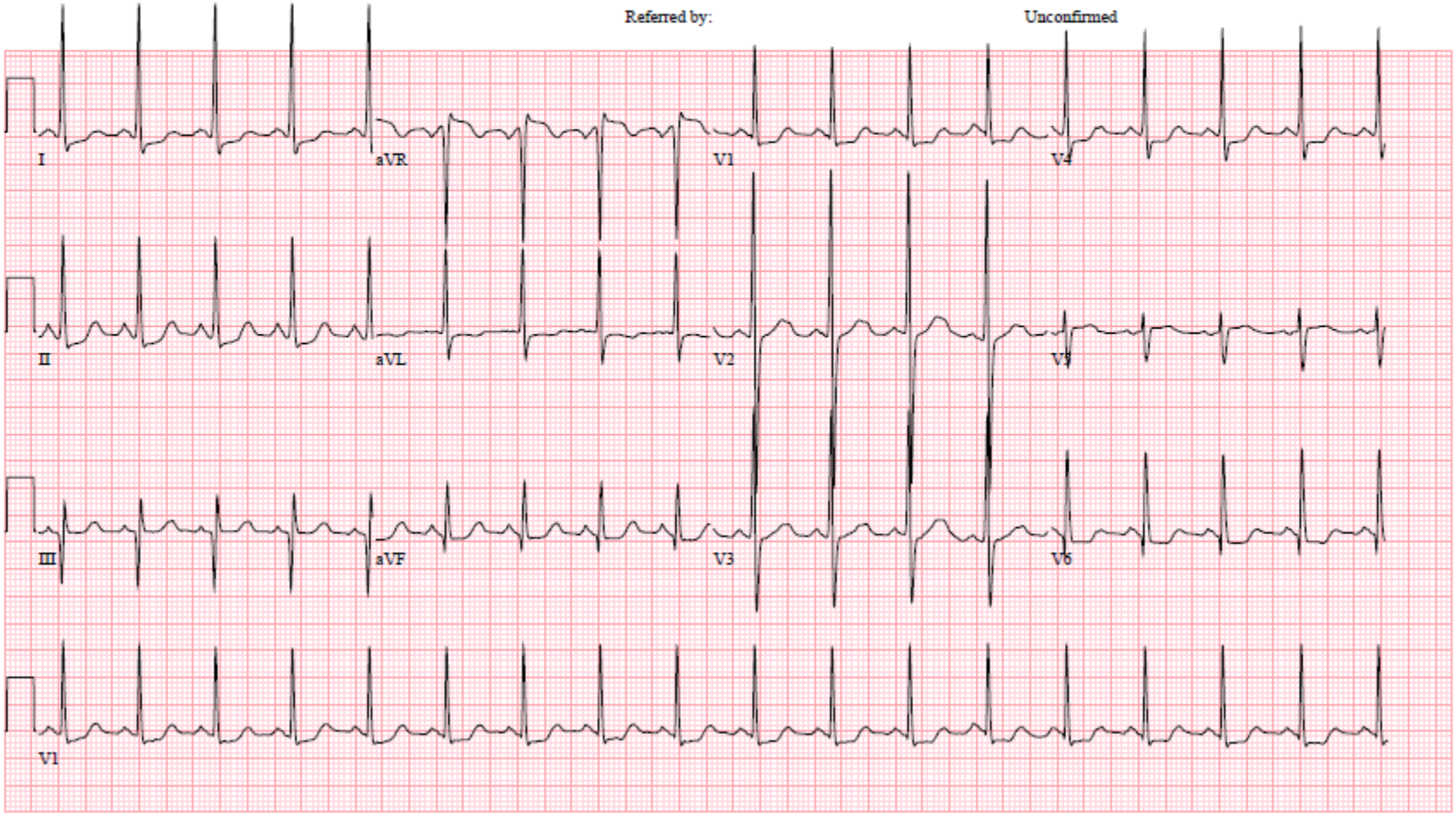
Electrocardiogram III

14 yr	Vent. rate	105	BPM	** ** ** ** * Pediatric ECG Analysis * ** ** ** **
Female	PR interval	140	ms	Normal sinus rhythm
	QRS duration	82	ms	Biatrial enlargement
Room:	QT/QTc	362/478	ms	Right ventricular hypertrophy
Loc:26	P-R-T axes	50 27	84	ST depression in Inferior leads

Technician:
Test ind:

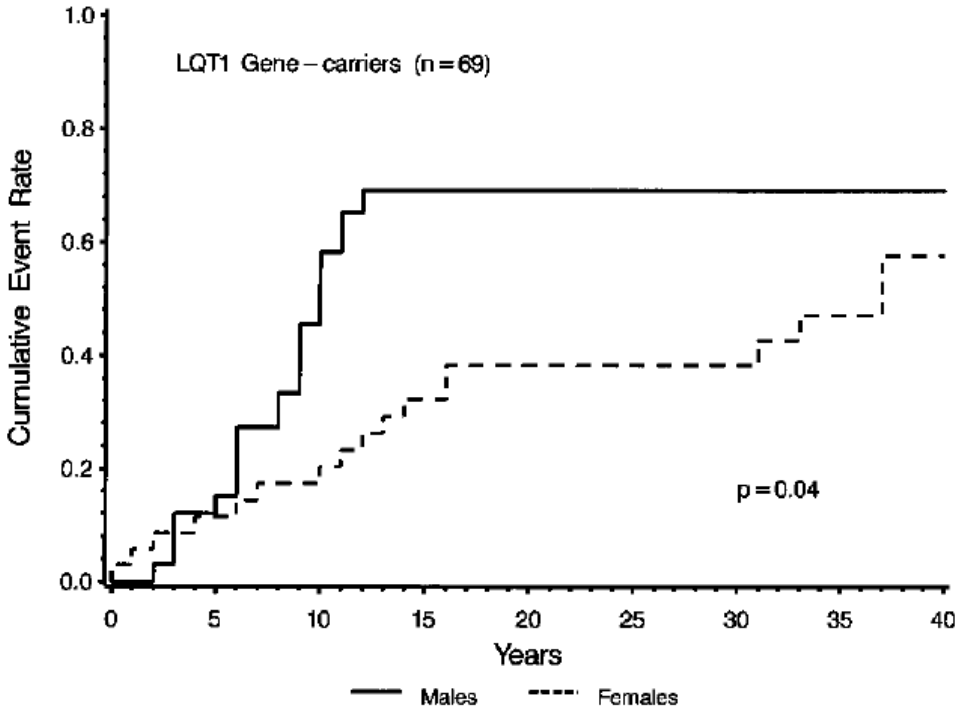
Referred by:

Unconfirmed



Management for a Girl With LQTS and Sinus Bradycardia

The Clinical Course in Individuals With LQTS

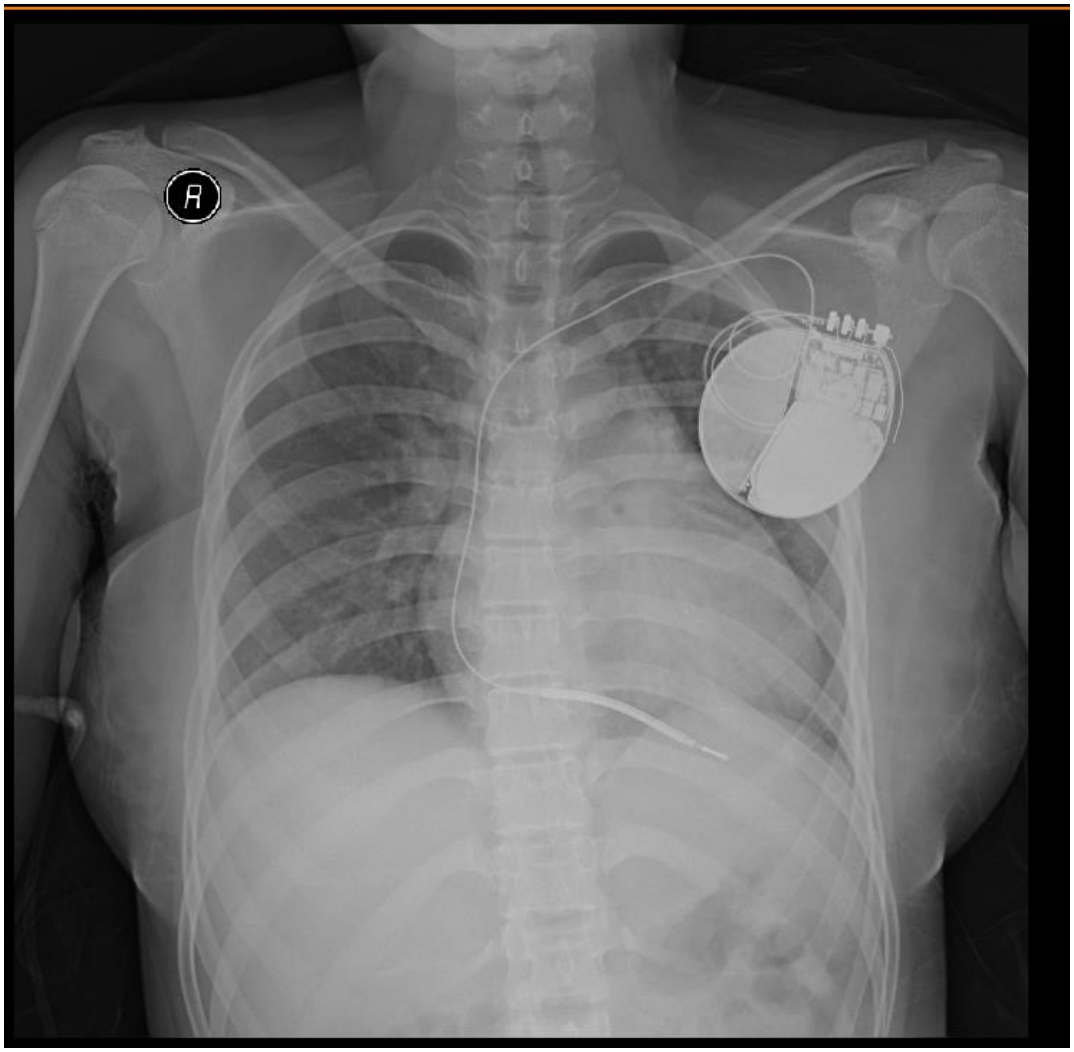


- Female gender is associated with higher risk (87%) of cardiac event after age 15, in both probands and affected family members

- Male gender is independently associated with increased risk (85%) of fatal and nonfatal cardiac events before age 15

Circulation 1998;97:2237-44

ICD Implantation



Take Home Messages

LQTS 환자에서

- **빈번한 실신이나 돌연사 환자의 심전도를 볼 때 QR 간격을 주의 깊게 관찰하고 환자의 가족력도 반드시 물어본다.**
- **약물 치료는 우선적으로 베타 차단제를 투여해야 하고 이때 propranolol을 선택한다**
- **돌연사를 경험한 경우 ICD를 우선적으로 고려한다**
- **서맥은 LQTS의 진단기준이자 나쁜 예후를 암시하는 소견이다**