LQTS & Brugada Syndrome

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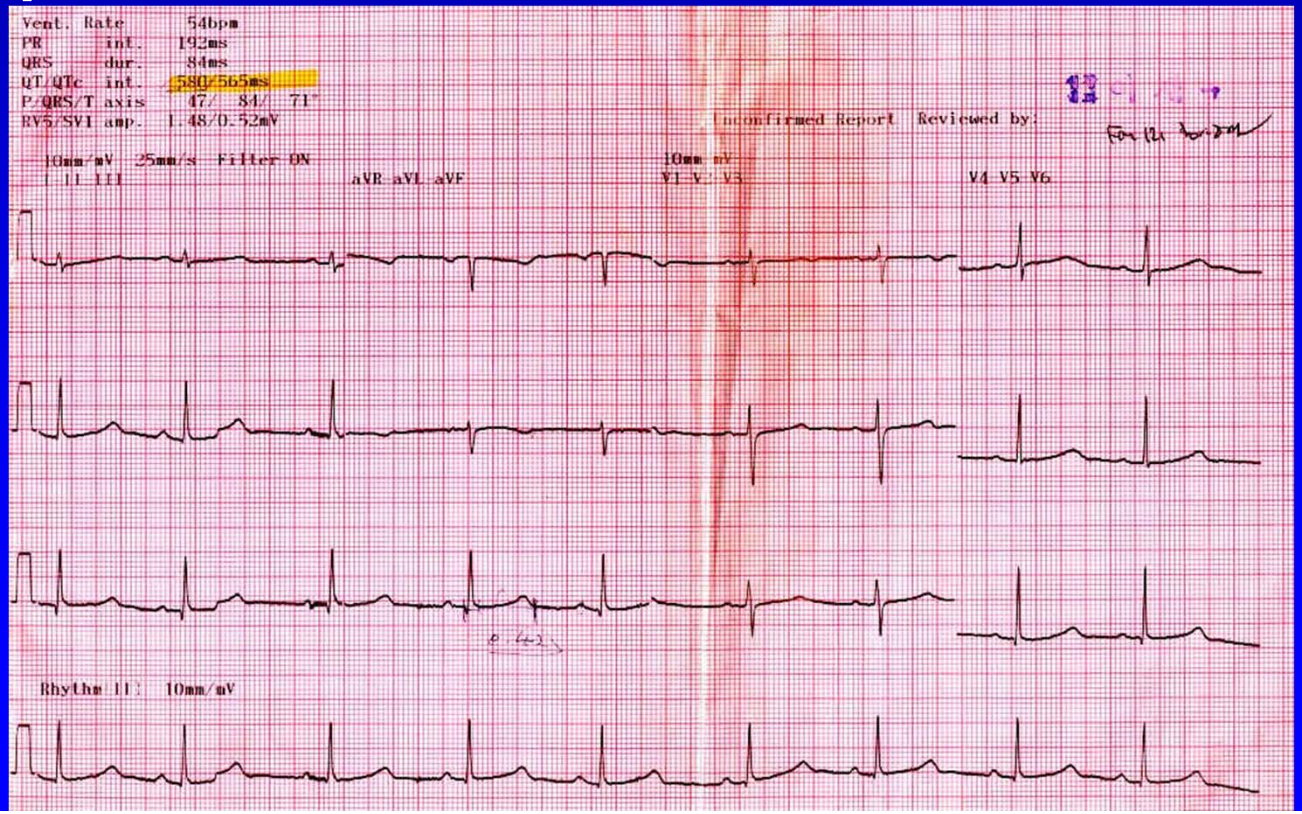
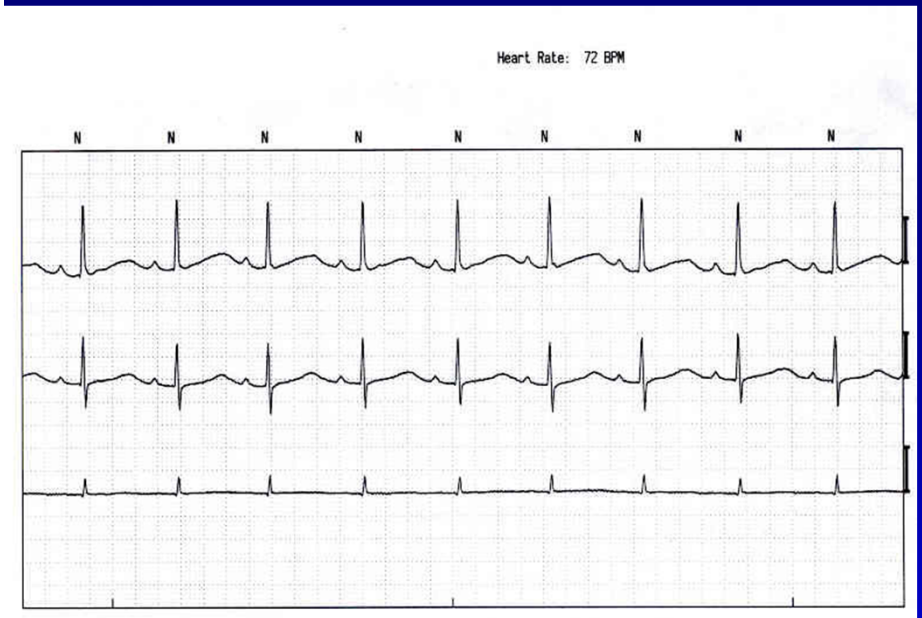
Case

- 21 yr old woman, transferred to cardiology department
- Patient has frequent syncopal attack since childhood, it was managed by dilantin
- Patient complained intermittent chest discomfort for 1 month
- Family history negative for syncope, palpitation, premature deafness. But elder sister has mental retardation
- ECG of her mother and brother shows unremarkable findings.
- Normal K^+ & Mg level
- ECG; long QT intervals.
- What is next step?

Diagnostic Procedure to LQTS

- Treadmill test; increased QT interval during and after exercise
- Holter monitoring; T wave changes
- Head up tilt test; T wave alternans, TdPs after isoproterenol infusion

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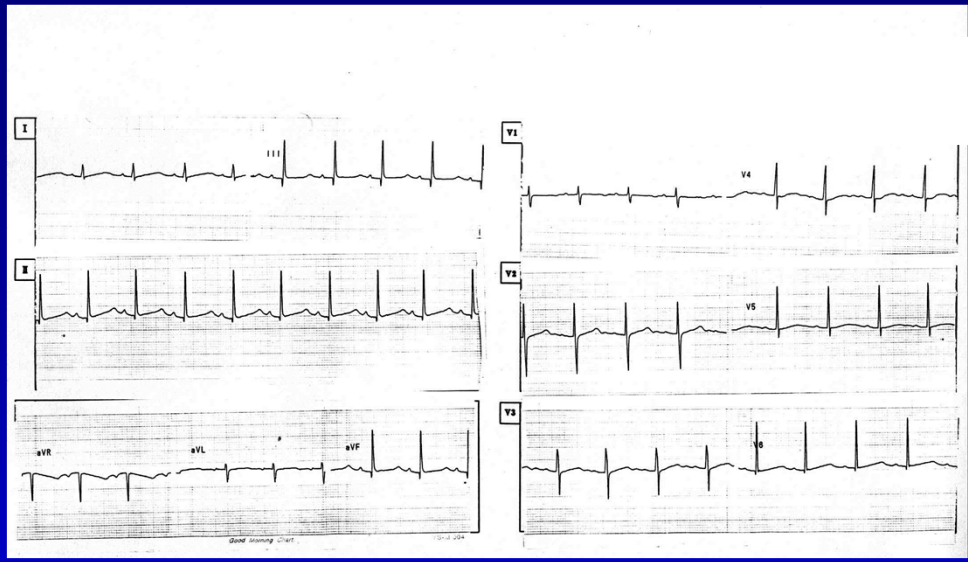
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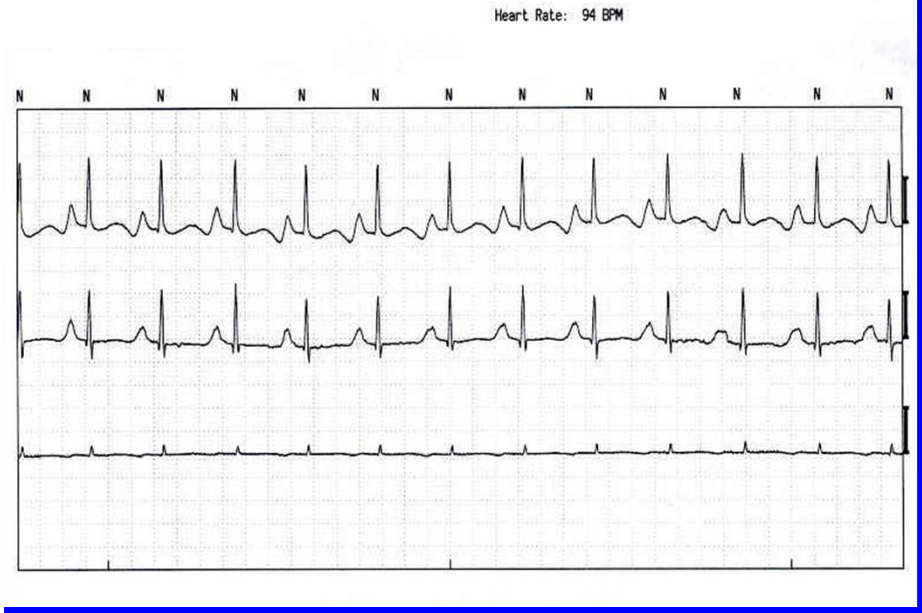
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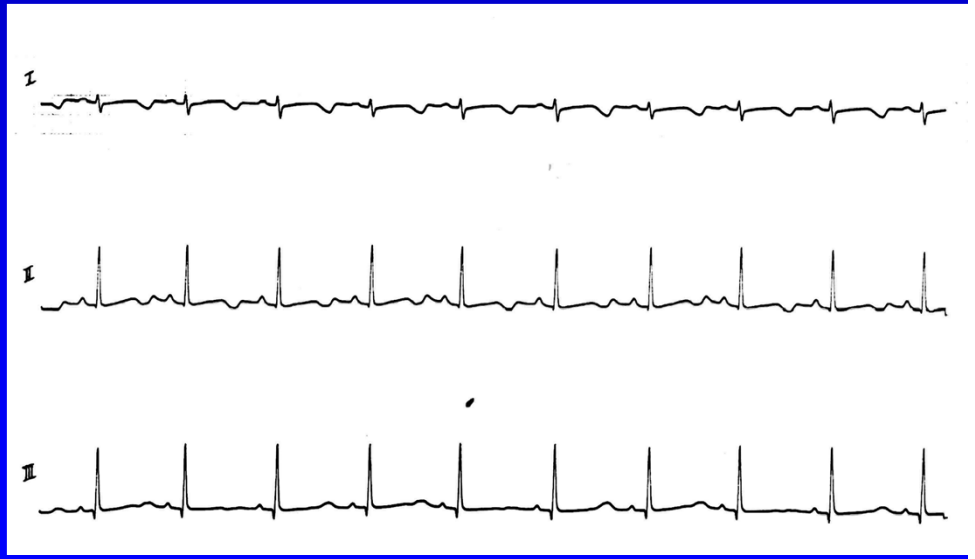
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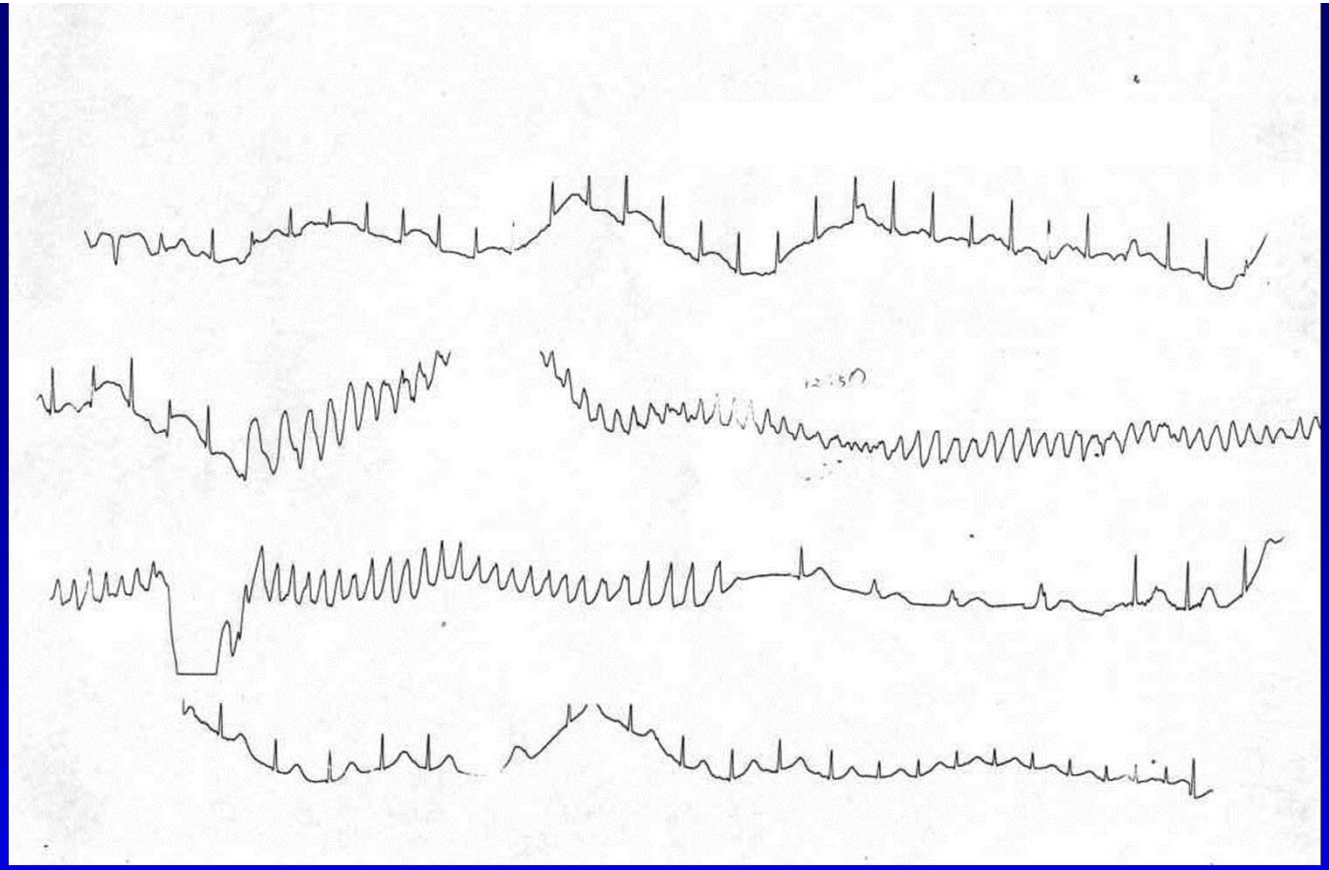
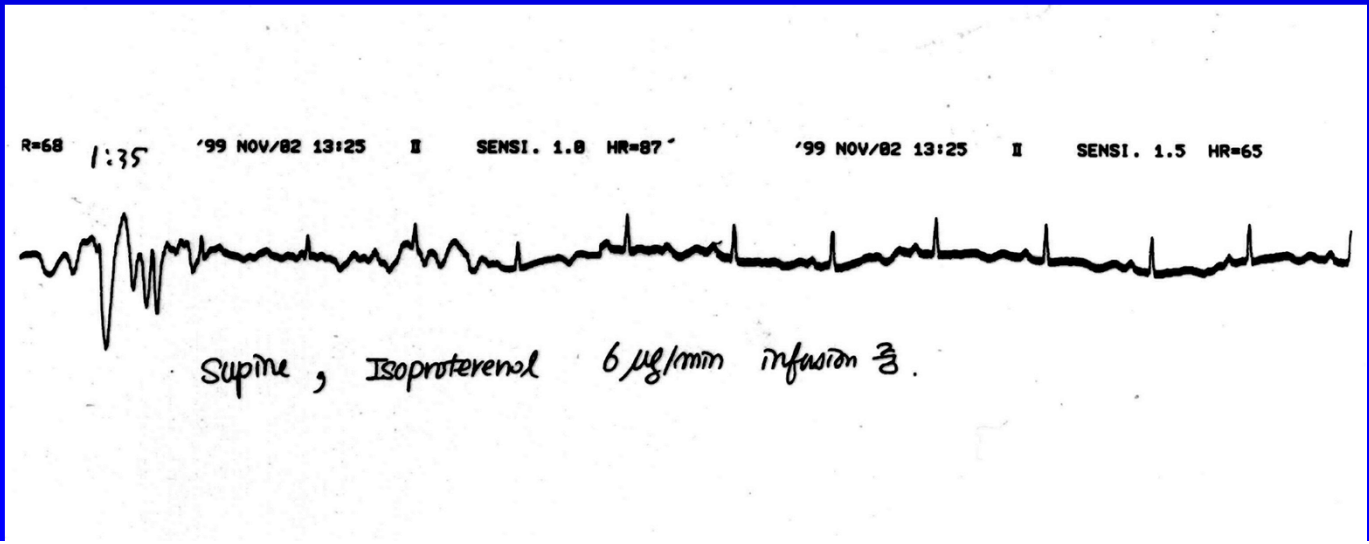




Supine, Isoproterenol 6 μg/min infusion 중.

Clinical Diagnosis of LQTS

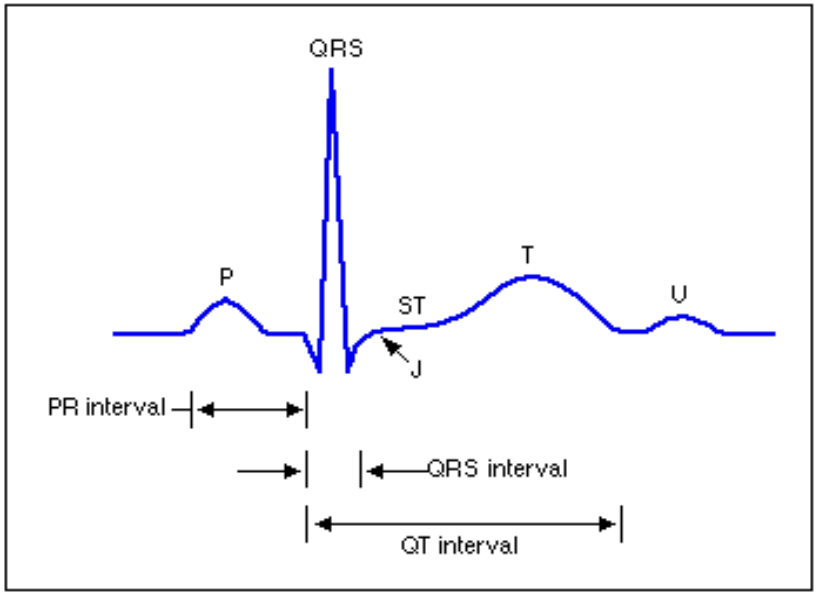
- Affected persons may present with sudden death, syncope, or QT prolongation on an incidental ECG.
- When QTc prolongation is identified following a syncopal event, the diagnosis of LQTS is certain

ECG Findings in LQTS

- **QT interval should be measured from the onset of Q wave to the end of T wave in an ECG leads, usually lead II.**
- **QTc=QT/√RR**
- **QTc prolonged**

  Men > 0.45 s

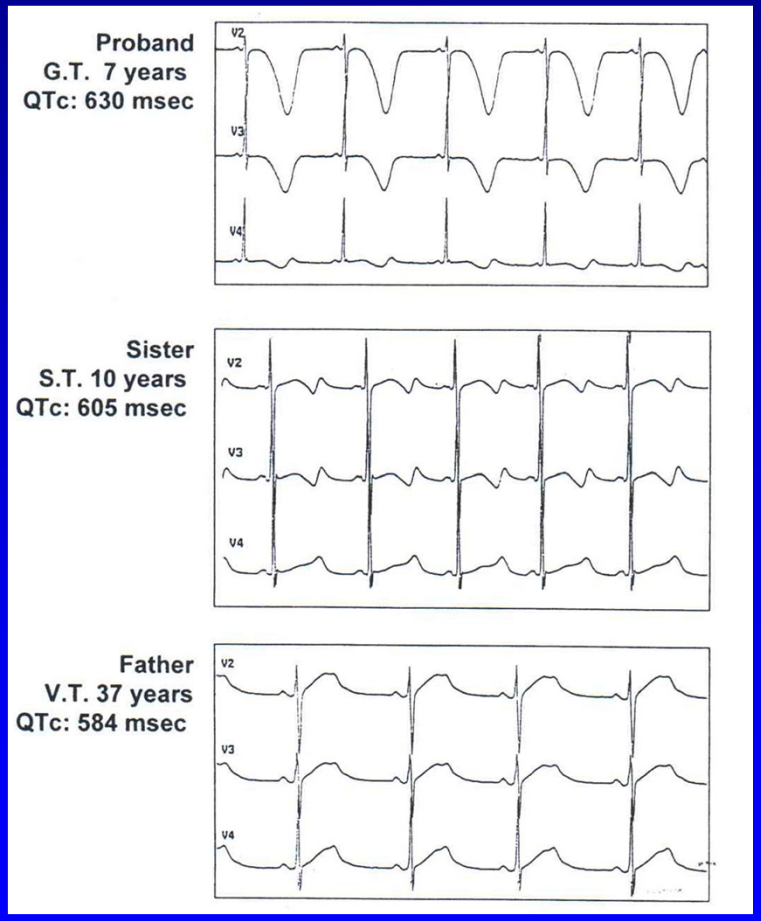
  Women > 0.46 s



ECG abnormalities

- Notched or bifid T wave in the V_2 - V_5
- Repolarization abnormalities: more frequent in those patients with cardiac events.
- Notched T wave in recovery phase of exercise

T wave morphology



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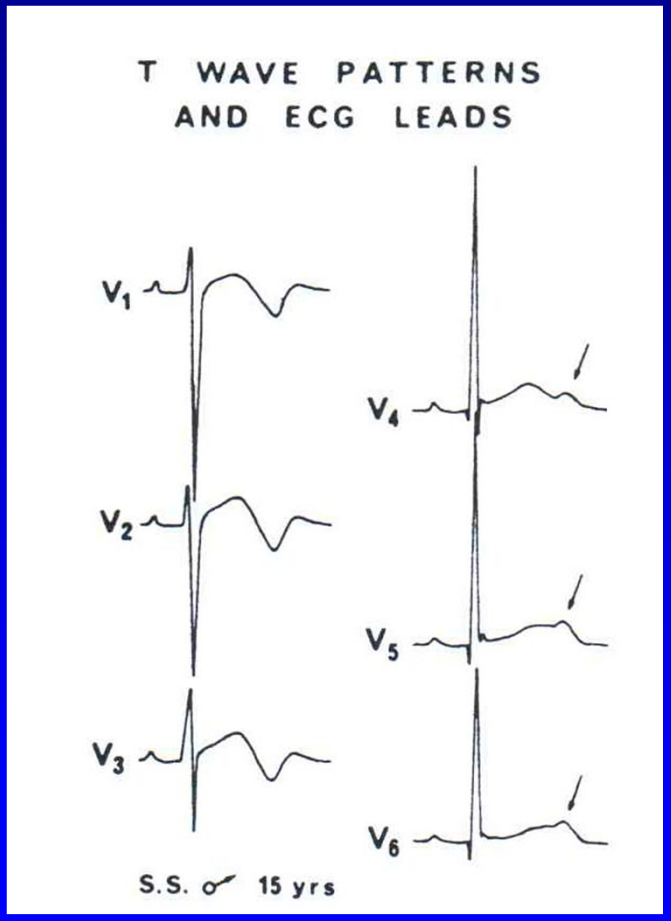

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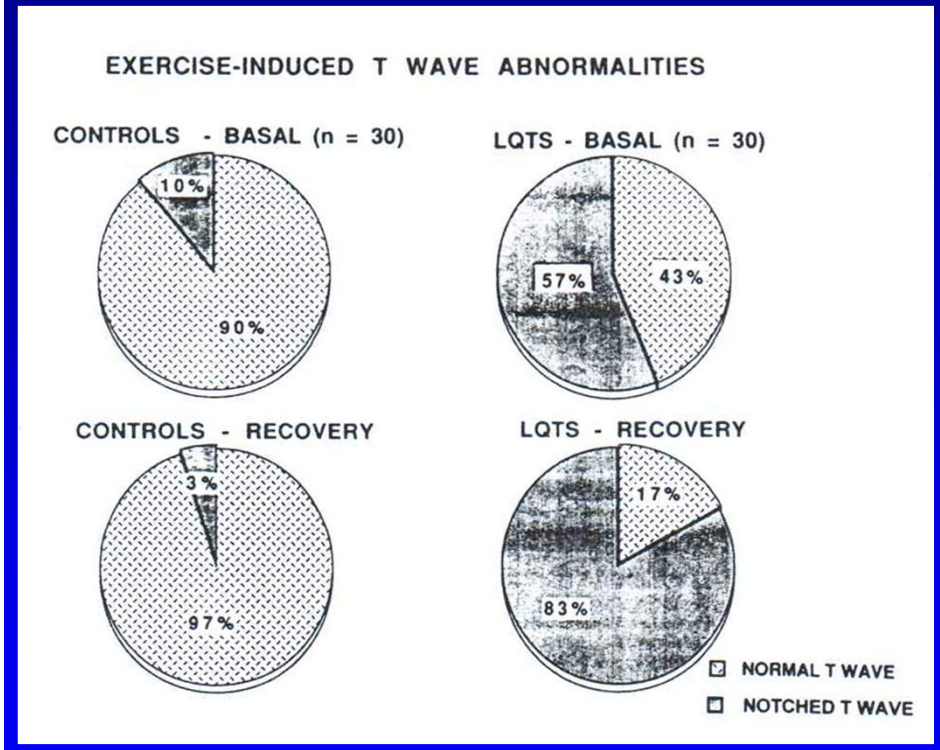
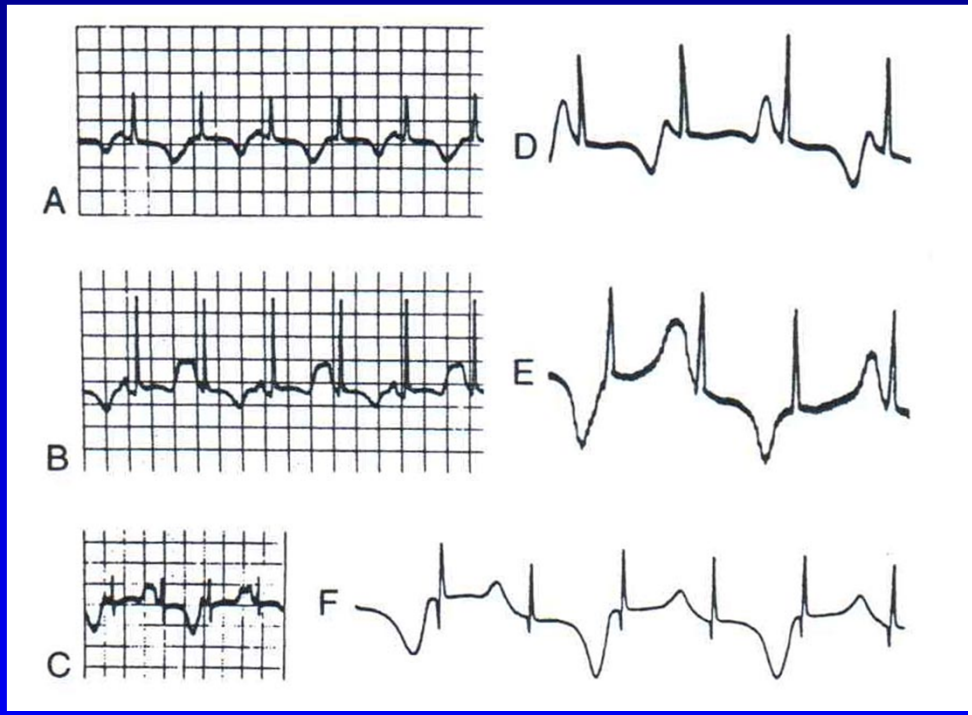
T wave abnormalities





Jervell A. et al. Adv Intern Med 1971;17:425-438

LQTS Diagnostic Criteria

Electrocardiographic Finding	Points
– QTc	
>480 ms	3
460-470 ms	2
450 (male) ms	1
– Torsade de pointes	2
– T wave alternans	1
– Notched T wave in 3 leads	1
– Low heart rate for age	0.5

Clinical History	Points
– Syncope	
With stress	2
Without stress	1
– Congenital deafness	0.5
Family History	
– (+) family Hx of LQTS	1
– Unexplained sudden death < 30	0.5

<2 points: low probability

2 to 3 points: intermediate probability

>4 points: high probability of LQTS

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Value of history-taking in syncope patients: in whom to suspect long QT syndrome?

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Aims Long QT syndrome (LQTS), a potentially fatal disorder, has to be distinguished from non-fatal conditions. Our aim was to investigate whether history-taking can be used in identifying patients likely to have LQTS.

Methods and results We compared the characteristics of a group of LQTS patients with syncope patients presenting at the emergency department (ED) and vasovagal patients younger than 40 years of age. Thirty-two LQTS patients were included. We included 113 patients at the ED and 69 vasovagal patients. Family history of syncope, sudden cardiac death, or cardiovascular disease was found more often in LQTS patients. Palpitations were the only symptom reported more often in this group. Syncope while supine, during emotional stress and associated with exercise was also more common among LQTS. Standing as a trigger was found more often in ED and vasovagal patients.

Conclusion We conclude that a family history for syncope and sudden cardiac death, palpitations as a symptom, supine syncope, syncope associated with exercise, and emotional stress place patients at higher risk for LQTS. These findings should alert physicians to the potentially life-threatening illness of LQTS, and act accordingly by obtaining an electrocardiogram and paying specific attention to the QT interval.

Keywords Syncope • Long QT syndrome • History-taking

Table 4 Frequency of triggers/circumstances in LQTS patients and in vasovagal patients

	LQTS patients ($n = 32$)[a]	Vasovagal patients ($n = 69$)[b]	*P*-value	LR (95% CI)	PPV for having LQTS (range)
Supine	24 (80%)	18 (27%)	**<0.001**	**2.8 (1.5–5.1)**	**0.09–0.20**
Standing	10 (33%)	58 (87%)	**<0.001**	**0.20 (0.10–0.39)**	**0.007–0.017**
Sitting	13 (43%)	41 (61%)	0.10	0.69 (0.44–1.06)	–
Emotion/pain/loud noise/startle	21 (70%)	17 (25%)	**<0.001**	**2.3 (1.36–3.93)**	**0.07–0.17**
Associated with exercise	10 (33%)	22 (32%)	0.92	1.02 (0.75–1.37)	–
Venipuncture	1 (3.3%)	12 (17.6%)	**0.04**	**0.85 (0.75–0.97)**	**0.028–0.069**
Bad night rest	4 (13%)	11 (16,4%)	0.48	0.96 (0.81–1.15)	–
Situational (micturition, defaecation, coughing)	4 (13%)	12 (17%)	0.40	0.95 (0.80–1.13)	–
Turning of the head	2 (3%)	4 (13%)	0.07	1.12 (0.97–1.13)	–
After eating	1 (3.3%)	5 (7.5%)	0.39	0.96 (0.87–1.05)	–

LR, likelihood ratio. Values in bold face are statistically significant.

[a]In two patients data of at least one trigger are missing.

[b]In two patients data of two triggers are missing.

Risk of Aborted Cardiac Arrest or Sudden Cardiac Death During Adolescence in the Long-QT Syndrome

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Li Zhang, MD

Context Analysis of predictors of cardiac events in hereditary long-QT syndrome (LQTS) has primarily considered syncope as the predominant end point. Risk factors specific for aborted cardiac arrest and sudden cardiac death have not been investigated.

Objective To identify risk factors associated with aborted cardiac arrest and sudden cardiac death during adolescence in patients with clinically suspected LQTS.

Design, Setting, and Participants The study involved 2772 participants from the International Long QT Syndrome Registry who were alive at age 10 years and were followed up during adolescence until age 20 years. The registry enrollment began in 1979 at 5 cardiology centers in the United States and Europe.

Main Outcome Measures Aborted cardiac arrest or LQTS-related sudden cardiac death; follow-up ended on February 15, 2005.

Results There were 81 patients who experienced aborted cardiac arrest and 45 who had sudden cardiac death; 9 of the 81 patients who had an aborted cardiac arrest event experienced subsequent sudden cardiac death. Significant independent predictors of aborted cardiac arrest or sudden cardiac death during adolescence included recent syncope, QTc interval, and sex. Compared with those with no syncopal events in the last 10 years, patients with 1 or 2 or more episodes of syncope 2 to 10 years ago (but none in the last 2 years) had an adjusted hazard ratio (HR) of 2.7; (95% confidence interval [CI], 1.3-5.7; $P<.01$) and an adjusted HR of 5.8 (95% CI, 3.6-9.4; $P<.001$), respectively, for life-threatening events; those with 1 syncopal episodes in the last 2 years had an adjusted HR of 11.7 (95% CI, 7.0-19.5; $P<.001$) and those with 2 or more syncopal episodes in the last 2 years had an adjusted HR of 18.1 (95% CI, 10.4-31.2; $P<.001$). Irrespective of events occurring more than 2 years ago, QTc of 530 ms or longer was associated with increased risk (adjusted HR, 2.3; 95% CI, 1.6-3.3; $P<.001$) compared with those having a shorter QTc. Males between the ages of 10 and 12 years had higher risk than females (HR, 4.0; 95% CI, 1.8-9.2; $P=.001$), but there was no significant risk difference between males and females between the ages of 13 and 20 years. Among individuals with syncope in the past 2 years, β-blocker therapy was associated with a 64% reduced risk (HR, 0.36; 95% CI, 0.18-0.72; $P<.01$).

Conclusions In LQTS, the timing and frequency of syncope, QTc prolongation, and sex were predictive of risk for aborted cardiac arrest and sudden cardiac death during adolescence. Among patients with recent syncope, β-blocker treatment was associated with reduced risk.

JAMA. 2006;296:1249-1254 www.jama.com

THE HEREDITARY LONG-QT SYNdrome (LQTS) is characterized by prolonged ventricular repolarization and an increased risk for ventricular tachyarrhythmias (torsades de pointes) and sudden cardiac death.[1] The clinical course of LQTS is influenced by many factors, including sex,[2-4] congenital deafness,[5] prior cardiac events,[1,6] family history,[7] QT-interval length,[1,2,4,7,8] and genotype.[3,4,9,10] Previous investiga-

Table 2. Time-Dependent Multivariable Cox Model: Risk of Aborted Cardiac Arrest or Sudden Cardiac Death (Ages 10-20 Years)

Factor	No. of Events	Hazard Ratio (95% Confidence Interval)	*P* Value
Recent syncope vs no syncope in past 10 y			
1 Syncopal event in past 2-10 y and no events within 2 y	9	2.7 (1.3-5.7)	<.01
≥2 Syncopal events in past 2-10 y and no events within 2 y	29	5.8 (3.6-9.4)	<.001
1 Syncopal event in past 2 y	26	11.7 (7.0-19.5)	<.001
≥2 Syncopal events in past 2 y	20	18.1 (10.4-31.2)	<.001
QTc ≥530 ms	51	2.3 (1.6-3.3)	<.001
Males aged 10-12 y vs age-matched females*	19	4.0 (1.8-9.2)	<.01
Time-dependent β-blocker therapy for those with recent syncope†	10	0.36 (0.2-0.7)	<.01

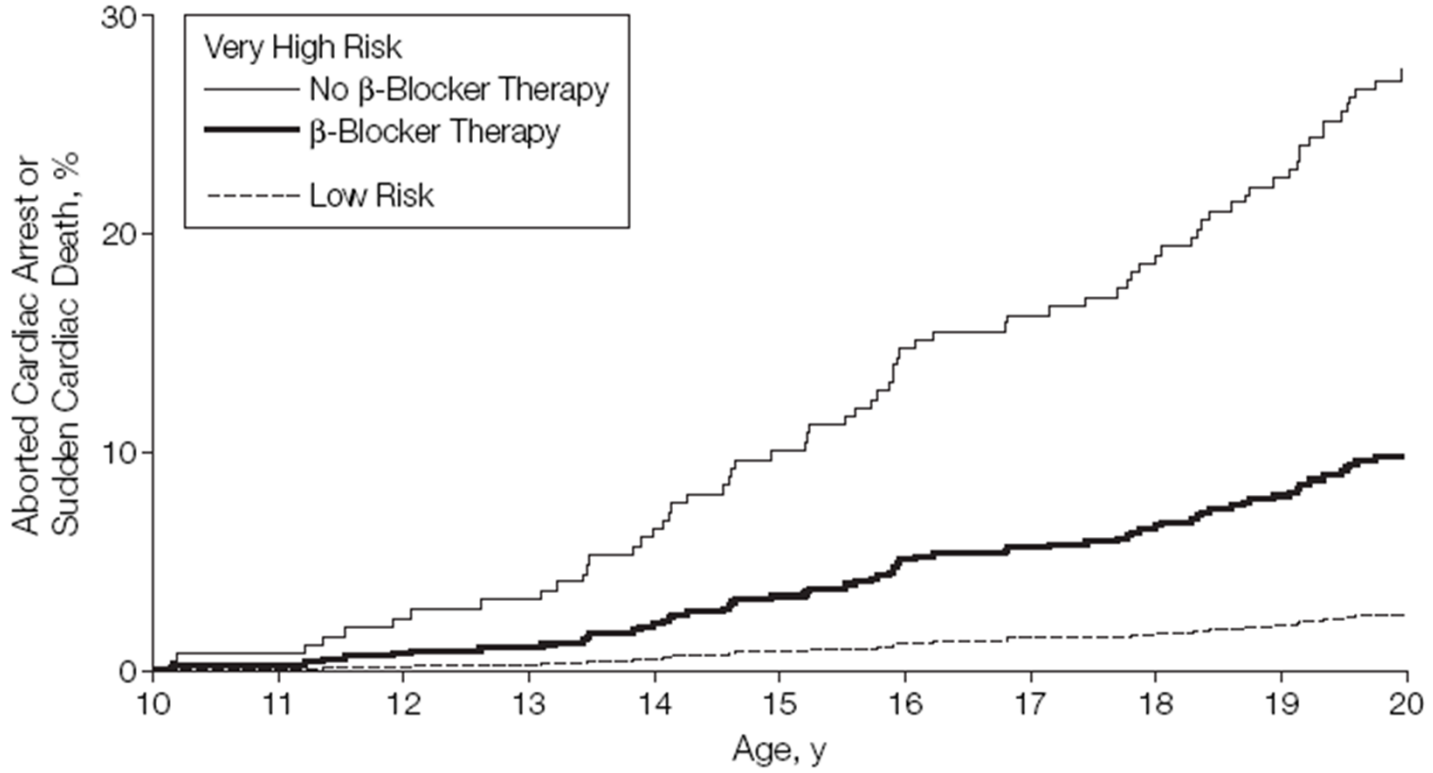
*Between the ages of 13 and 20 years, there was no significant difference in risk between the sexes.
†β-Blocker therapy was significant only among those who had experienced syncope in the past 2 years.

Table 3. Time-Dependent Multivariable Cox Model: Risk of Sudden Cardiac Death (Ages 10-20 Years)

Factor	No. of Events	Hazard Ratio (95% Confidence Interval)	*P* Value
Recent syncope vs no syncope in past 10 y			
1 Syncopal event in past 2-10 y and no events within 2 y	5	4.2 (1.7-10.9)	<.01
≥2 Syncopal events in past 2-10 y and no events within 2 y	13	6.2 (3.0-12.8)	<.001
1 Syncopal event in past 2 y	8	8.2 (3.4-19.4)	<.001
≥2 Syncopal events in past 2 y	9	15.0 (6.2-36.0)	<.001
QTc ≥530 ms	26	3.1 (1.8-5.3)	<.001
Males aged 10-12 y vs age-matched females*	8	11.6 (1.4-94.2)	.02
Time-dependent β-blockers for those with recent syncope†	4	0.49 (0.2-1.4)	.18

*Between the ages of 13 and 20 years, there was no significant difference in risk between the sexes.
†β-Blocker therapy was significant only among those who had experienced syncope in the past 2 years.

Figure. Cox Model–Based Time to First Aborted Cardiac Arrest or Sudden Cardiac Arrest Between Ages 10 and 20 Years for Females with Long-QT Syndrome



Event rates are based on estimates from the time-independent Cox model (see "Methods" section). Only the 2 highest and the lowest risk groups are shown in order to display the entire range of event rates. Males are at higher risk than females earlier in adolescence, with a range of risk at age 20 years similar to those for females.

Long-QT Syndrome After Age 40

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Background—Previous studies that assessed the risk of life-threatening cardiac events in patients with congenital long-QT syndrome (LQTS) have focused mainly on the first 4 decades of life, whereas the clinical course of this inherited cardiac disorder in the older population has not been studied.

Methods and Results—The risk of aborted cardiac arrest or death from age 41 though 75 years was assessed in 2759 subjects from the International LQTS Registry, categorized into electrocardiographically affected (corrected QT interval [QTc] ≥470 ms), borderline (QTc 440 to 469 ms), and unaffected (QTc <440 ms) subgroups. The affected versus unaffected adjusted hazard ratio for aborted cardiac arrest or death was 2.65 ($P<0.001$) in the age range of 41 to 60 years and 1.23 ($P=0.31$) in the age range of 61 to 75 years. The clinical course of study subjects displayed gender differences: Affected LQTS women experienced a significantly higher cumulative event rate (26%) than borderline (16%) and unaffected (12%) women ($P=0.001$), whereas event rates were similar among the 3 respective subgroups of men (29%, 26%, and 27%; $P=0.16$). Recent syncope (<2 years in the past) was the predominant risk factor in affected subjects (hazard ratio 9.92, $P<0.001$), and the LQT3 genotype was identified as the most powerful predictor of outcome in a subset of 871 study subjects who were genetically tested for a known LQTS mutation (hazard ratio 4.76, $P=0.02$).

Conclusions—LQTS subjects maintain a high risk for life-threatening cardiac events after age 40 years. The phenotypic expression of affected subjects is influenced by age-specific factors related to gender, clinical history, and the LQTS genotype. (***Circulation***. **2008;117:2192-2201.**)

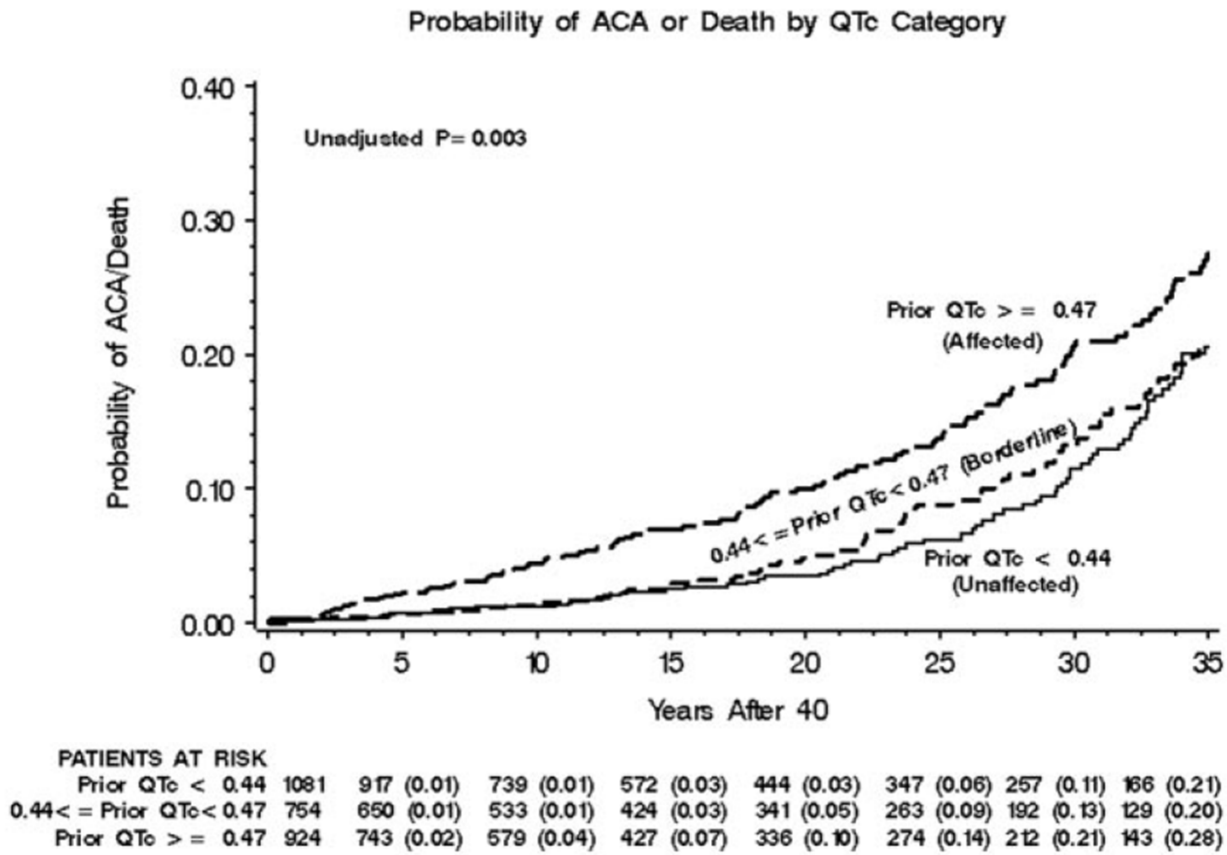

Figure 1. Kaplan–Meier estimates of the probability of ACA or death by QTc category (values in parentheses are probability estimates).

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Risk Factors for Recurrent Syncope and Subsequent Fatal or Near-Fatal Events in Children and Adolescents With Long QT Syndrome

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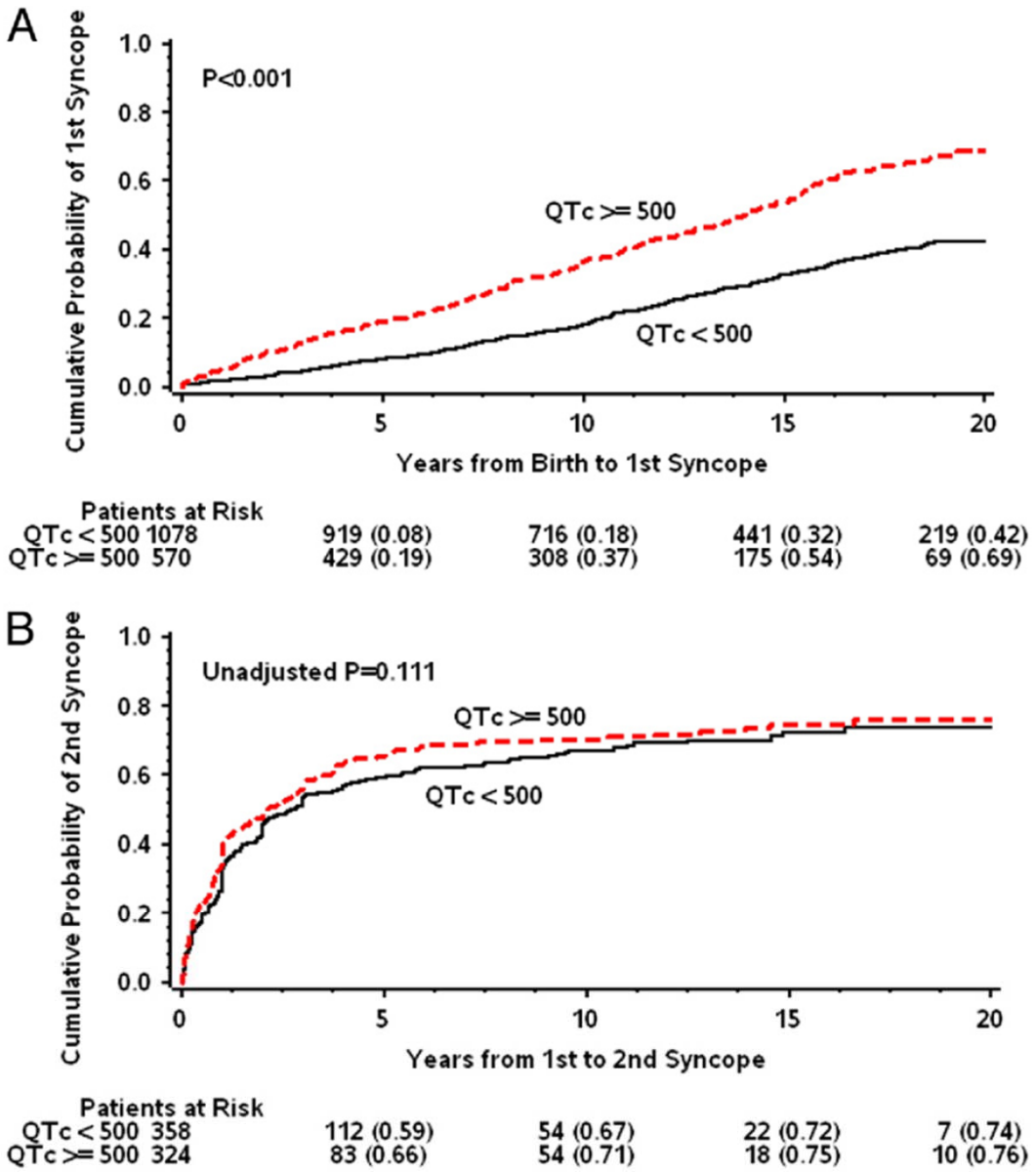

Figure 1 **Probability of Cardiac Events by QTc Duration**

Kaplan-Meier estimates of the probability of a first episode, of syncope (with follow-up time starting at birth) **(A)** and a second episode of syncope (among patients who experienced a first syncope episode, with follow-up time starting at the time of the first syncope event) **(B)** by corrected QT interval (QTc) duration (dichotomized at ≥500 ms).

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STATE-OF-THE-ART PAPER

Long QT Syndrome

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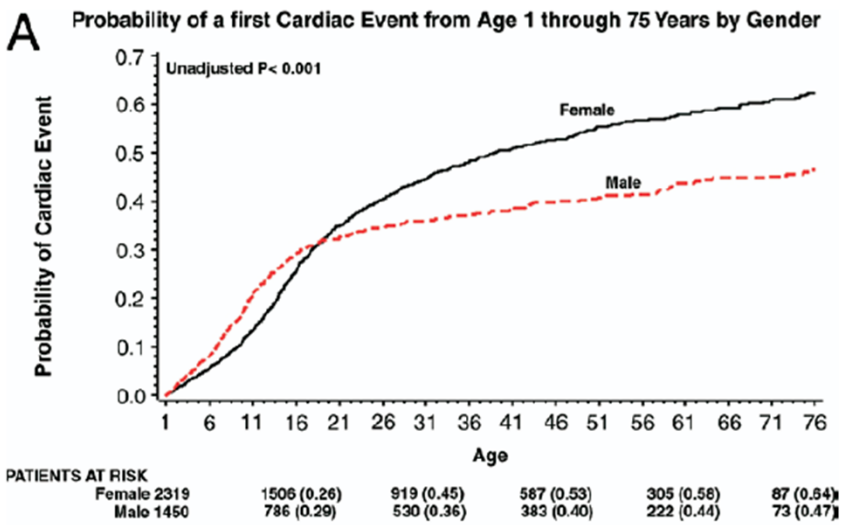
Rochester, New York

The hereditary long QT syndrome (LQTS) is a genetic channelopathy with variable penetrance that is associated with increased propensity to syncope, polymorphous ventricular tachycardia (torsades de pointes), and sudden arrhythmic death. This inherited cardiac disorder constitutes an important cause of malignant ventricular arrhythmias and sudden cardiac death in young individuals with normal cardiac morphology. Risk assessment in affected LQTS patients relies upon a constellation of electrocardiographic, clinical, and genetic factors. Administration of beta-blockers is the mainstay therapy in affected patients, and primary prevention with an implantable cardioverter defibrillator or left cervicothoracic sympathetic denervation are therapeutic options in patients who remain symptomatic despite beta-blocker therapy. Accumulating data from the International LQTS Registry have recently facilitated a comprehensive analysis of risk factors for aborted cardiac arrest or sudden cardiac death in pre-specified age groups, including the childhood, adolescence, adulthood, and post-40 periods. These analyses have consistently indicated that the phenotypic expression of LQTS is time dependent and age specific, warranting continuous risk assessment in affected patients. Furthermore, the biophysical function, type, and location of the ion-channel mutation are currently emerging as important determinants of outcome in genotyped patients. These new data may be used to improve risk stratification and for the development of gene-specific therapies that may reduce the risk of life-threatening cardiac events in patients with this inherited cardiac disorder.
(J Am Coll Cardiol 2008;51:2291–300)



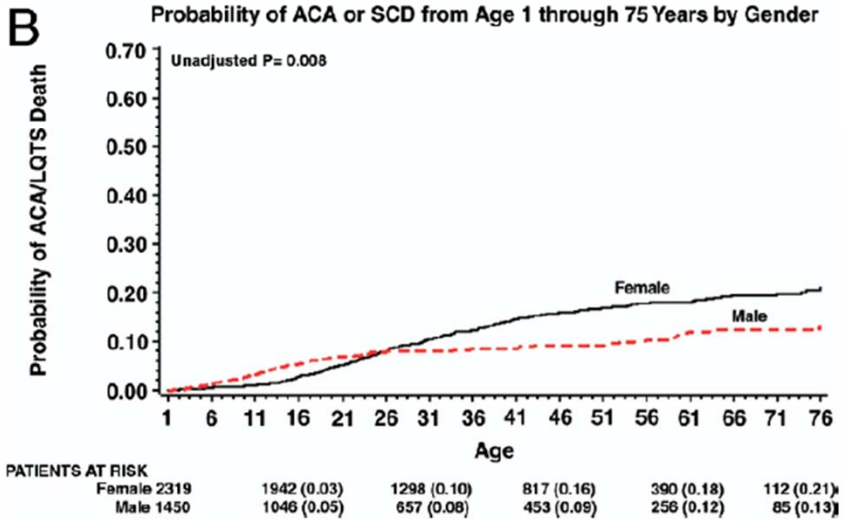


Figure 2 **Probability of LQTS-Related Events by Gender**

Kaplan-Meier estimates of the cumulative probability of **(A)** a first cardiac event (syncope, aborted cardiac arrest [ACA], or sudden cardiac death [SCD]) and **(B)** a first life-threatening cardiac event (ACA or SCD) from age 1 through 75 years by gender in 3,779 long QT syndrome (LQTS) patients from the International LQTS Registry. Reprinted, with permission, from Goldenberg et al. (30).

Table 3 Age-Specific Risk Factors for Life-Threatening Cardiac Events in LQTS Patients*

Age Group (Ref. #)	Risk Factor	Hazard Ratio (p Value)	Beta-Blocker Efficacy, % Reduction (p Value)
Childhood (1–12 yrs) (33)	Male gender	3.96 (<0.001)	73% (0.002)
	QTc >500 ms	2.12 (0.02)	
	Prior syncope		
	Recent (<2 yrs)	14.34 (<0.001)	
	Remote (≥2 yrs)	6.45 (<0.001)	
Adolescence (10–20 yrs) (28)	QTc >530 ms	2.3 (<0.001)	64% (0.01)
	Syncope		
	≥2 syncopal events in past 2 yrs	18.1 (<0.001)	
	1 syncopal event in past 2 yrs	11.7 (<0.001)	
	≥2 syncopal events in past 2–10 yrs	5.8 (<0.001)	
	1 syncopal events in past 2–10 yrs	2.7 (<0.001)	
Adulthood (18–40 yrs) (29)	Female gender	2.68 (<0.05)	60% (<0.01)
	QTc duration		
	QTc ≥500 ms	6.35 (<0.01)	
	QTc 500–549 ms	3.34 (<0.01)	
	Prior syncope	5.10 (<0.01)	
Adulthood (41–60 yrs) (53)†	Recent syncope (<2 yrs)	9.92 (<0.001)	42% (0.40)‡
	QTc >530 ms	1.68 (0.06)	
	LQT3 genotype	4.76 (0.02)	

*Findings are from separate multivariable Cox models in each age group for the end point of aborted cardiac arrest or sudden cardiac death. †Because long QT syndrome (LQTS)–related events are more difficult to delineate in the older age group, the end point in the 41 to 60 years age group comprised aborted cardiac arrest or death from any cause. ‡Lack of a statistically significant beta-blocker effect in this age group may relate to the broad end point of death from any cause.

QTc = corrected QT interval.

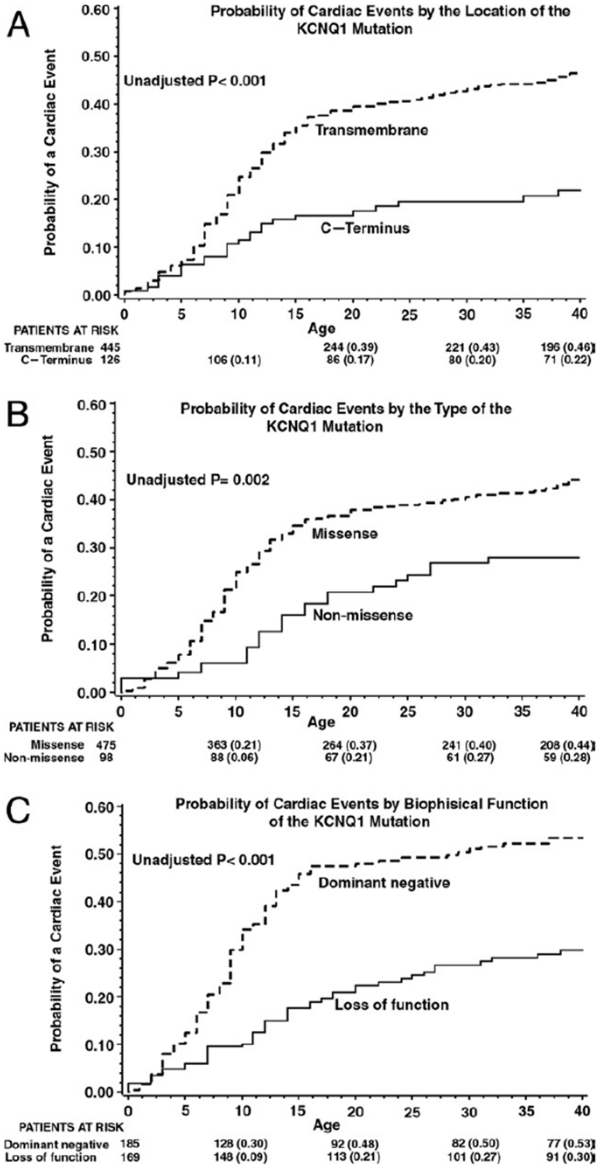


Figure 3 **Probability of Cardiac Events in LQT1 Patients**

Kaplan-Meier estimates of the cumulative probability of a first cardiac event in KCNQ1 mutation carriers (LQT1 genotype) by **(A)** location, **(B)** type, and **(C)** biophysical function of the mutation. Reprinted, with permission, from Moss et al. (47).

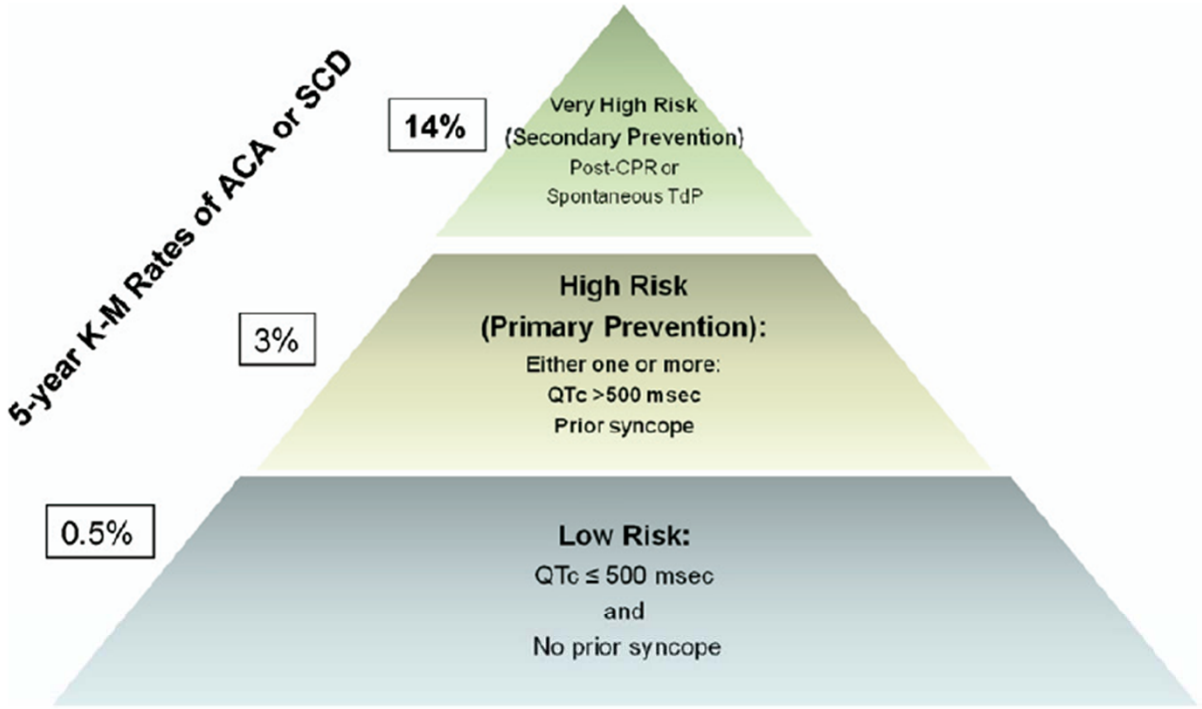


Figure 4 **Suggested Risk-Stratification Scheme for ACA or SCD in LQTS Patients**

Risk stratification categories for LQTS patients based on published event rates; more specific risk subsets by age group are detailed in Table 3. Kaplan-Meier (K-M) estimates are based on a series of 869 LQTS patients (52). CPR = cardiopulmonary resuscitation; TdP = torsades de pointes; other abbreviations as in Figure 2.

Inherited long QT syndrome

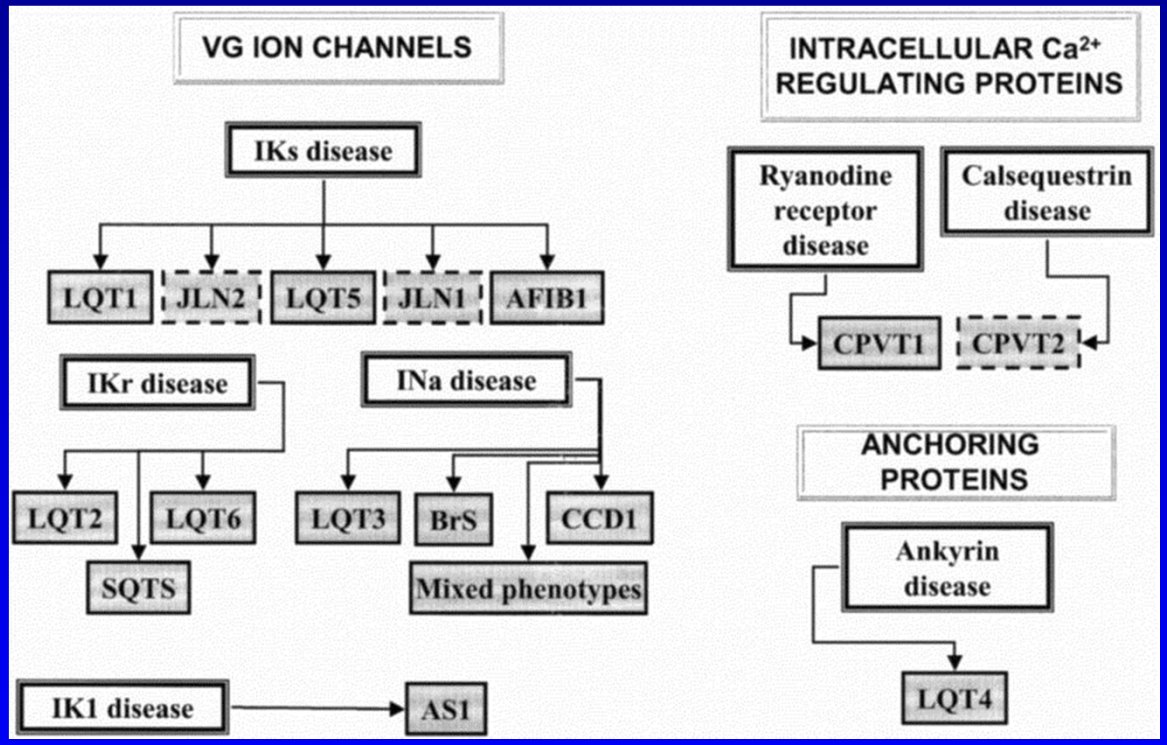
- Autosomal dominant
  - Romano and Ward (1960).
  - Prolongation of QT interval and predisposition to torsades de pointes
  - No other obvious physical abnormalities
- Autosomal recessive
  - Jervell and Lange-Neilsen (1957)
  - congenital neural deafness.
  - 1 % of congenital deaf children had prolongation of the long QT interval

Molecular Genetics of LQTS

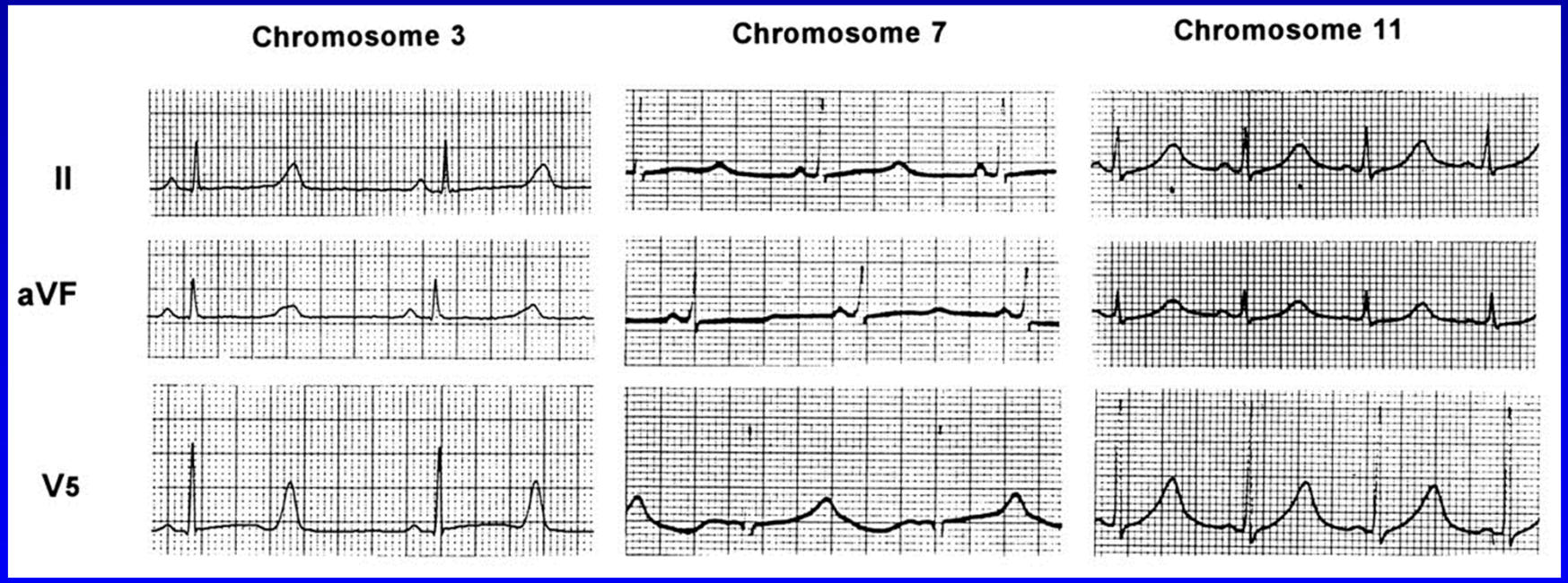
Table. Human Long QT Syndrome–Associated Genes and Functions

LQTS Subtype	Gene	Gene Location	Protein	Protein Function	Mutant Protein Phenotype
LQT1 (RWS, JLNS)	*KCNQ1*	11p15.5	Kv7.1	I_{Ks} α subunit	Loss-of-function
LQT2 (RWS)	*KCNH2*	7q35–36	Kv11.1	I_{Kr} α subunit	Loss-of-function
LQT3 (RWS)	*SCN5A*	3p21	Nav1.5	I_{Na} α subunit	Gain-of-function
LQT4 (AnkB syndrome)	*ANK2*	4q25–27	Ankyrin-B	Targeting protein	Loss-of-function
LQT5 (RWS, JLNS)	*KCNE1*	21q22	minK	I_{Ks} beta subunit	Loss-of-function
LQT6 (RWS)	*KCNE2*	21q22	miRP1	I_{Kr} beta subunit	Loss-of-function
LQT7 (Anderson-Tawil syndrome, ATS1)	*KCNJ2*	17q23.1–24.2	Kir2.1	I_{K1} α subunit	Loss-of-function
LQT8 (Timothy syndrome, TS1)	*CACNA1C*	12p13.3	Cav1.2	$I_{Ca,L}$ α subunit	Gain-of-function
LQT9	*CAV3*	3p25	Caveolin-3	Caveolae coat protein	Secondary gain-of-function to Nav1.5
LQT10	*SCN4B*	11q23	Navbeta4	Channel beta subunit	Secondary gain-of-function to Nav1.5
LQT11	*AKAP9*	7q21–22	Yotiao	Adaptor molecule	Loss-of-function
LQT12	*SNTA1*	20q11.2	Alpha1-syntrophin	Membrane scaffold	Secondary gain-of-function to Nav1.5

Circ Res. 2010;107:457–46



Priori SG. *Circ Res*. 2004;94:140–145



LQT3 LQT2 LQT1

Moss et al. Circulation 1995,92:2929-2934

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

	LQT1	LQT2	LQT3
Sensitivity to sympathetic stimulation	Yes	To some degree	No
Torsade de pointes	Exercise related	Startle	Sleep/rest
Specific triggers/occurrence	Swimming	Telephone, alarm clock, postpartum	Inactivity
Risk by mutation	Dominant neg., transmembrane location, A341V	Pore location, K28E	ΔKPQ
Exercise restriction	+++	++	?
β-blockers	+++	++	?
Potassium supplement	+	++	+
Mexiletine	+	+	++
Flecainide	No data	No data	+++ (ΔKPQ, D1790G)
Ranolazine	No data	No data	++ (ΔKPQ)
LCSD in high-risk patients	++	++	++
ICD in high-risk patients	+++	+++	+++

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

Reproduced and modified with permission from ref. 28.

Trigger for EADs

- Reopening of $I_{Ca.L}$ during the prolonged plateau phase of the cardiac action potential.
- The beneficial effect of β-adrenergic blockers in individuals with LQTS may be caused by a blunting of the increase in L-type calcium current by sympathetic nerve stimulation.

Clinical course of LQTS

- The risk of cardiac events is significantly higher among patients with LQT1 and LQT2 mutations
- Risk of cardiac events is higher in males before puberty and higher in females during adulthood.
- The most significant risk factor for cardiac events is the length of the QTc interval, with the risk an exponential function of the QTc duration.

Social Life Modification

- Avoid adrenergic-type stimuli that can trigger life-threatening arrhythmia.
- Competitive athletics should be prohibited.
- Alarm clocks should be removed.
- Good β-blocker compliance is important.

management strategy among LQTS patients who present for risk assessment after a syncope episode may include the following:

1) initiation of beta blocker therapy in those who experience a syncope event without therapy

2) additional interventions, including primary ICD therapy and/or left cardiac sympathetic denervation in patients who experience syncope during beta-blocker therapy;

3) careful follow-up for residual symptoms or arrhythmias after the initiation of beta blocker therapy, with consideration of ICD therapy for patients who experience 2 episodes of syncope during follow-up (who had a frequency of ICD implants similar to that of patients who experienced 1 or 2 episodes, but had a very high rate of subsequent of ACA or SCD at 5 years [approximately 20%]).

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JPT-06333; No of Pages 7

Pharmacology & Therapeutics xxx (2011) xxx–xxx

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Pharmacological and non-pharmacological management of the congenital long QT syndrome: The rationale

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Chair of Sudden Death, Department of Family and Community Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia

Propranolol and nadolol are the two most effective drugs. Their respective dosages are 3 mg/kg, sometime increased to 4 mg/kg, and 1 mg/kg.

The main advantages of propranolol are its lipophilicity, that allows it to cross the blood-brain barrier, and its well known tolerability for chronic therapy; its main disadvantages are the need of multiple daily administrations and the contraindications for patients with asthma and diabetes.

unquestionably less effective; this group includes : bisoprolol, metoprolol, atenolol, and carvedilol.

Effect of therapy on the survival, after the first syncopal episode

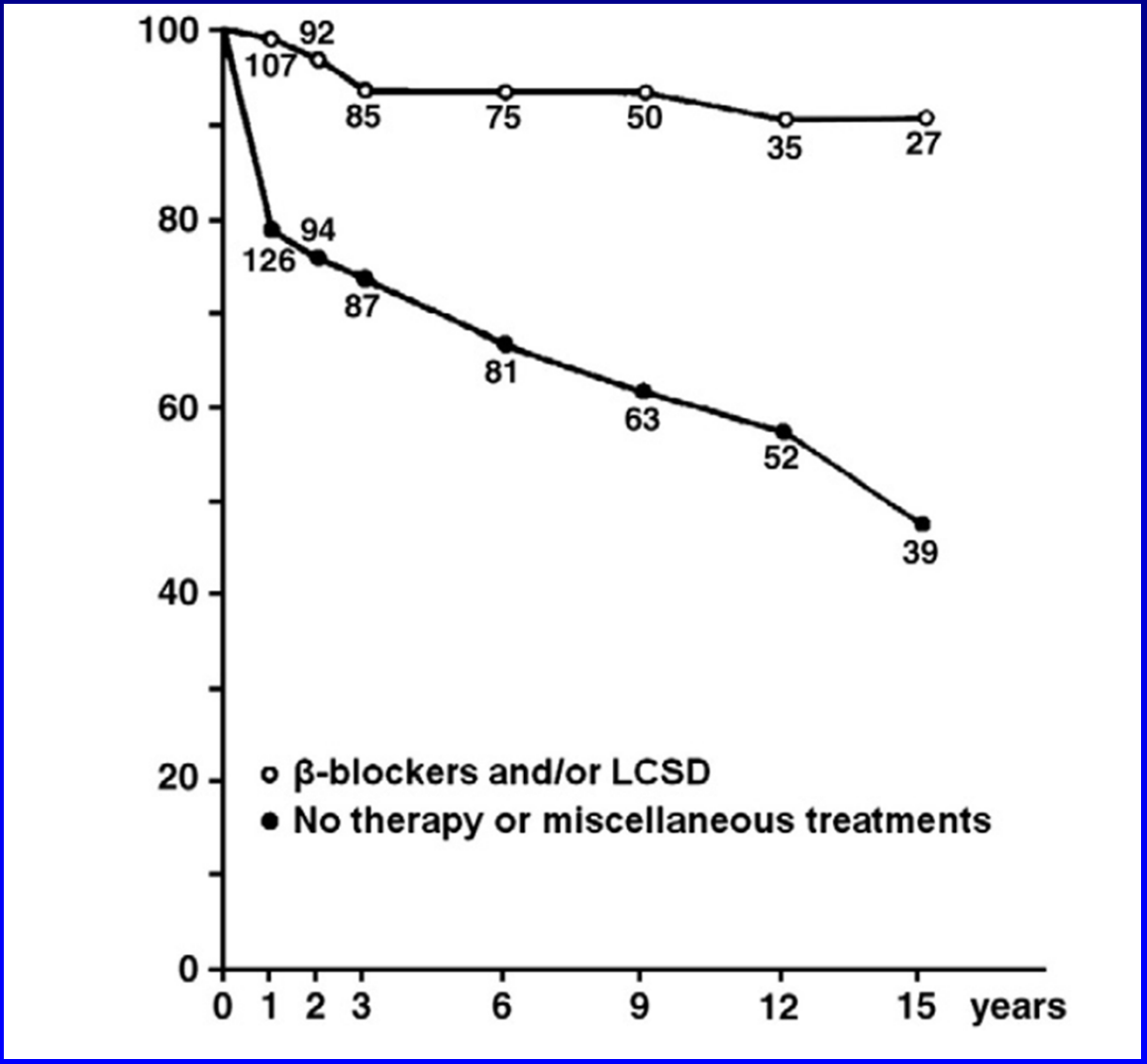
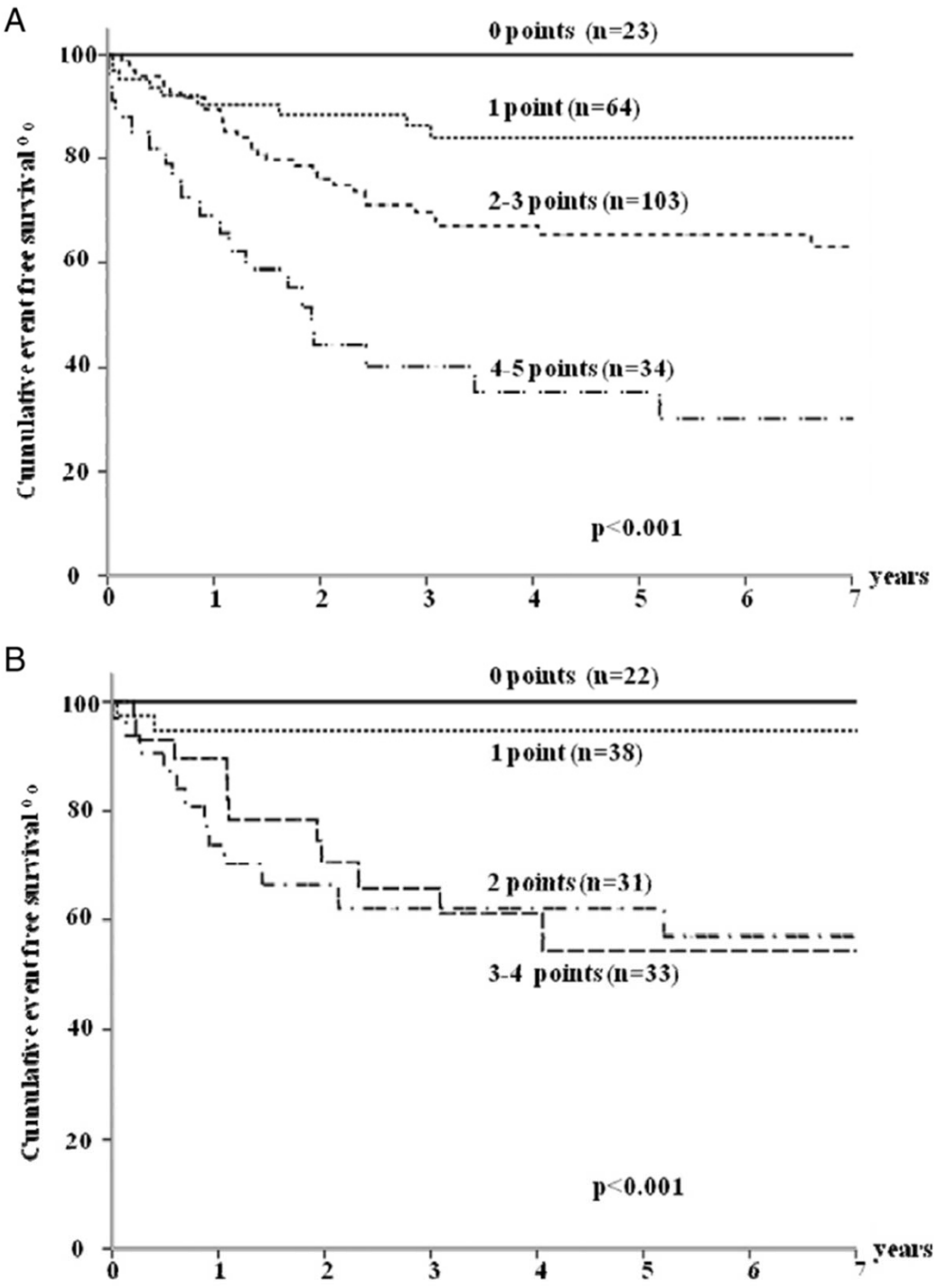


Table 1
M-FACT * risk score.
From Schwartz et al. (2010).

	−1 point	0 point	1 point	2 points
Event free on therapy for >10 years	Yes			
QTc (ms)		≤500	>500–≤550	>550
Prior ACA		No	Yes	
Events on therapy		No	Yes	
Age at implant		>20 years	≤20 years	

*Acronym derived from *M* (*M*inus 1 point for being free of cardiac events while on therapy for >10 years); *F* ("*F*ive Hundred" and "*F*ive hundred and *F*ifty ms QTc"); *A* for *A*ge ≤20>years at implant; *C* (*C*ardiac arrest); *T* (events on *T*herapy).
ACA = Aborted Cardiac Arrest.



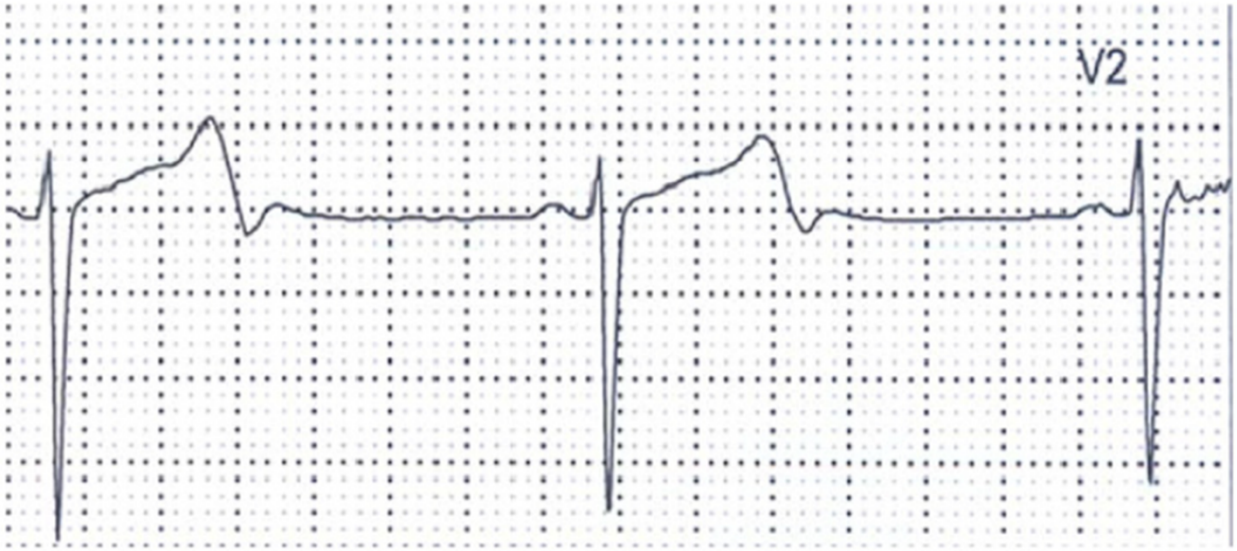
Cumulative event-free survival for a first appropriate ICD shock according to an increasing risk score

All patients

Patients with no prior ACA.

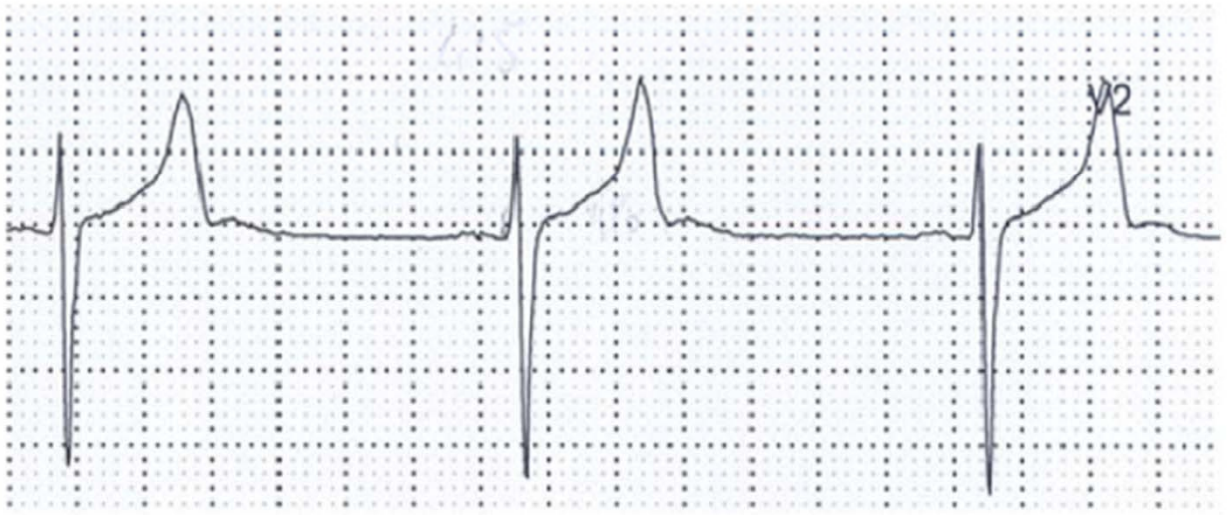
A.I., male, 17 yrs – LQT3

HR: 42 b min



RX: Propranolol → QTc 516 ms

HR: 44 b min



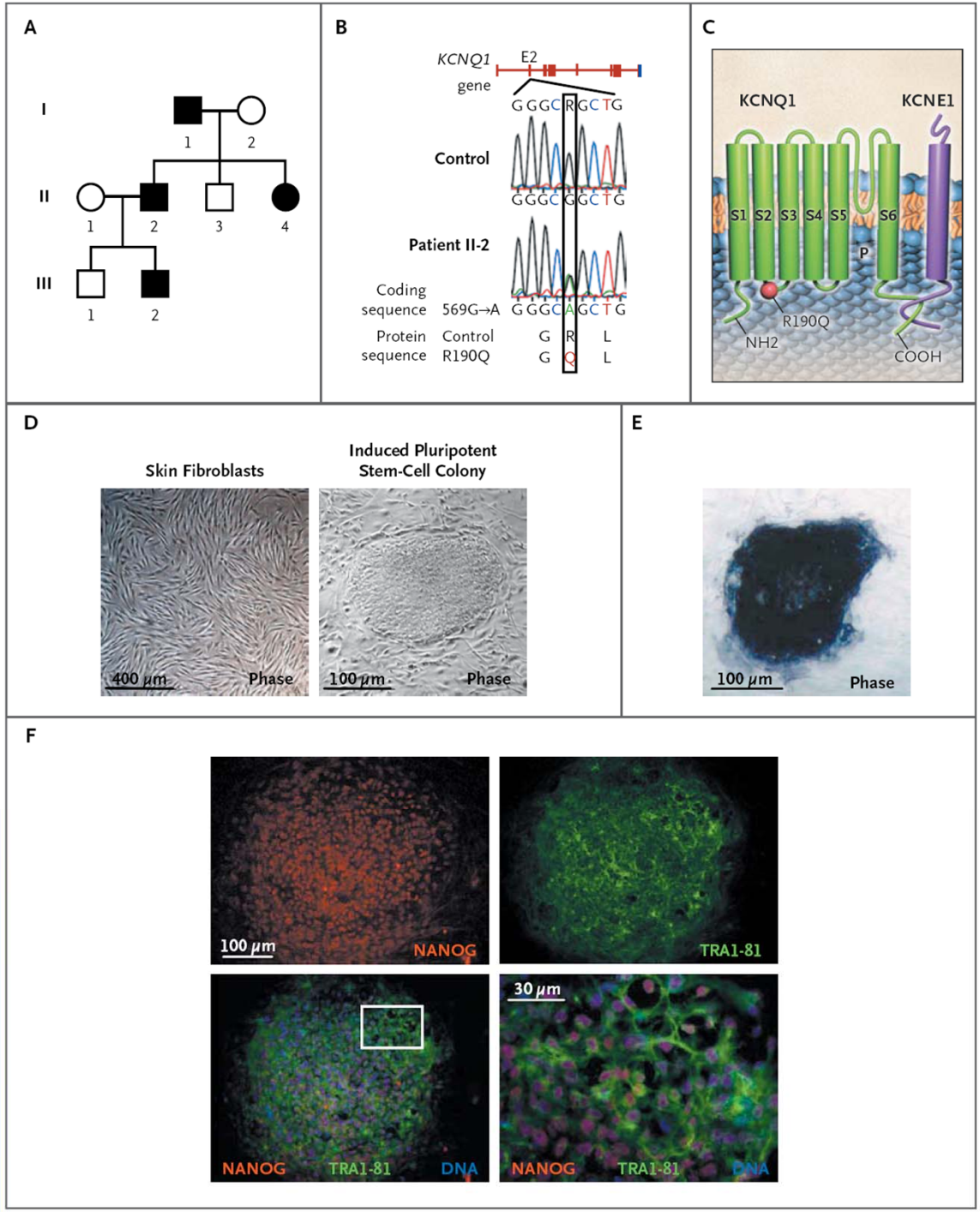
RX: Propranolol + Mexiletine → QTc 408 ms

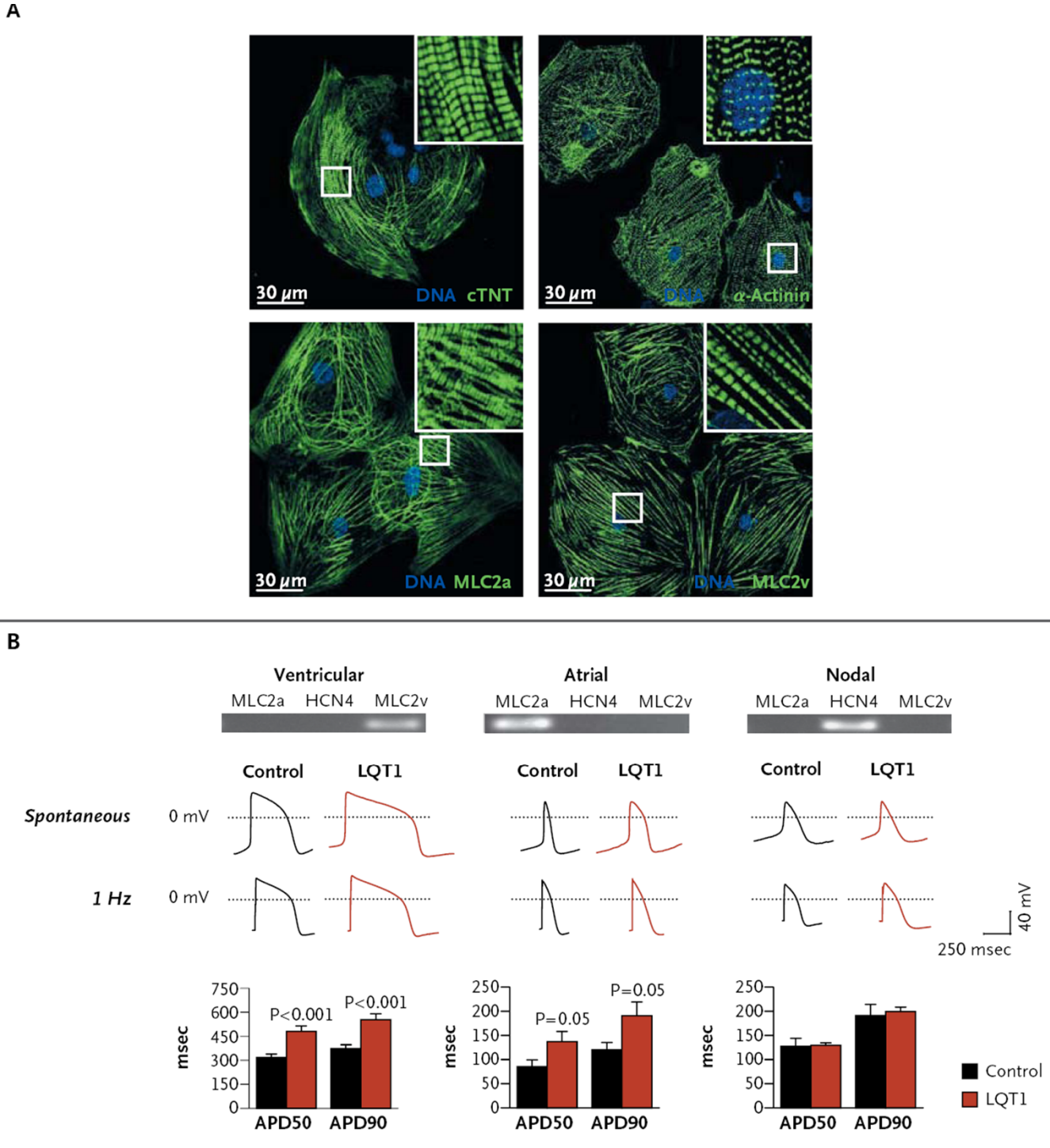
The NEW ENGLAND JOURNAL of MEDICINE

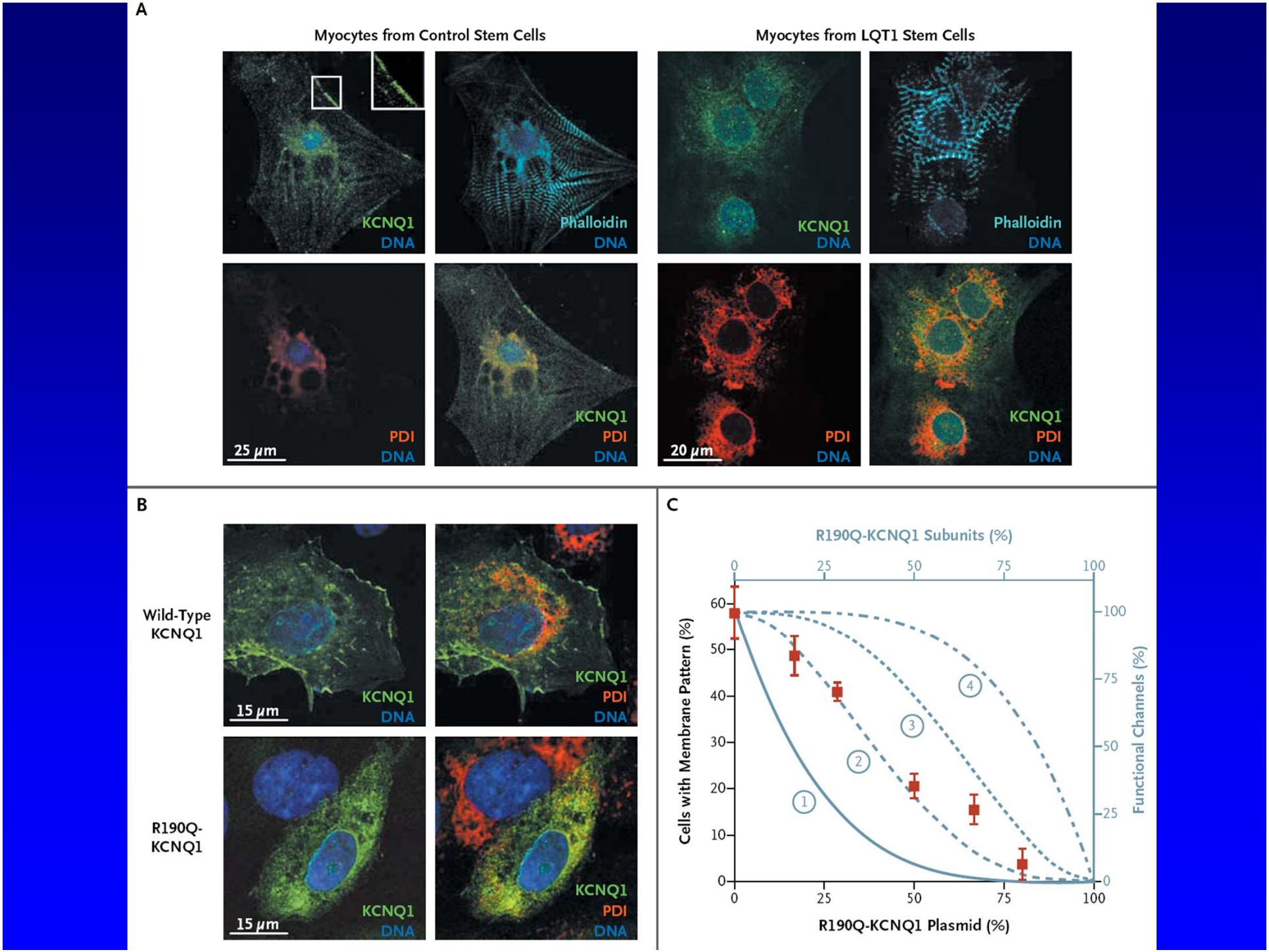
ESTABLISHED IN 1812 OCTOBER 7, 2010 VOL. 363 NO. 15

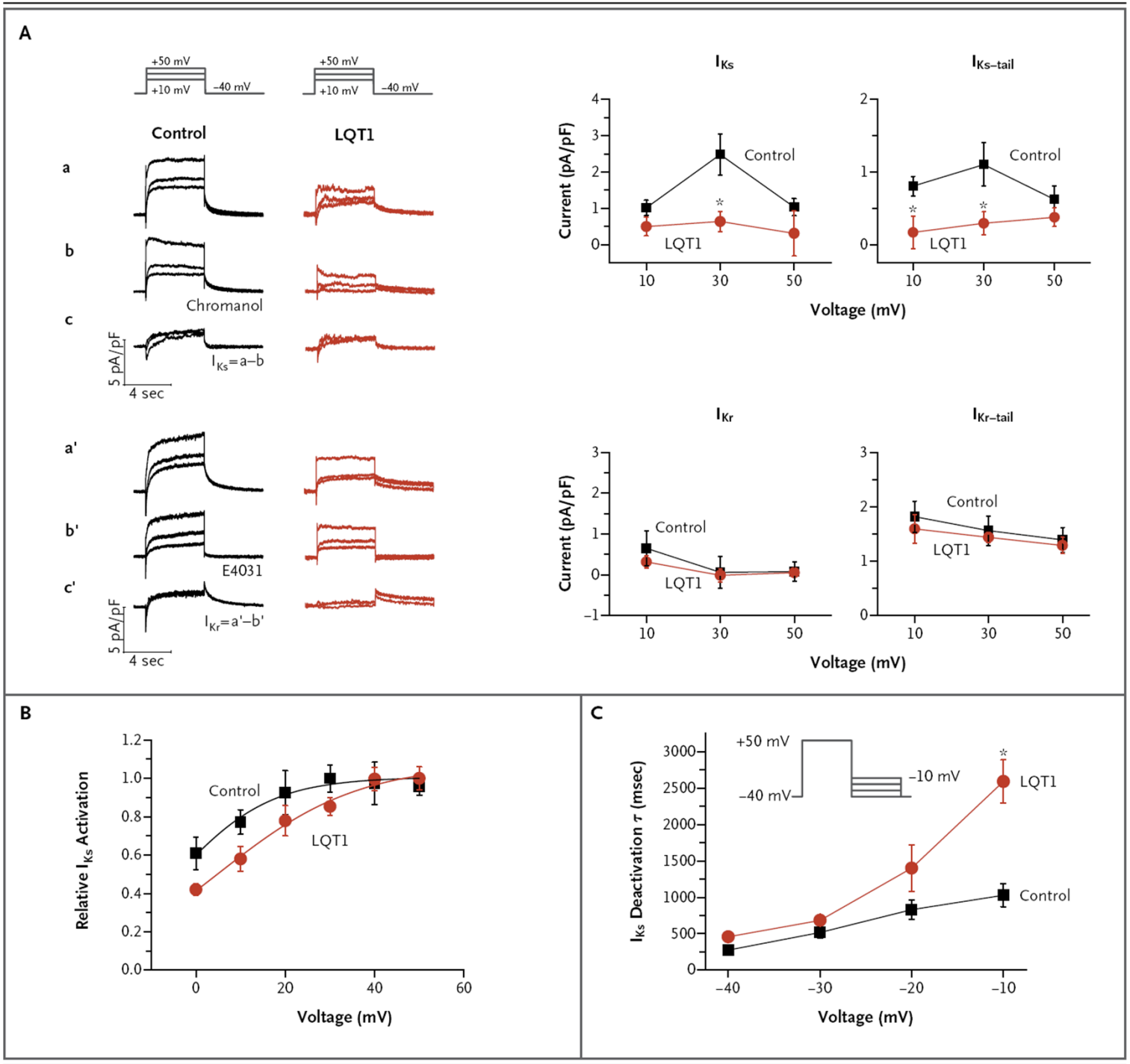
Patient-Specific Induced Pluripotent Stem-Cell Models for Long-QT Syndrome

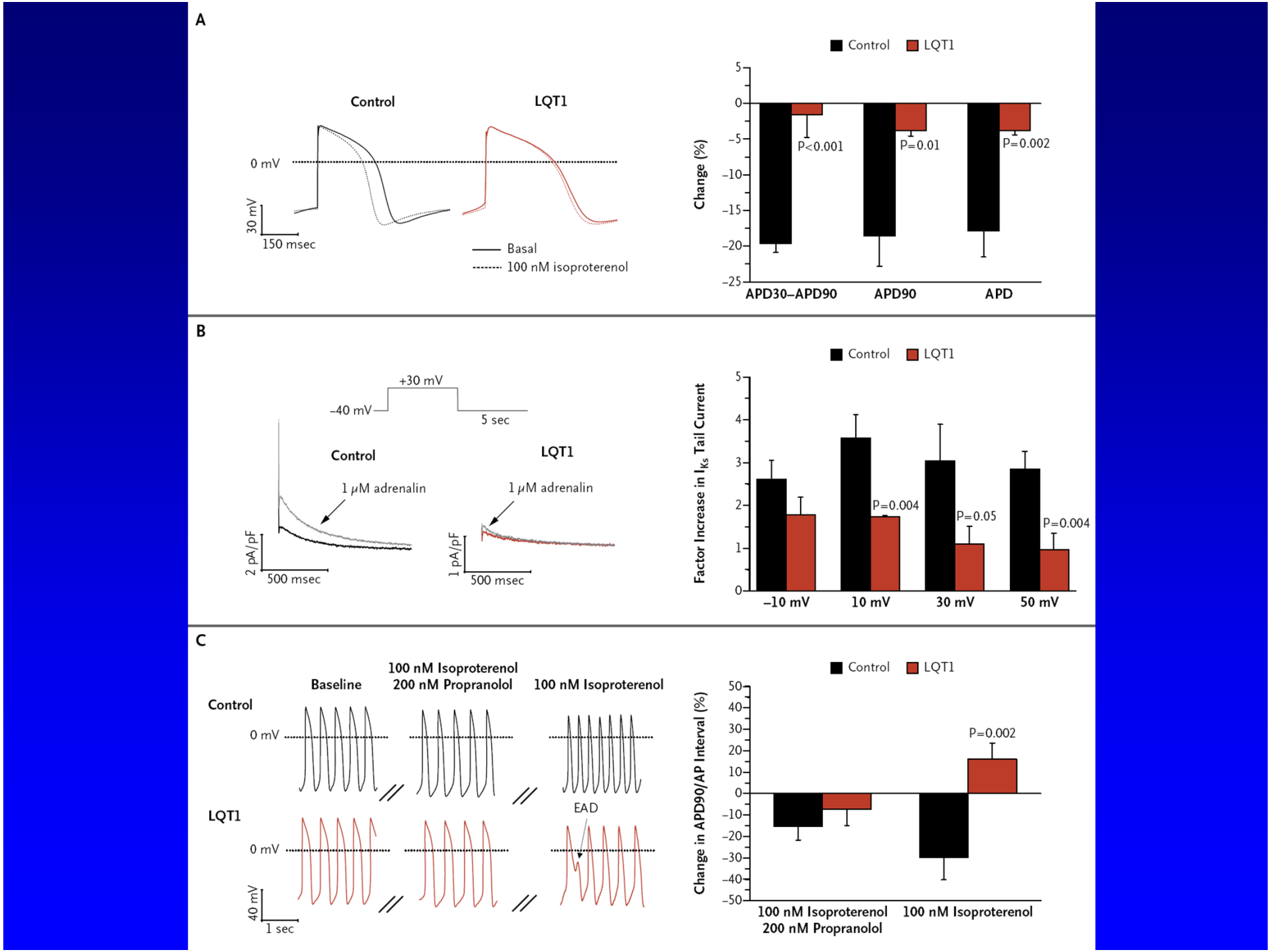
Alessandra Moretti, Ph.D., Milena Bellin, Ph.D., Andrea Welling, Ph.D., Christian Billy Jung, M.Sc., Jason T. Lam, Ph.D., Lorenz Bott-Flügel, M.D., Tatjana Dorn, Ph.D., Alexander Goedel, M.D., Christian Höhnke, M.D., Franz Hofmann, M.D., Melchior Seyfarth, M.D., Daniel Sinnecker, M.D., Albert Schömig, M.D., and Karl-Ludwig Laugwitz, M.D.


A
I
1
2
II
1
2
3
4
III
1
2
B
KCNQ1
gene
E2
G G G C R G C T G
Control
G G G C G G C T G
Patient II-2
G G G C A G C T G
Coding sequence
569G→A
Protein sequence
Control
R190Q
G R L
G Q L
C
KCNQ1
KCNE1
S1
S2
S3
S4
S5
S6
P
R190Q
NH2
COOH
D
Skin Fibroblasts
Induced Pluripotent Stem-Cell Colony
400 μm
Phase
100 μm
Phase
E
100 μm
Phase
F
100 μm
NANOG
TRA1-81
NANOG
TRA1-81
DNA
30 μm
NANOG
TRA1-81
DNA


A
30 μm
DNA cTNT
30 μm
DNA α-Actinin
30 μm
DNA MLC2a
30 μm
DNA MLC2v
B
Ventricular
MLC2a HCN4 MLC2v
Atrial
MLC2a HCN4 MLC2v
Nodal
MLC2a HCN4 MLC2v
Control
LQT1
Control
LQT1
Control
LQT1
Spontaneous
0 mV
1 Hz
0 mV
40 mV
250 msec
msec
750
600
450
300
150
0
P<0.001
P<0.001
APD50
APD90
msec
250
200
150
100
50
0
P=0.05
P=0.05
APD50
APD90
msec
250
200
150
100
50
0
APD50
APD90
Control
LQT1


A
Myocytes from Control Stem Cells
Myocytes from LQT1 Stem Cells
KCNQ1
DNA
Phalloidin
DNA
PDI
DNA
KCNQ1
PDI
DNA
25 μm
20 μm
B
Wild-Type KCNQ1
R190Q-KCNQ1
15 μm
C
R190Q-KCNQ1 Subunits (%)
Cells with Membrane Pattern (%)
Functional Channels (%)
R190Q-KCNQ1 Plasmid (%)
0
25
50
75
100
10
20
30
40
60
1
2
3
4


A
+50 mV
+10 mV
–40 mV
Control
LQT1
a
b
Chromanol
c
5 pA/pF
4 sec
I_{Ks}=a–b
a'
b'
E4031
c'
I_{Kr}=a'–b'
I_{Ks}
$I_{Ks-tail}$
Current (pA/pF)
Voltage (mV)
I_{Kr}
$I_{Kr-tail}$
B
Relative I_{Ks} Activation
C
I_{Ks} Deactivation τ (msec)
–10 mV


A
Control
LQT1
0 mV
30 mV
150 msec
Basal
100 nM isoproterenol
Control
LQT1
Change (%)
5
0
−5
−10
−15
−20
−25
P<0.001
P=0.01
P=0.002
APD30–APD90
APD90
APD
B
+30 mV
−40 mV
5 sec
Control
LQT1
1 μM adrenalin
1 μM adrenalin
2 pA/pF
500 msec
1 pA/pF
500 msec
Control
LQT1
Factor Increase in I_{Ks} Tail Current
5
4
3
2
1
0
P=0.004
P=0.05
P=0.004
−10 mV
10 mV
30 mV
50 mV
C
Baseline
100 nM Isoproterenol
200 nM Propranolol
100 nM Isoproterenol
Control
0 mV
LQT1
0 mV
EAD
40 mV
1 sec
Control
LQT1
Change in APD90/AP Interval (%)
50
40
30
20
10
0
−10
−20
−30
−40
−50
P=0.002
100 nM Isoproterenol
200 nM Propranolol
100 nM Isoproterenol

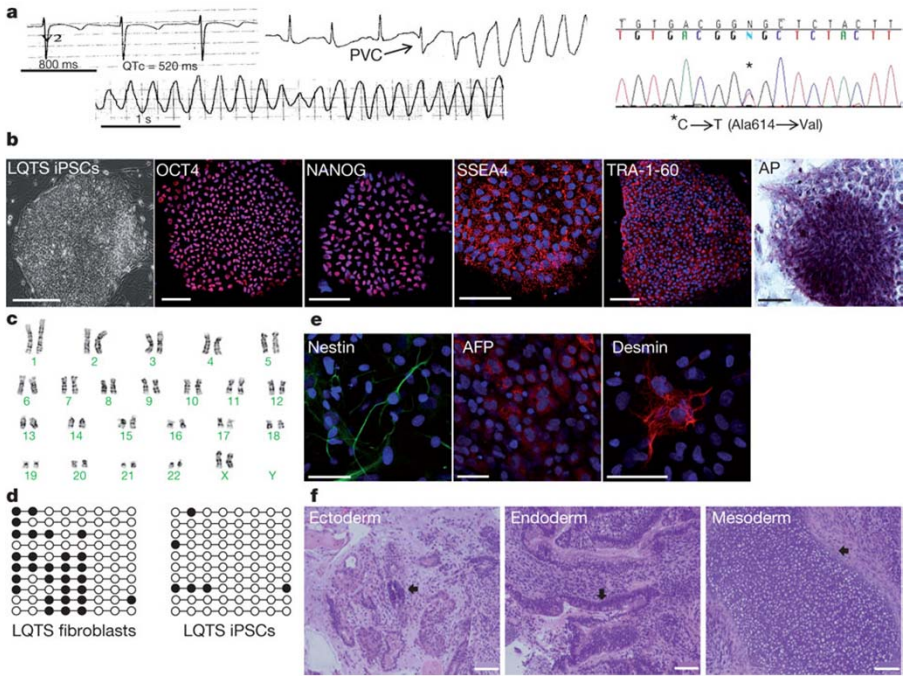
LETTER

doi:10.1038/nature09747

Modelling the long QT syndrome with induced pluripotent stem cells

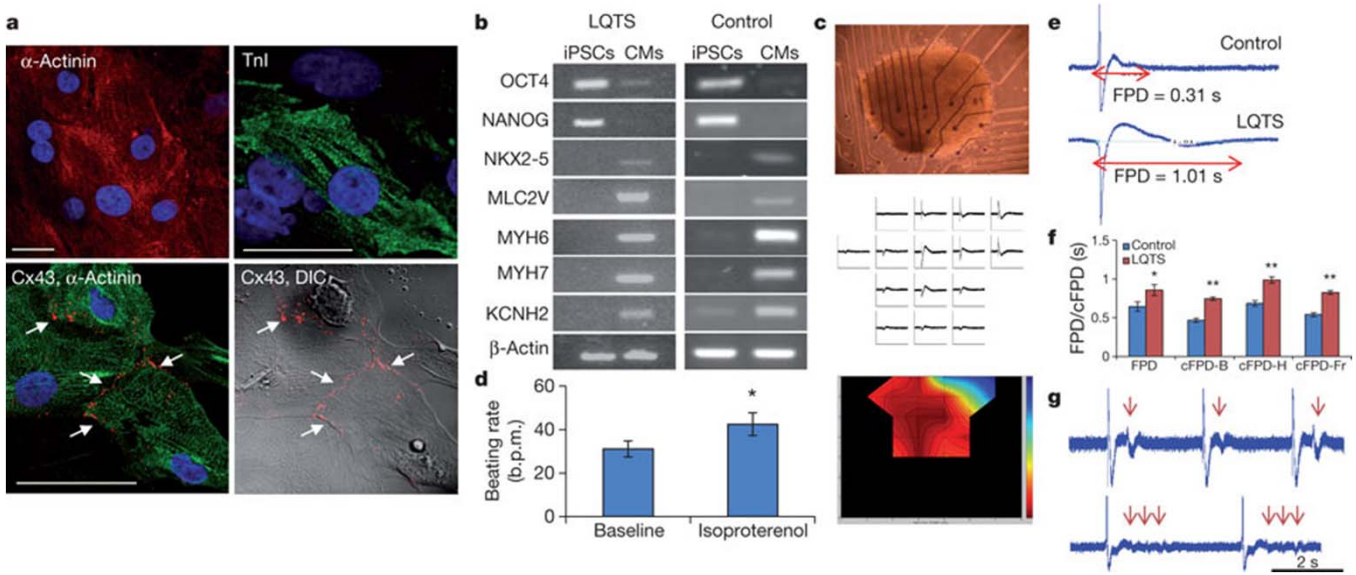
Ilanit Itzhaki[1]*, Leonid Maizels[1]*, Irit Huber[1]*, Limor Zwi-Dantsis[1], Oren Caspi[1], Aaron Winterstern[1], Oren Feldman[1], Amira Gepstein[1], Gil Arbel[1], Haim Hammerman[2], Monther Boulos[2] & Lior Gepstein[1,2]

Establishment and characterization of type-2LQTS human iPSCs (clone 1).



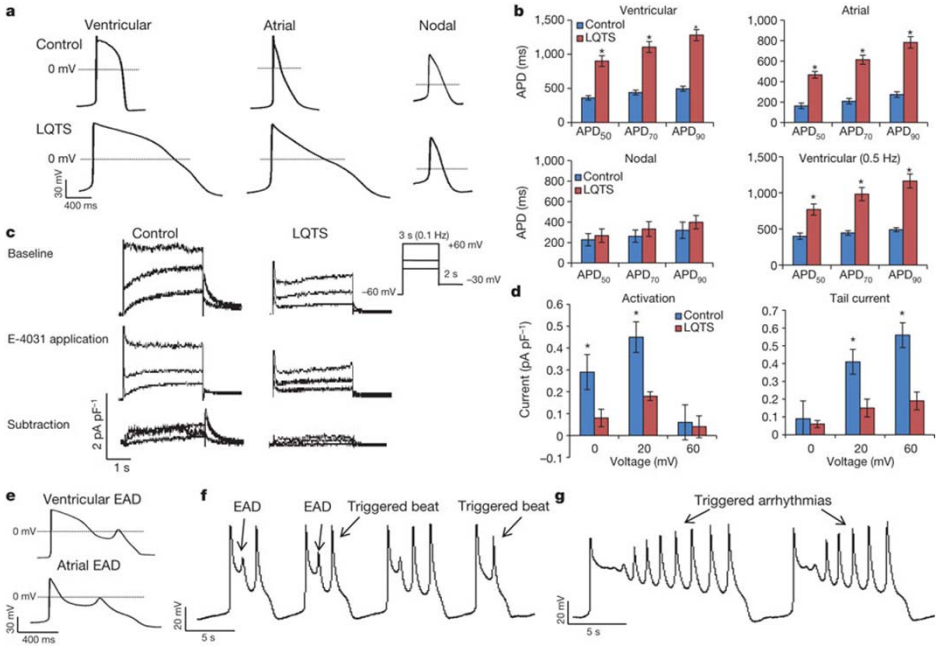
I Itzhaki *et al. Nature* **000**, 1-5 (2010) doi:10.1038/nature09747

Phenotypic characterization of LQTS human iPSC-derived cardiac-tissue.



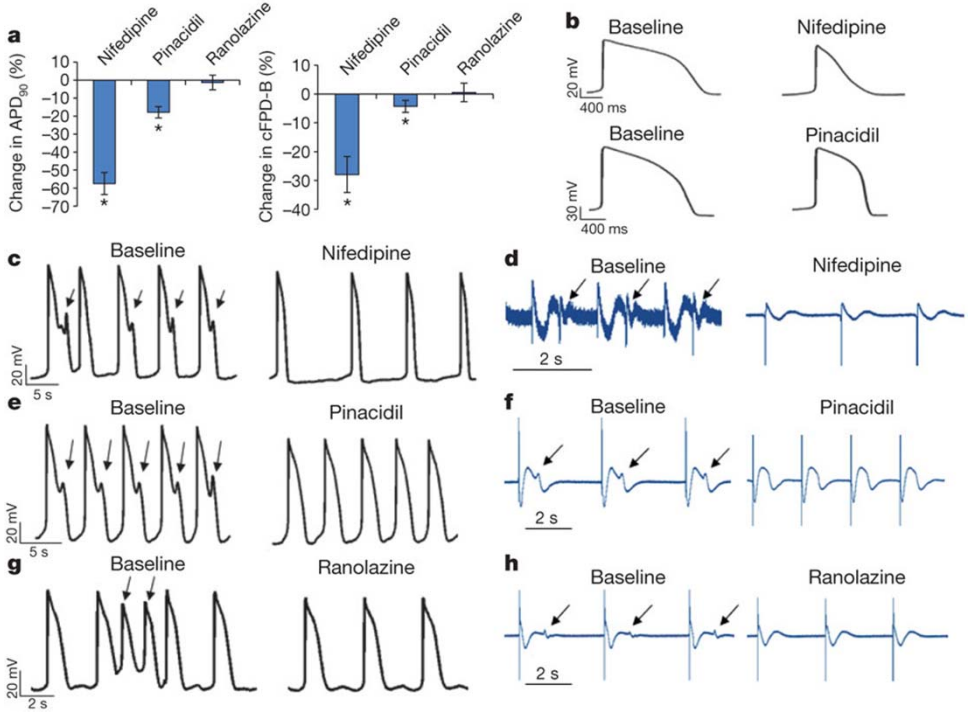
I Itzhaki *et al. Nature* **000**, 1-5 (2010) doi:10.1038/nature09747

Whole-cell patch-clamp recording from human iPSC-CMs.



I Itzhaki *et al. Nature* **000**, 1-5 (2010) doi:10.1038/nature09747

Drug screening using LQTS human iPSC-CMs.



I Itzhaki *et al. Nature* **000**, 1-5 (2010) doi:10.1038/nature09747

Brugada Syndrome

Table 1. Brugada and Related Arrhythmia Syndromes

Brugada Syndrome (BrS), Conduction Disease (CoD), Atrial Arrhythmia (AA)						
Gene	Locus	Syndrome	Protein & subunit	Function & abnormality	Occurs In [¶]	Ref.
SCN5A	3p21	BrS1, CoD	$Na_V1.5$ α	I_{Na} ↓	20-30%	3,14
GPD1L [+]	3p24	BrS2, SIDS [&]	G3PD1L	I_{Na} ↓	< 1%	15,16,25,26
SCN5A	3p21	SUND [*]	$Na_V1.5$ α	I_{Na} ↓	common	17
SCN5A	3p21	Progressive CoD [#]	$Na_V1.5$ α	I_{Na} ↓	common	4
SCN5A	3p21	BrS1, CoD, AA	$Na_V1.5$ α	I_{Na} ↓	?	18
SCN5A	3p21	BrS1, LQTS3	$Na_V1.5$ α	I_{Na} ↓	?	9,19,20
SCN5A	3p21	BrS1, LQTS3, CoD	$Na_V1.5$ α	I_{Na} ↓	?	21
SCN5A	3p21	iVF [$], CoD	$Na_V1.5$ α	I_{Na} ↓	?	22
SCN5A	3p21	DCM, CoD, AA (AF)	$Na_V1.5$ α	I_{Na} ↓	common	7,8,23
SCN5A	3p21	BrS1, SIDS [&]	$Na_V1.5$ α	I_{Na} ↓	?	24
SCN5A	3p21	BrS1, CoD, SIDS [&]	$Na_V1.5$ α	I_{Na} ↓	common	11

For a review of inherited conduction system abnormalities including mutations of genes not related to ion membrane transport, please see Wolf & Berul.[183] Genes contributing to distinct phenotypes are marked similarly for ease of comparison within and between tables 1 through 5. ↓ indicates loss of function; ?, unknown.

[¶]Relative syndromic occurrence for a given genetic syndrome (in %).

[+]Glycerol-3-phosphate dehydrogenase 1–like gene.

[&]Sudden infant death syndrome: An estimated 10 to 15% of SIDS stems from LQTS-, BrS-, and CPVT-causing mutations. Approximately 50% of ion channel–related SIDS involves defects in *SCN5A* or other components of the Na^+ channel macromolecular complex.

*Sudden unexpected nocturnal death syndrome: estimated mortality rate 26 to 38/100 000 in young Thai men.

[#]Lenègre-Lev disease (fibrofatty atrophy of the His-Purkinje system).

[$]Idiopathic ventricular fibrillation without ECG signs of BrS1.

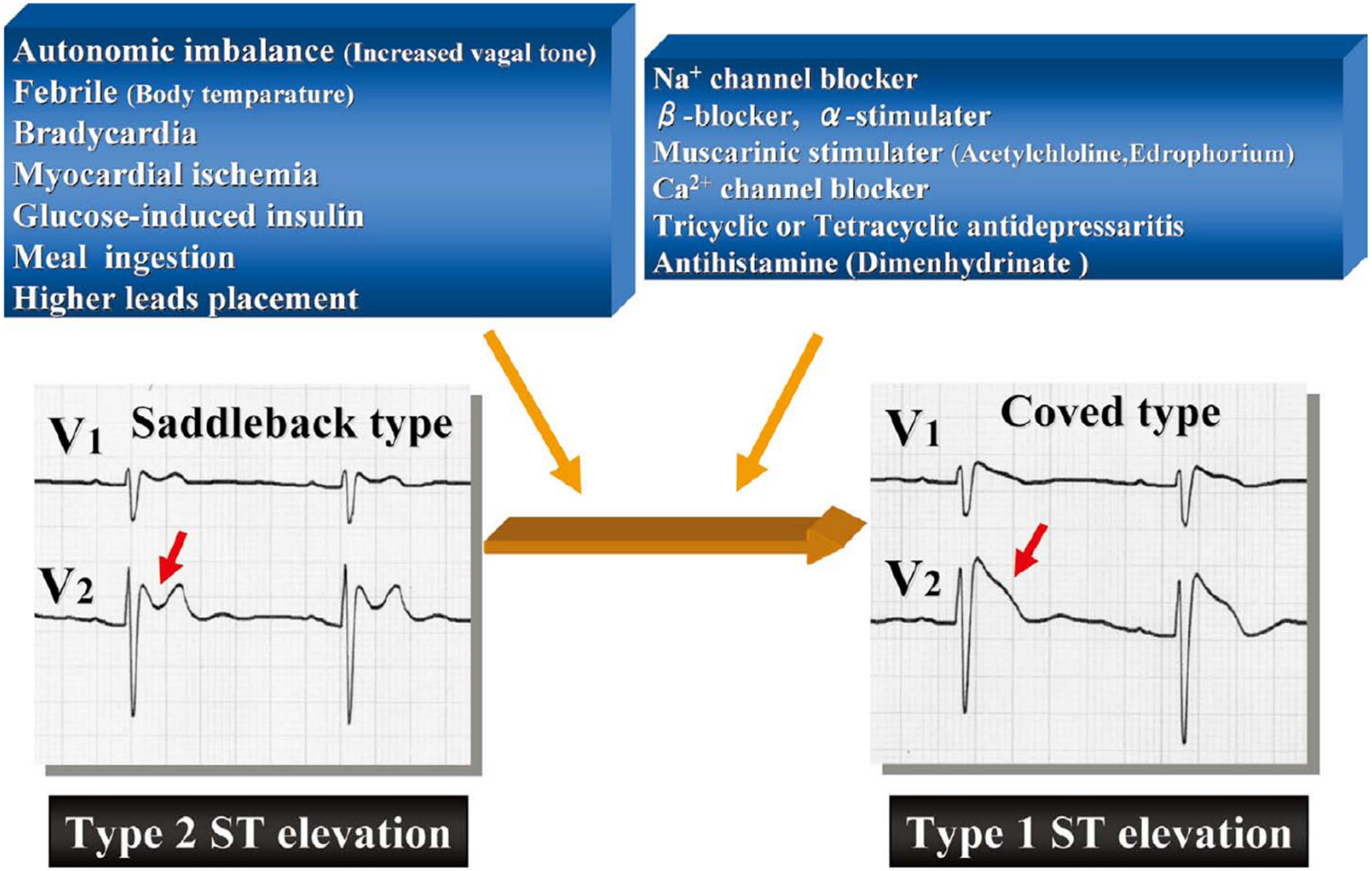


Figure 1. Multiple factors influencing ST-T wave in Brugada syndrome. Type 1 ECG (coved type ST-segment elevation) developed from non-type 1 (saddleback type) by various factors, including antiarrhythmic drugs.

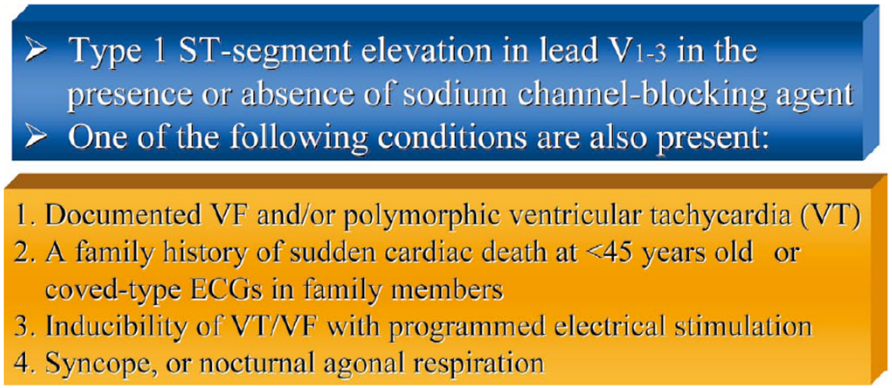


Figure 2. Diagnostic criteria of Brugada syndrome. (Adapted from the Report of the Second Consensus Conference.[12]) VF, ventricular fibrillation.

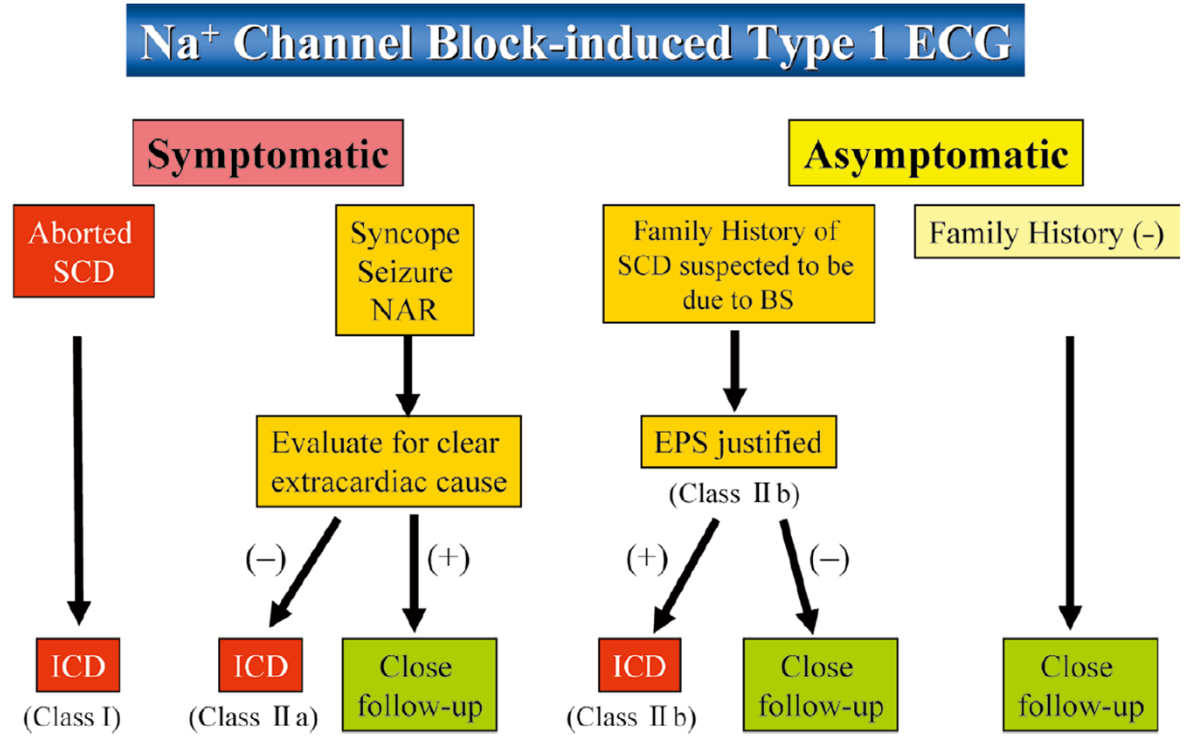
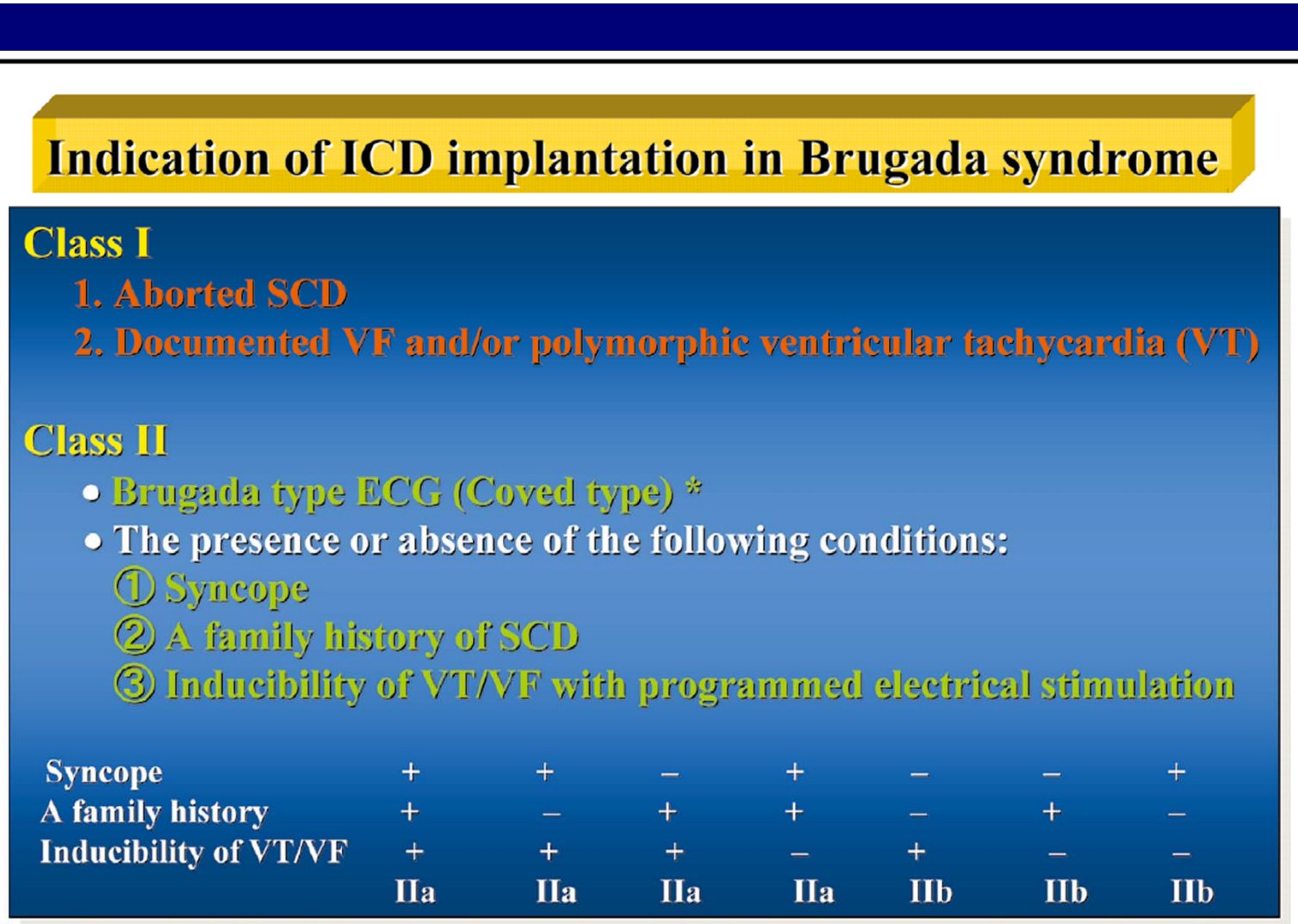
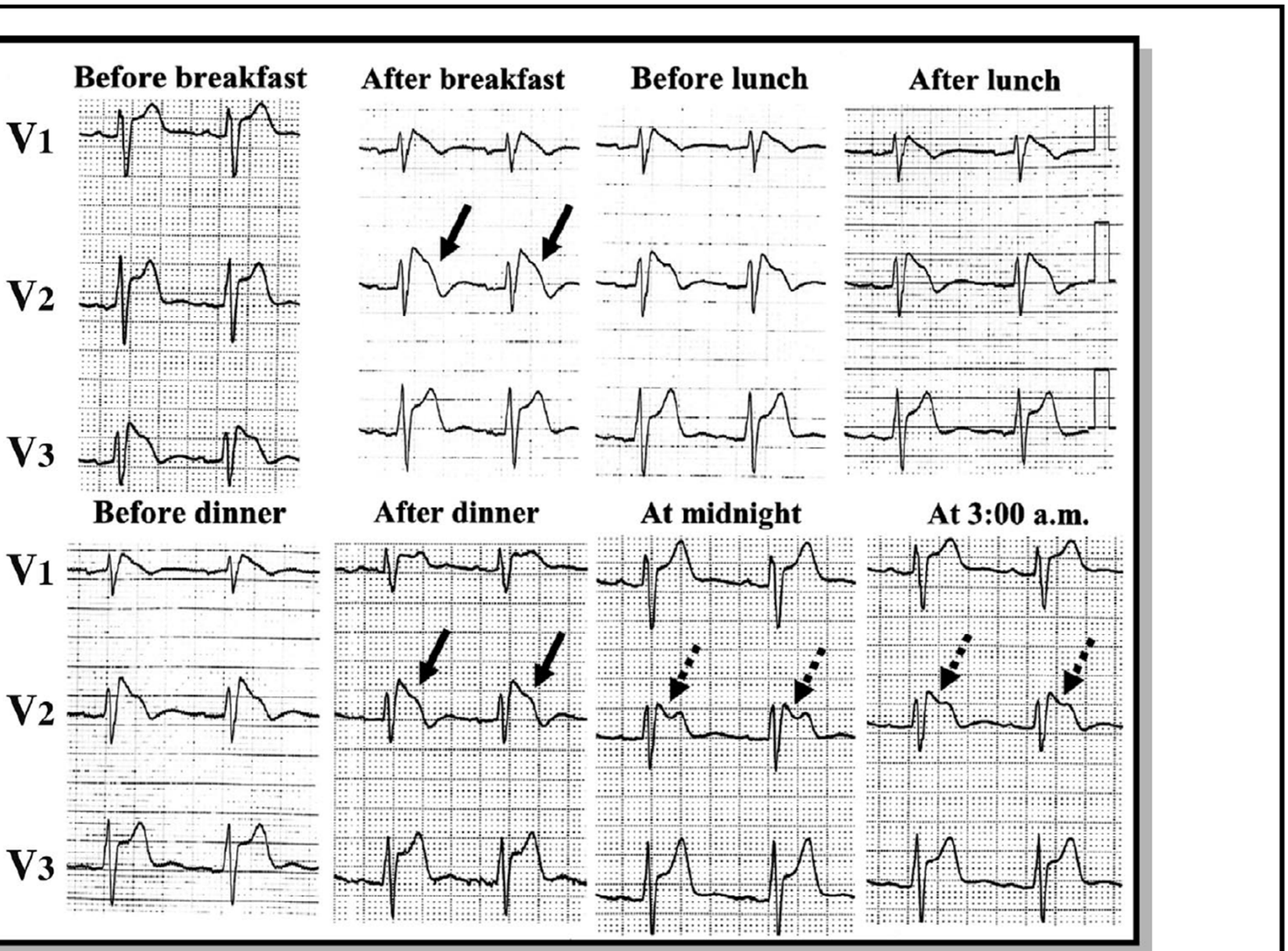
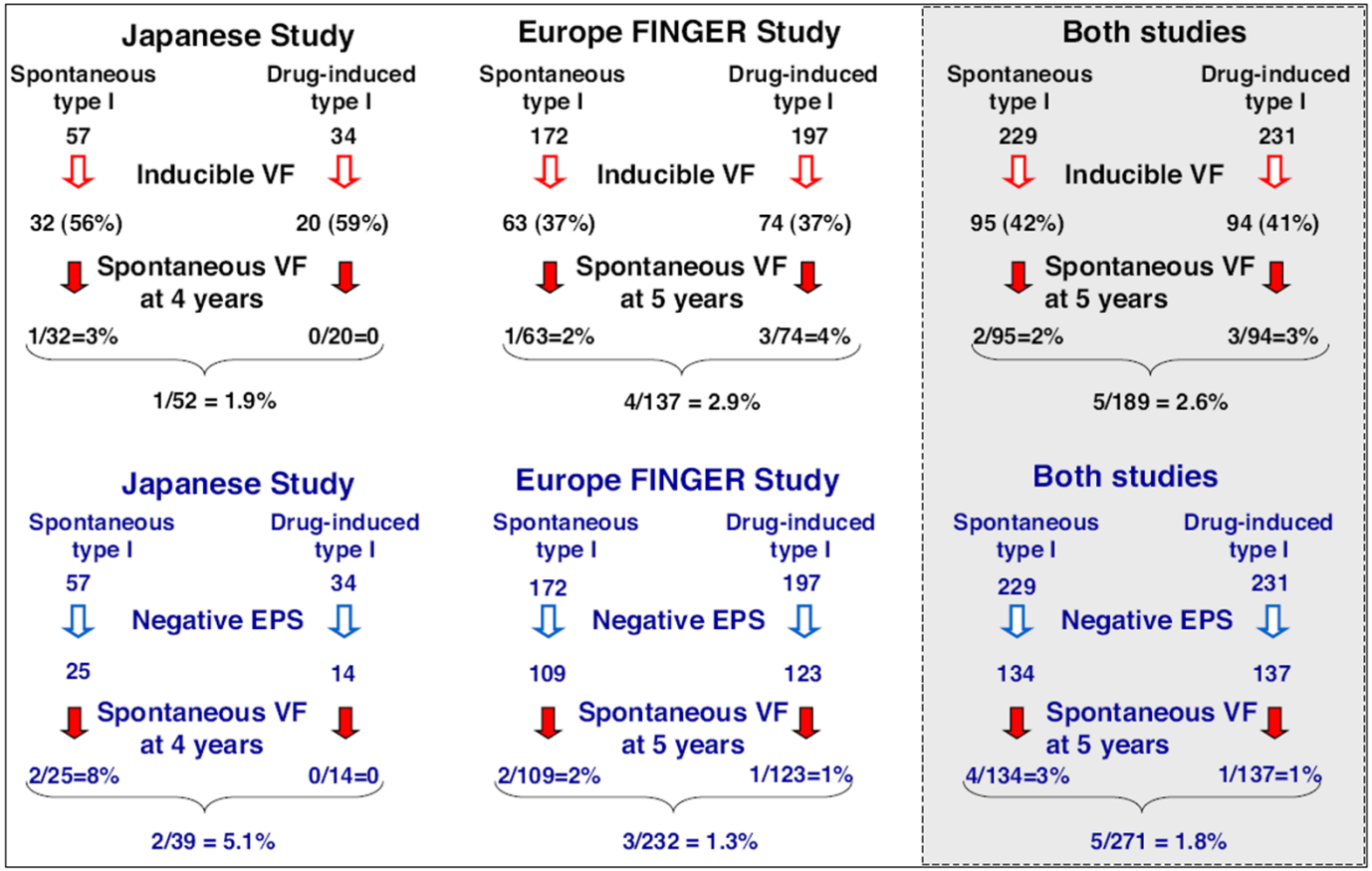


Figure 3. Proposed recommendation for ICD implantation in patients with a sodium-channel-blocker-induced type 1 ECG in Brugada syndrome. (Adapted from the Report of the Second Consensus Conference.[12]) BS, Brugada syndrome; EPS, electrophysiologic study; ICD, implantable cardioverter defibrillator; NAR, nocturnal agonal respiration; SCD, sudden cardiac death.



Indication for ICD implantation in Brugada syndrome. (Adapted from the guideline of Japanese Circulation Society.[36])
ng coved type ECG after drug provocation or in a superior lead position (at third intercostal space). ICD, implantable


Before breakfast
After breakfast
Before lunch
After lunch
V1
V2
V3
Before dinner
After dinner
At midnight
At 3:00 a.m.
V1
V2
V3



Outcomes of Patients With Asymptomatic Brugada Syndrome*

a from 2 recent large prospective studies (10,11). EPS = electrophysiologic study; VF = ventricular fibrillation.

감사합니다