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Medizinische Fakultät Mannheim
der Universität Heidelberg

Universitätsklinikum Mannheim

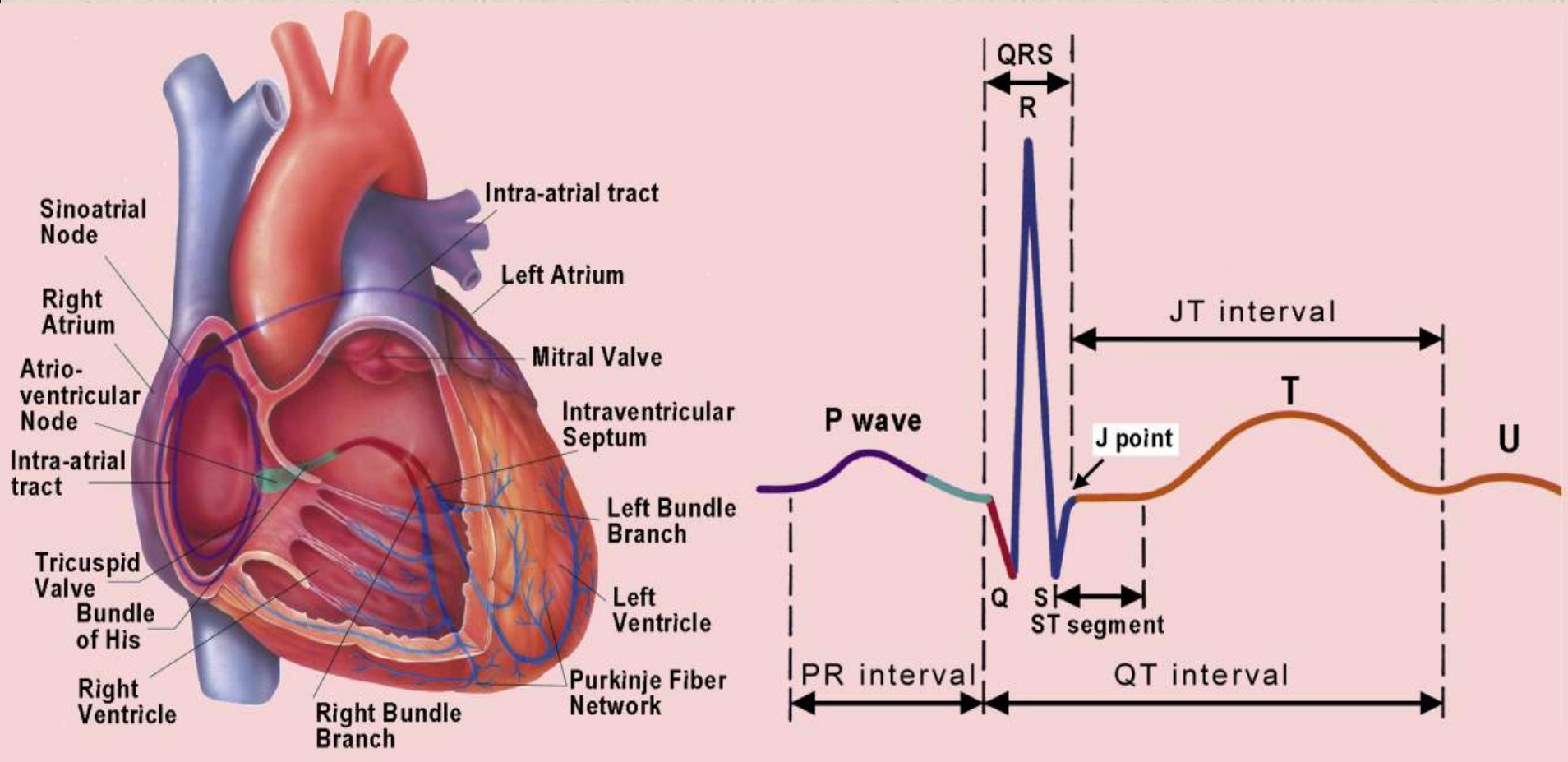
Session IX
Personalized risk assessment of sudden cardiac death

How to manage a patient with long QT Syndrome?

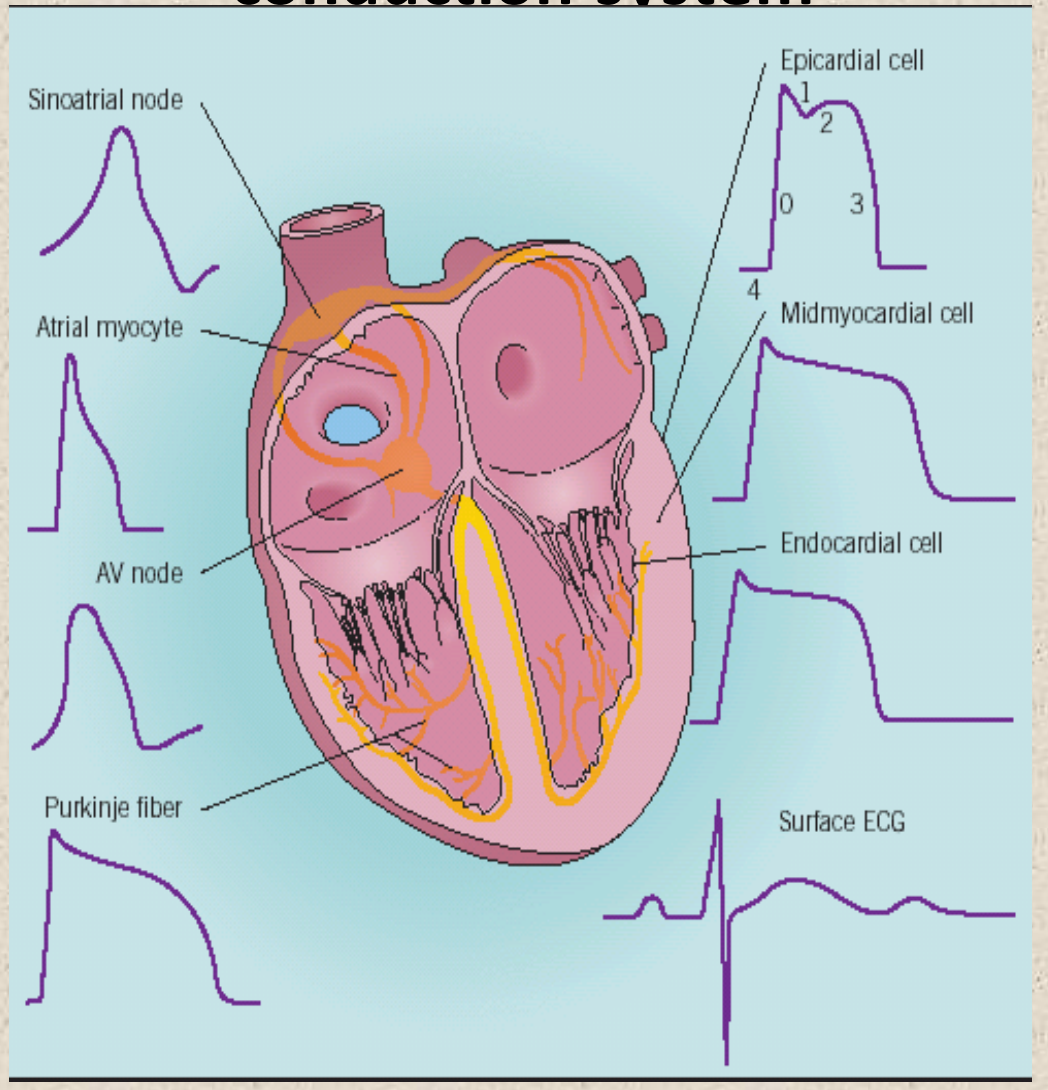
Prof. Martin Borggrefe
Universitätsmedizin Mannheim

10. Symposium on Advances in Cardiac Disease
25.10. – 27.10.2012, Torino

Correlation of Cardiac Electrical System Anatomy and ECG

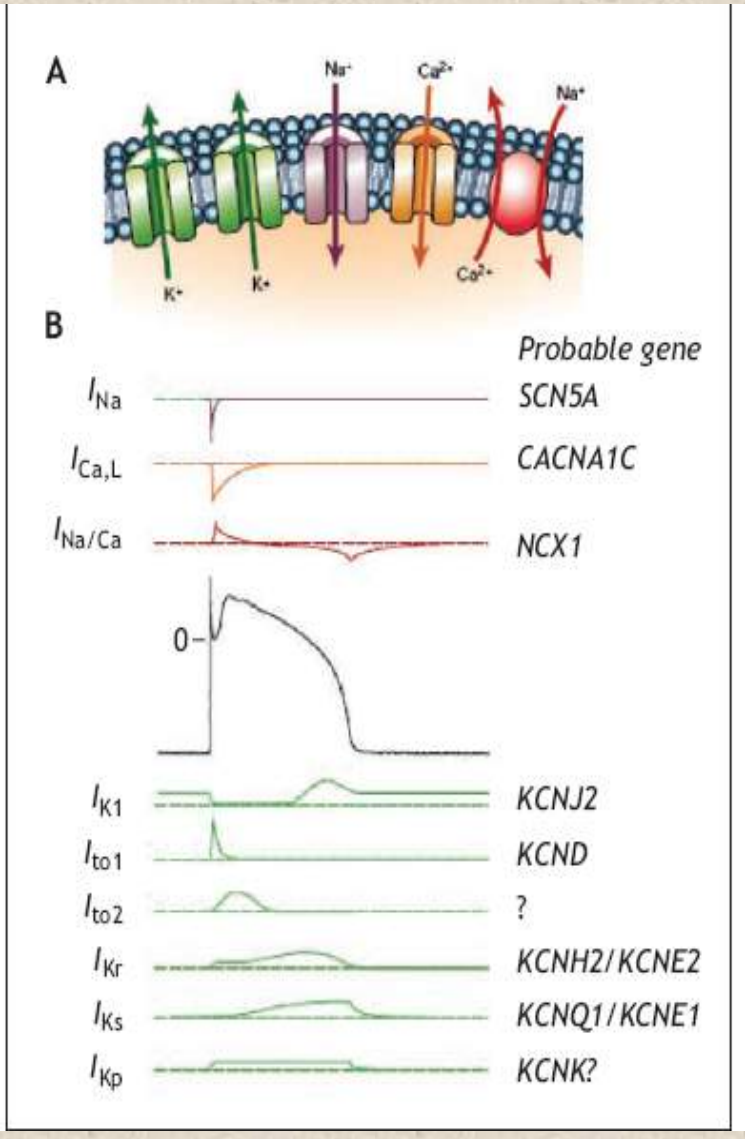


Action potential morphologies in different parts of the conduction system



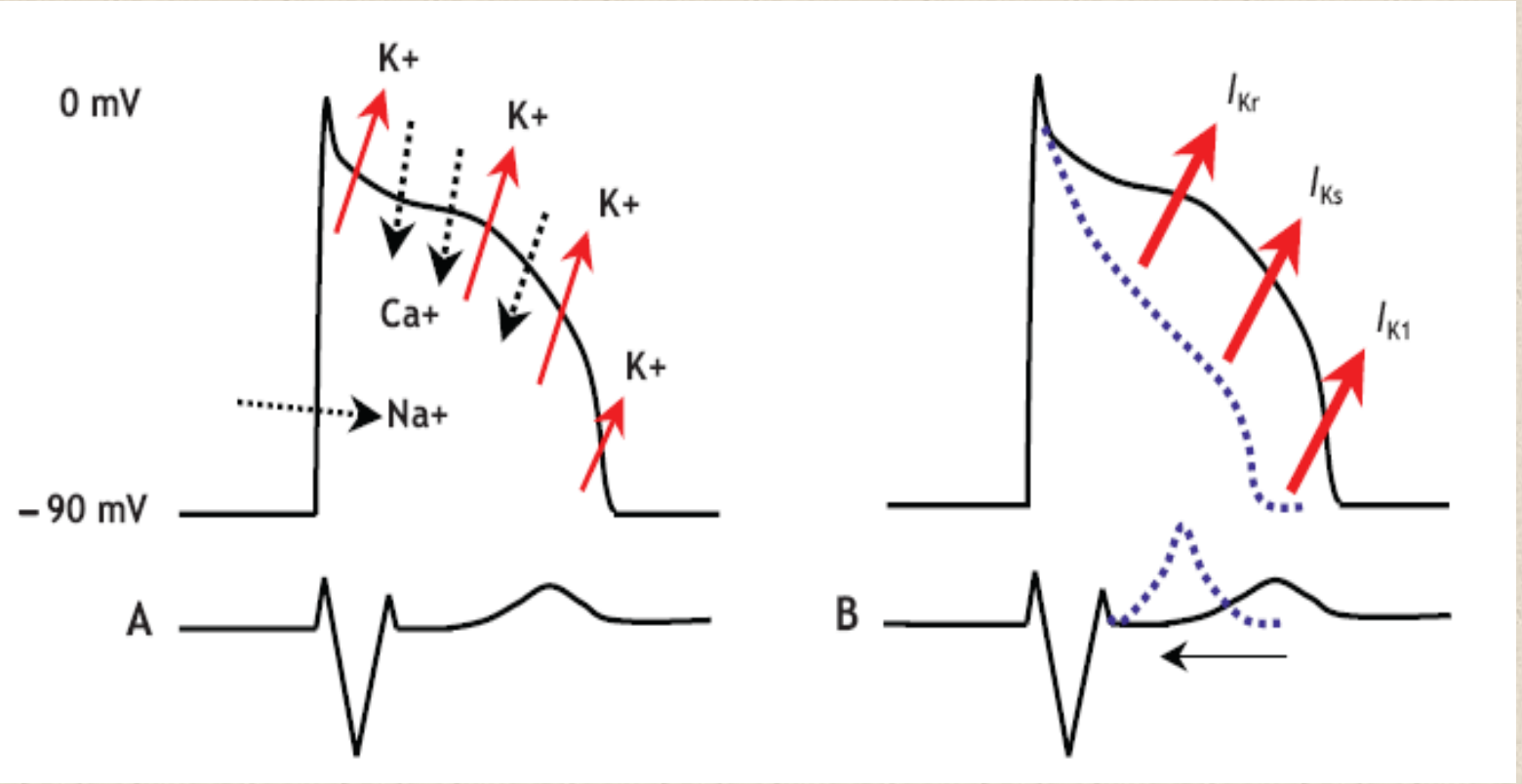
Anderson & Roden, Cardiac Arrhythmias: Basic Cardiac Electrophysiology and Anatomy in Cardiology 2E, edited by Crawford, DiMarco and Paulus, 2004 Elsevier

Cardiac AP

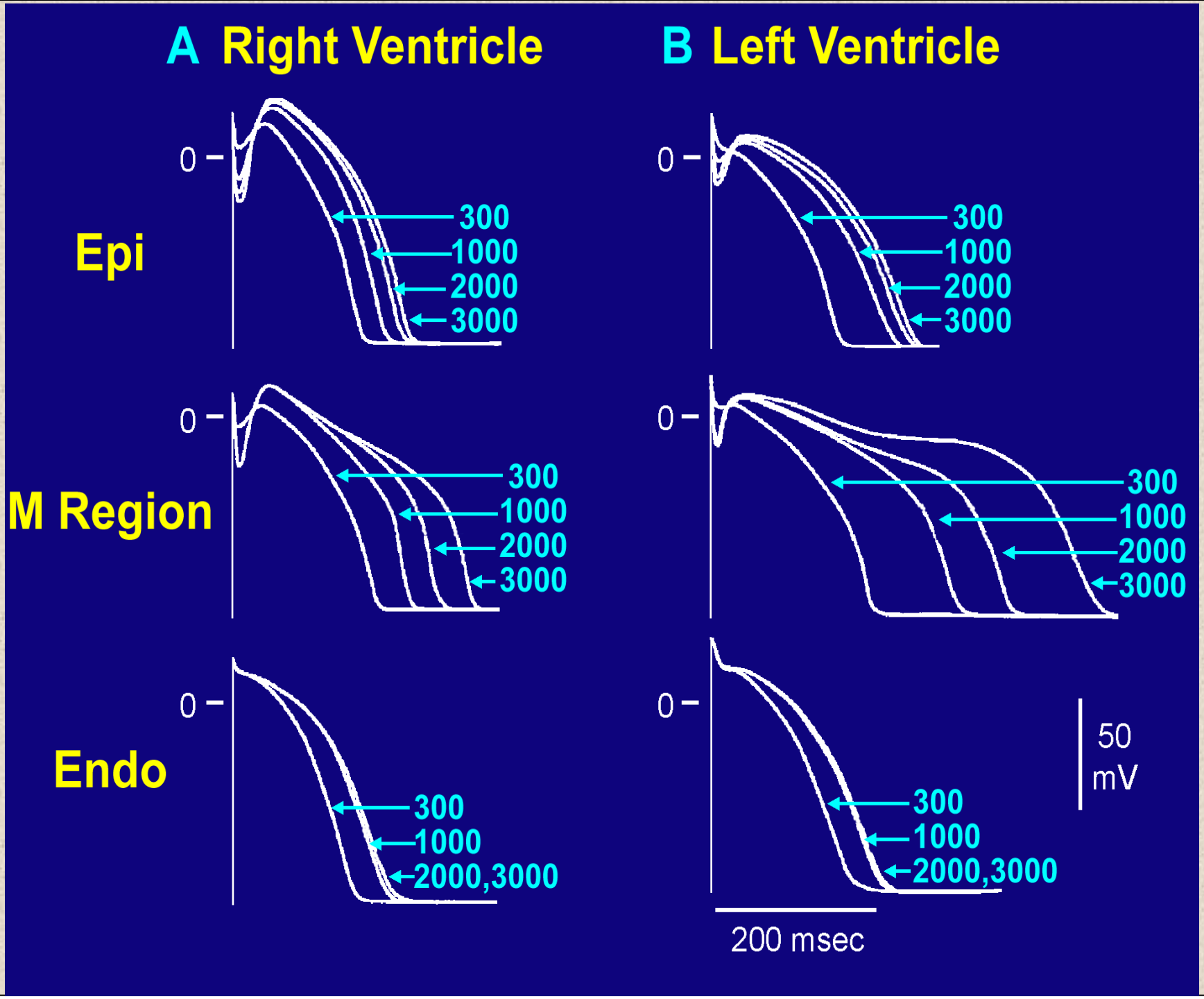


Brugada et al, CMAJ 2005; 3: 1349 - 1354

Cardiac AP



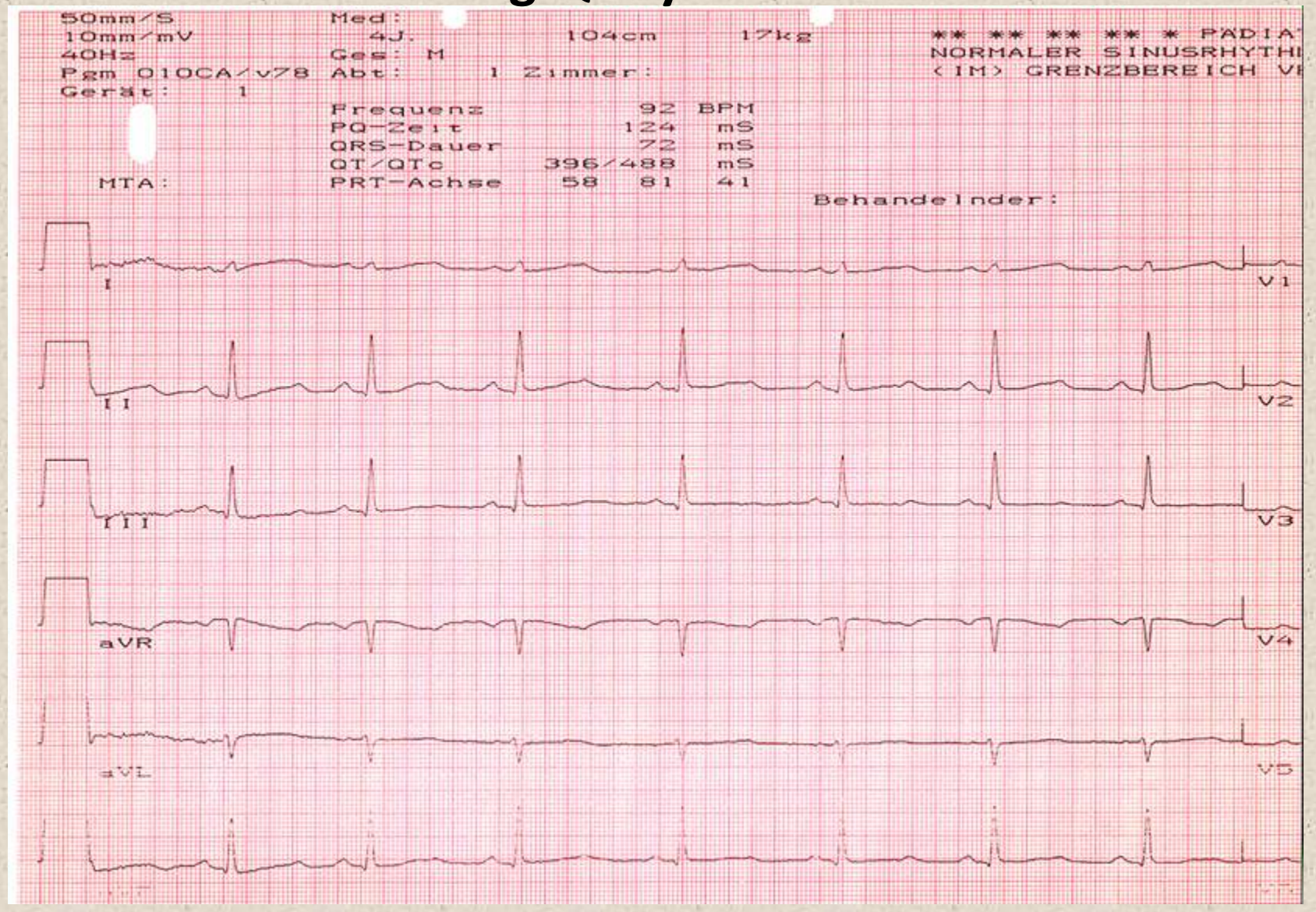
Brugada et al, CMAJ 2005; 3: 1349 - 1354


A Right Ventricle
B Left Ventricle
Epi
M Region
Endo
0
300
1000
2000
3000
2000,3000
50
mV
200 msec

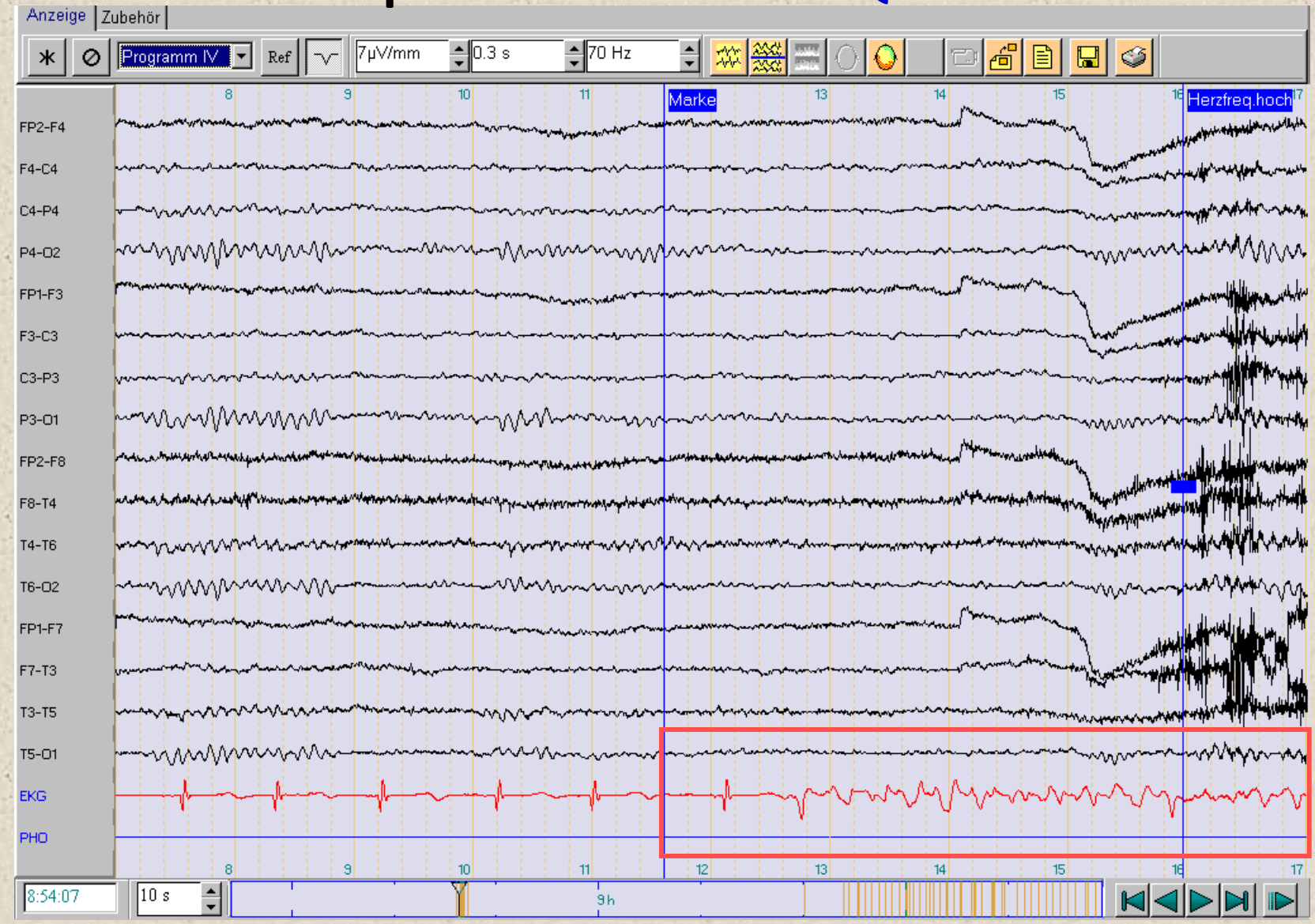
Amplification of Spatial Dispersion of Repolarization Underlies Polymorphic VT/VF

➢ Long QT Syndrome	Preferential prolongation of APD of M cells
➢ Brugada Syndrome	Preferential abbreviation of APD of RV epicardium
➢ Short QT Syndrome	Preferential abbreviation of APD of Endo- or Epicardium
➢ Catecholaminergic VT	Reversal of the direction of activation of the ventricular wall

Long QT Syndrome



Spontaneous VF in LQTS

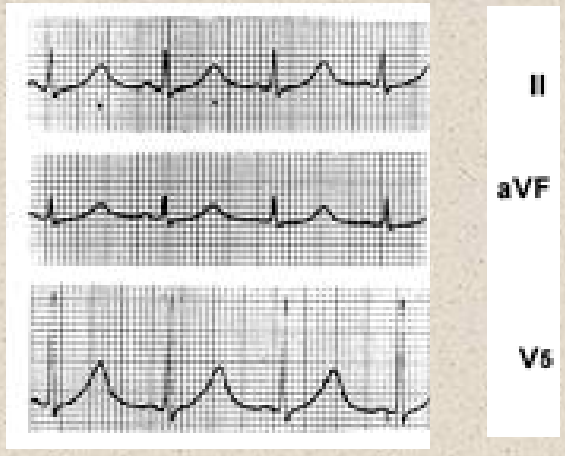


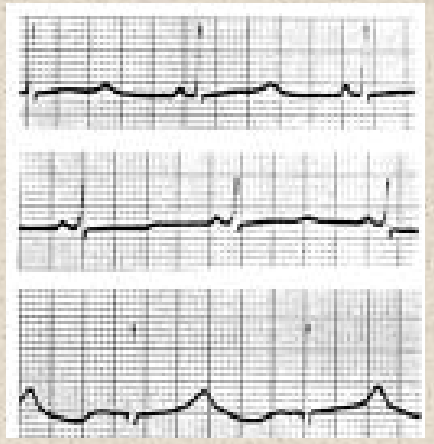
Gene Defects Responsible for the LQTS

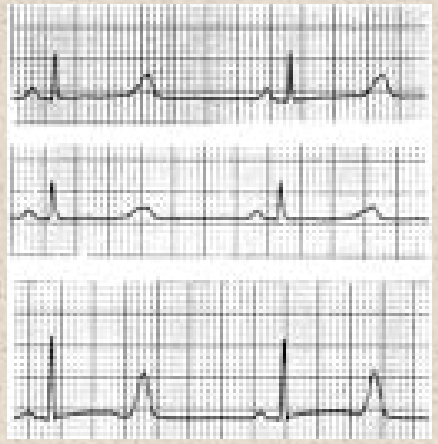
	Chromosome	Gene	Ion Channel
LQT1	11	KCNQ1, KvLQT1	↓ I_{Ks}
LQT2	7	KCNH2, HERG	↓ I_{Kr}
LQT3	3	SCN5A, $Na_V1.5$	↑ Late I_{Na}
LQT4	4	Ankyrin-B, ANK2	↑ Ca_i, ↑Late I_{Na} ?
LQT5	21	KCNE1, minK	↓ I_{Ks}
LQT6	21	KCNE2, MiRP1	↓ I_{Kr}
LQT7*	17	KCNJ2, Kir2.1	↓ I_{K1}
LQT8**	6	CACNA1C, $Ca_V1.2$	↑ I_{Ca}
LQT9	3	CAV3, Caveolin-3	↑ Late I_{Na}
LQT10	11	SCN4B, NavB4	↑ Late I_{Na}
Others?			

* Andersen –Tawil Syndrome
** Timothy Syndrome

ECG in Long QT-1-3 Syndrome







LQT-1

Broad based, prolonged and elevated T wave

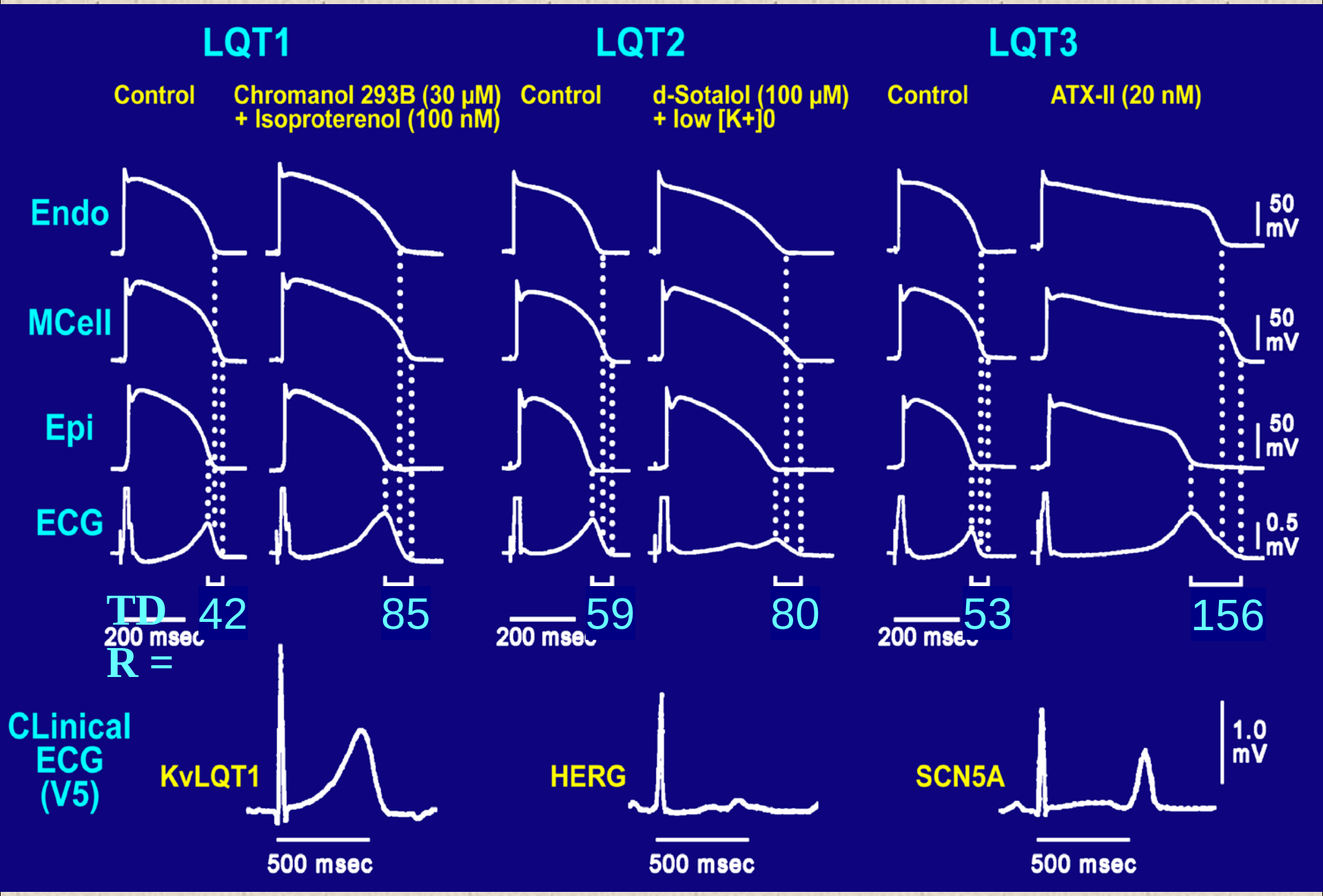
LQT-2

T wave with small amplitude biphasic

LQT-3

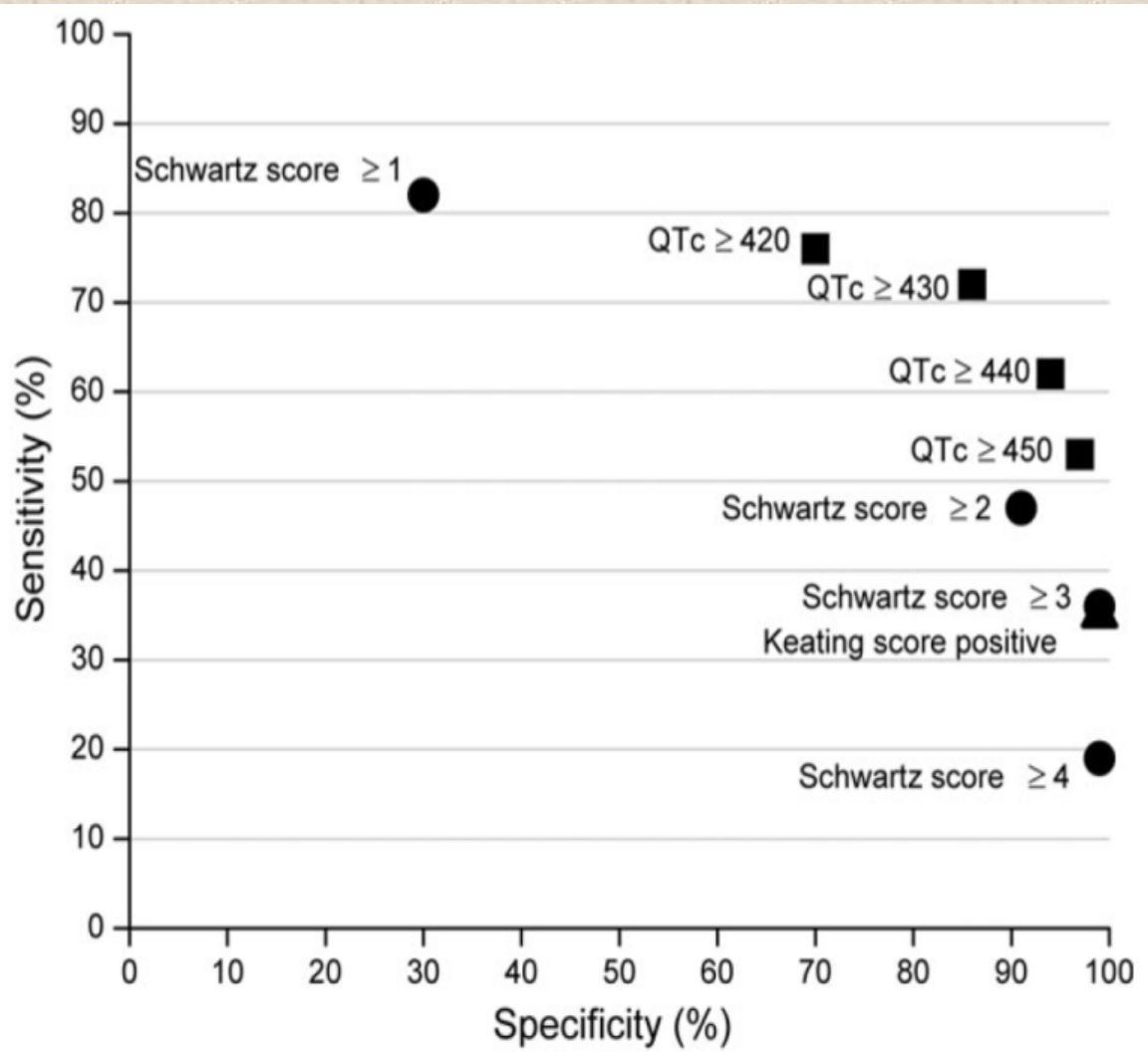
prolonged isoelectric with late T wave

Moss et al. Circulation 1995



Antzelevitch and Shimizu. Curr Opin Cardiol 17, 43-51, 2002

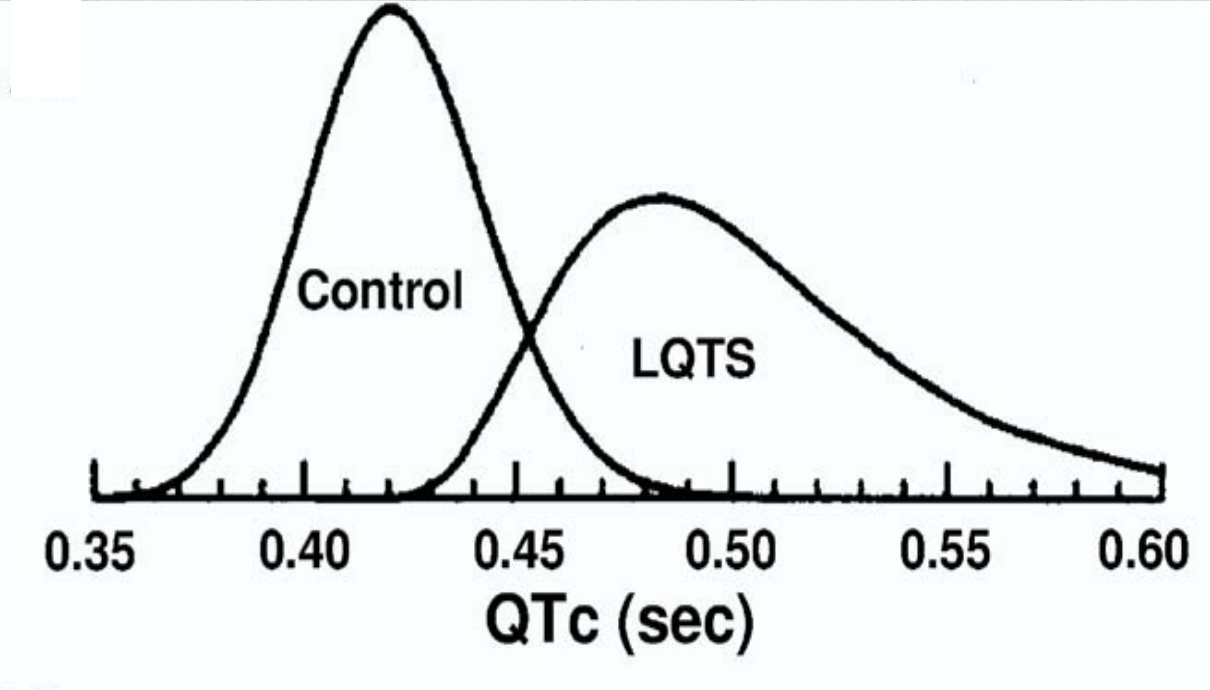
Sensitivity adn specificity of QTc duration in LQTS



Hofman et al, Eur Heart J 2007; 28:575-580

QT interval

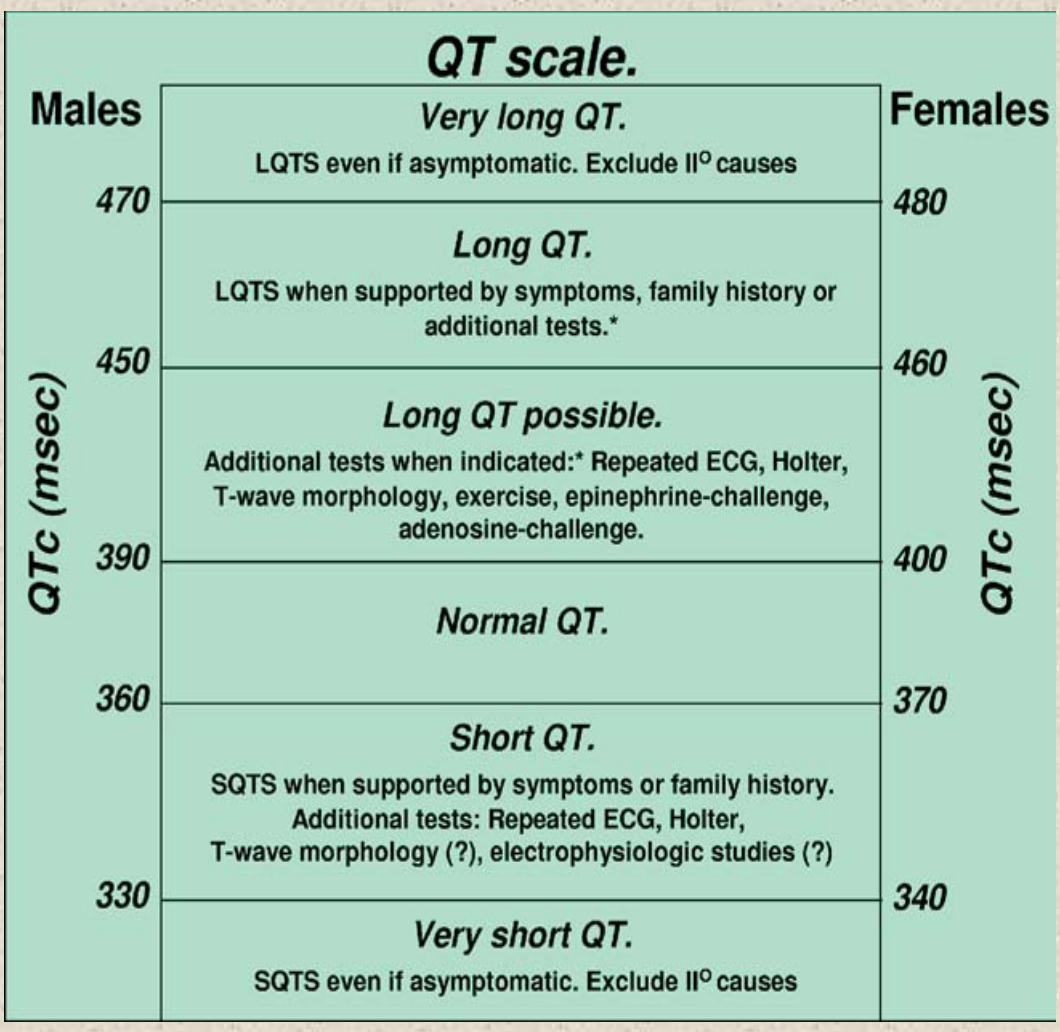
Distribution of QTc intervals of 117 LQTS mutation carriers and 113 healthy relatives (noncarriers) as reported by Vincent's group



Viskin S, Heart Rhythm 2009; 6: 711-715

QT interval

Spectrum of QT intervals



Viskin S, Heart Rhythm 2009; 6: 711-715

Suggested Bazett-Corrected QTc values for diagnosing QT Prolongation

Rating	1–15 yrs	Adult Male	Adult Female
Normal	<440	<430	<450
Borderline	440–460	430–450	450–470
Prolonged	>460	>450	>470

Goldenberg and Moss, JACC, 2008; 51: 2291-2300

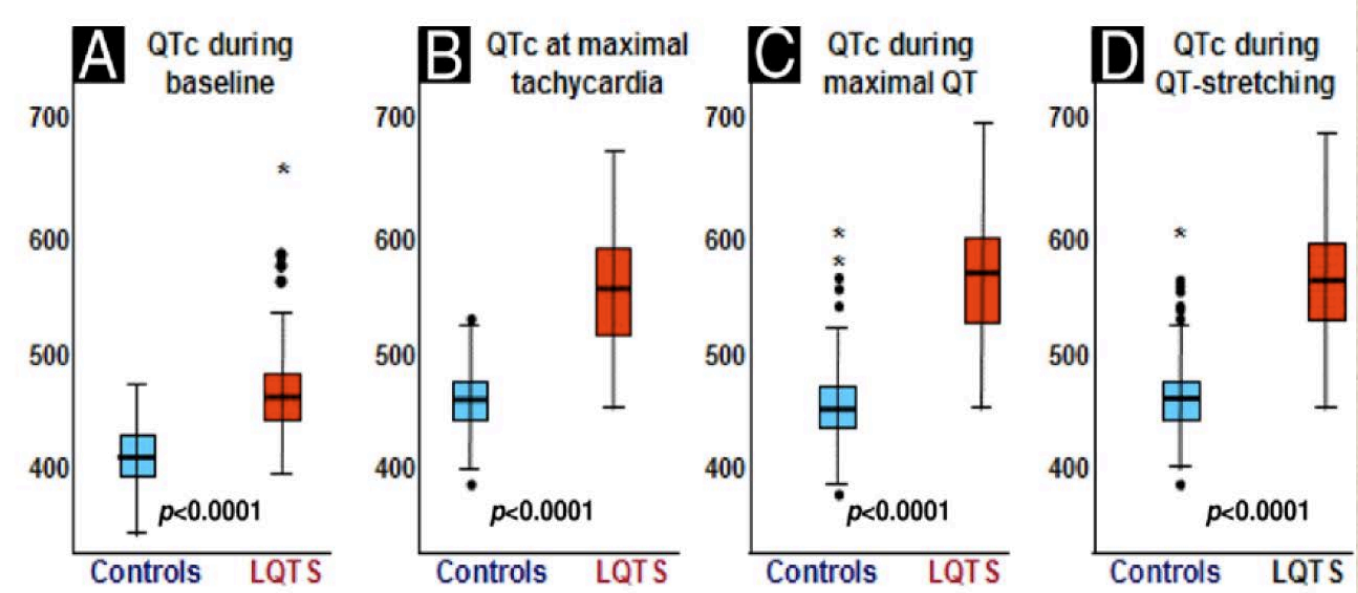
Diagnostic criteria for LQTS

Finding	Score
Electrocardiographic†	
Corrected QT interval, ms	
≥480	3
460–470	2
450 (in males)	1
Torsades de pointes‡	2
T-wave alternans	1
Notched T-wave in 3 leads	1
Low heart rate for age§	0.5
Clinical history	
Syncope‡	
With stress	2
Without stress	1
Congenital deafness	0.5
Family history‖	
Family members with definite LQTS	1
Unexplained SCD in immediate family members <30 yrs old	0.5

Goldenberg and Moss, JACC, 2008; 51: 2291-2300

„Bedside test“ for LQTS Diagnosis

- Incompetence of QT shorting during sudden tachycardia in LQTS
- 68 patients with LQTS, 82 controls, basal QTc 390 – 480ms
- 12 ECG in supine position and after standing up
- ECG analysis at rest, maximal heart rate and maximal QT



Viskin et al JACC 2010

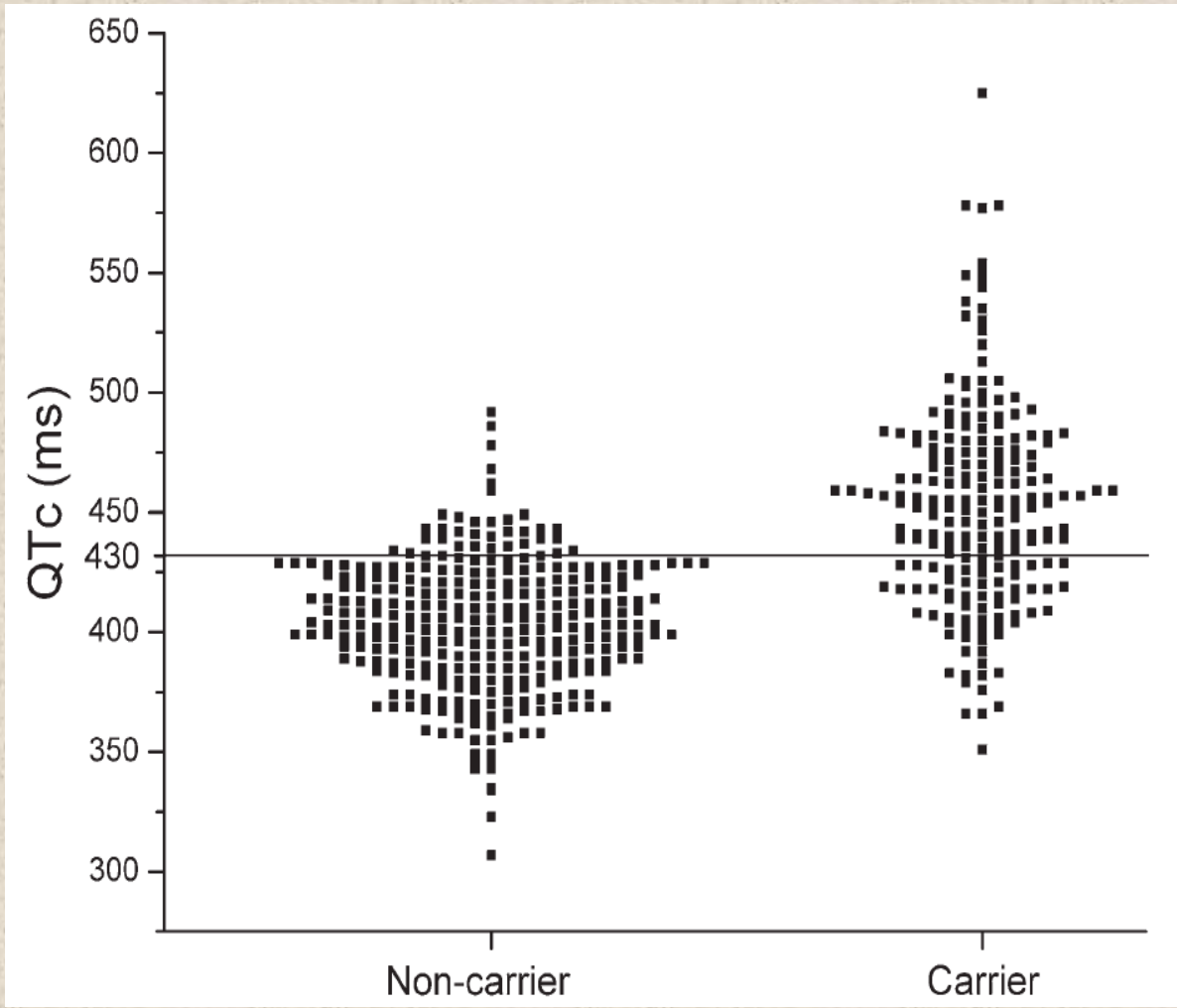
„Bedside test“ for LQTS Diagnosis

Table 3 ROC Curve Analysis of Variables

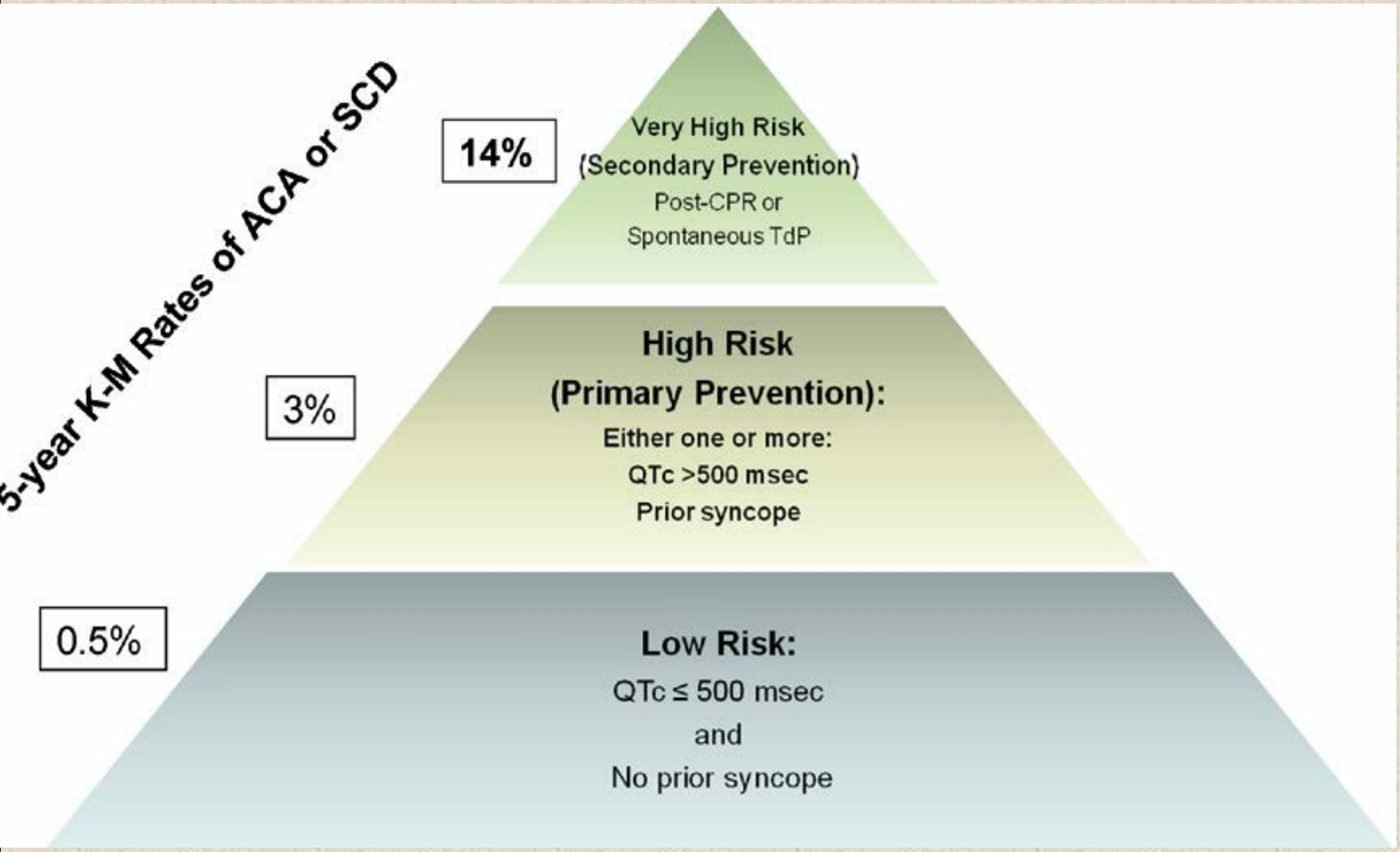
	AUC	95% CI	90% Sensitivity	
			Cutoff	Specificity
Baseline QT interval	0.836	0.758–0.914*	395	50.9%
Baseline QTc interval	0.850	0.775–0.925*	423	61.4%
QT interval at maximal heart rate	0.900	0.840–0.960*	375	70.2%
QTc interval at maximal heart rate	0.933	0.889–0.978*	474	75.4%
QTc interval during QT interval stretching	0.923	0.874–0.973*	487	86.0%

Viskin et al JACC 2010

QTc duration in LQTS



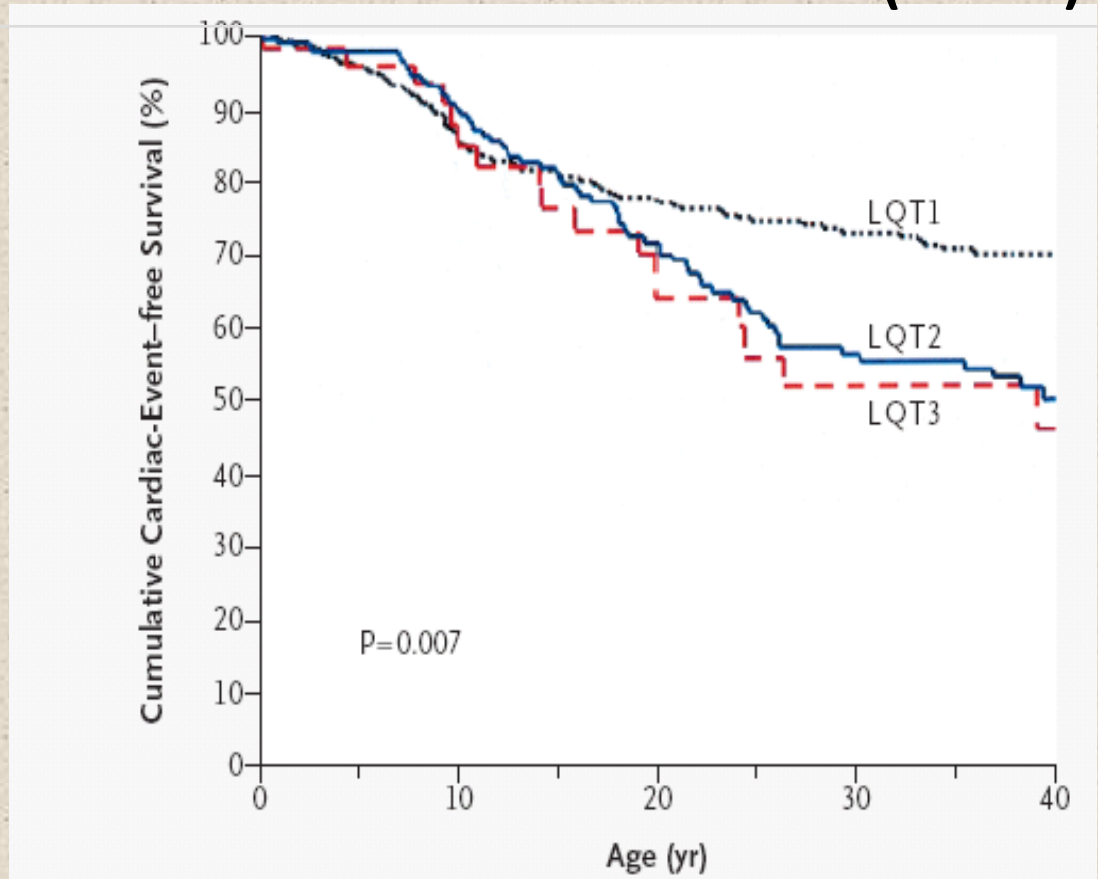
Hofman et al, Eur Heart J 2007; 28:575-580



Goldenberg et al, JACC 2008

Long QT Syndrome

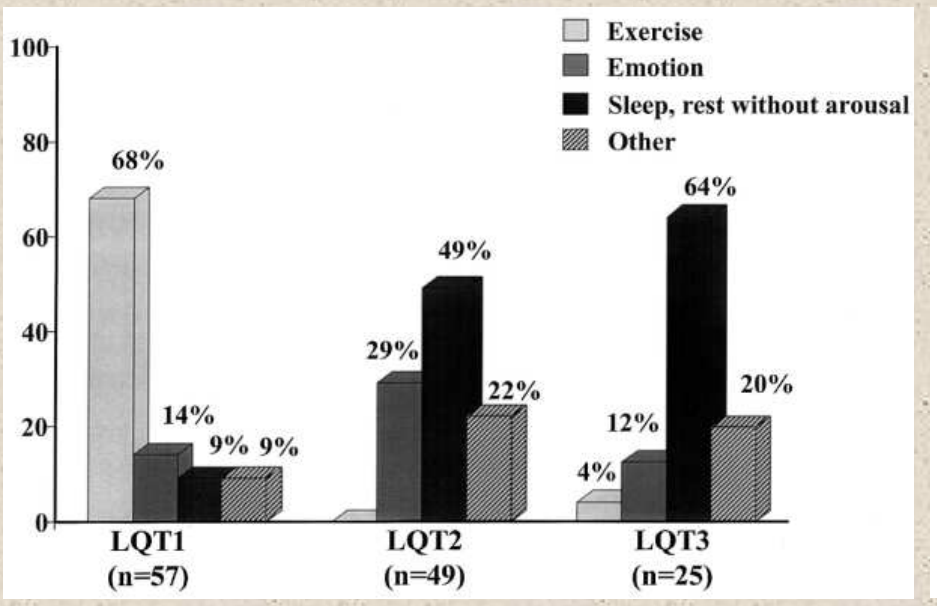
Survival Free of Cardiac Events (n=580)

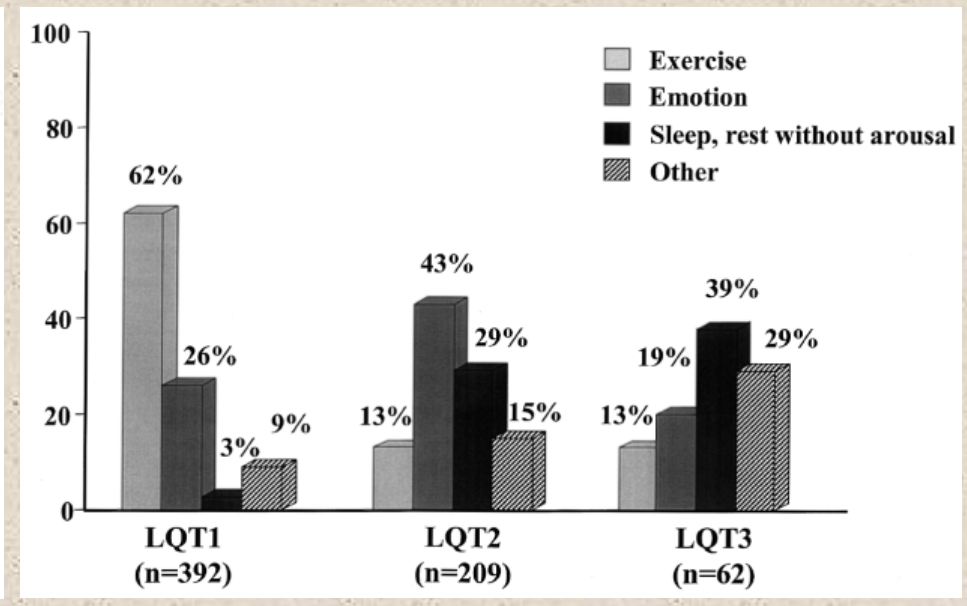


No. at Risk					
LQT1	355	249	192	146	100
LQT2	176	130	187	57	34
LQT3	49	30	20	9	7

Priori et al, N Engl J Med 2003; 348:1866-74

Triggers for sudden death





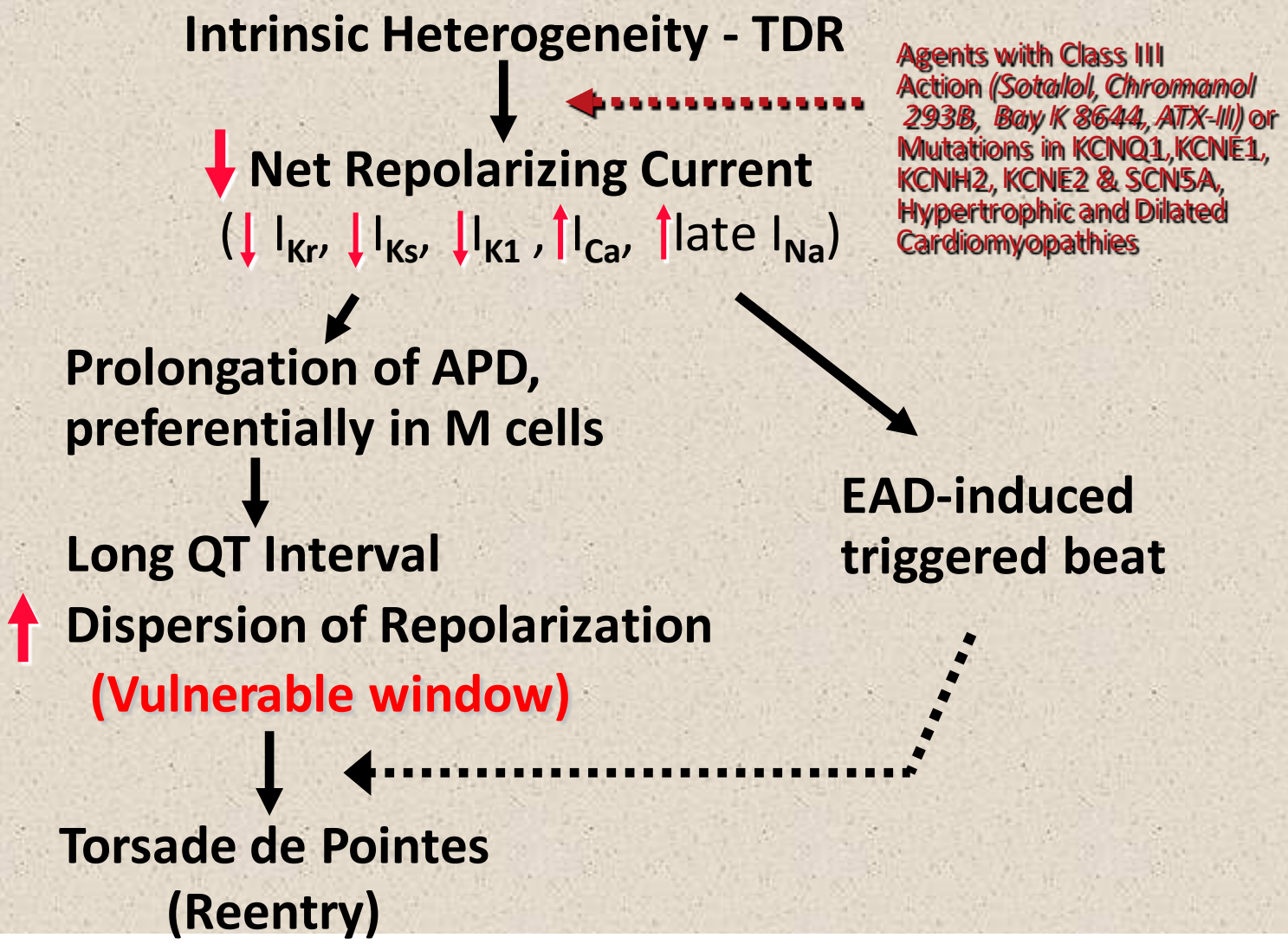
Sudden cardiac death ***Cardiac event***

LQT 1: Emotional, physical stress (swimming)

LQT 2: Emotional, physical stress, sudden loud noise (alarm clock)

LQT 3: rest, sleep

Long QT Syndrome



Drugs associated with LQTS and Torsade de Pointes

Anesthetics
Propofol

Antianginal
Bepridil, Israpidine, Nicardipine

Antiarrhythmic Drugs
Class IA

Quinidine, Procainamide

Disopyramide

Class III

N-acetylprocainamide, sotalol,

Ibutilide, dofetilide

Antibiotics
Erythromycin, Trimethoprim & Sulfamethaxazole, Pentamidine, Clarithromycin

Antihistamines
Terfenedine, Astemizole, diphenhydramine

Muscle Relaxant
Tizanidine

Antifungal Agents
Ketoconazole

Flucoconazole

Itraconazole

Diuretics
Indapamide

Gastrointestinal
Cisapride

Lipid Lowering
Probucol

Psychotropics
Phenothiazines, Tricyclic antidepressants (Amitriptyline)

Haloperidol, Pimozide

Immunosuppressives
Tacrolimus

Sedative/Hypnotics
Chloral hydrate

Positive Inotropic
DPI 201-106

Toxins
Antopleurin-A, ATX-II

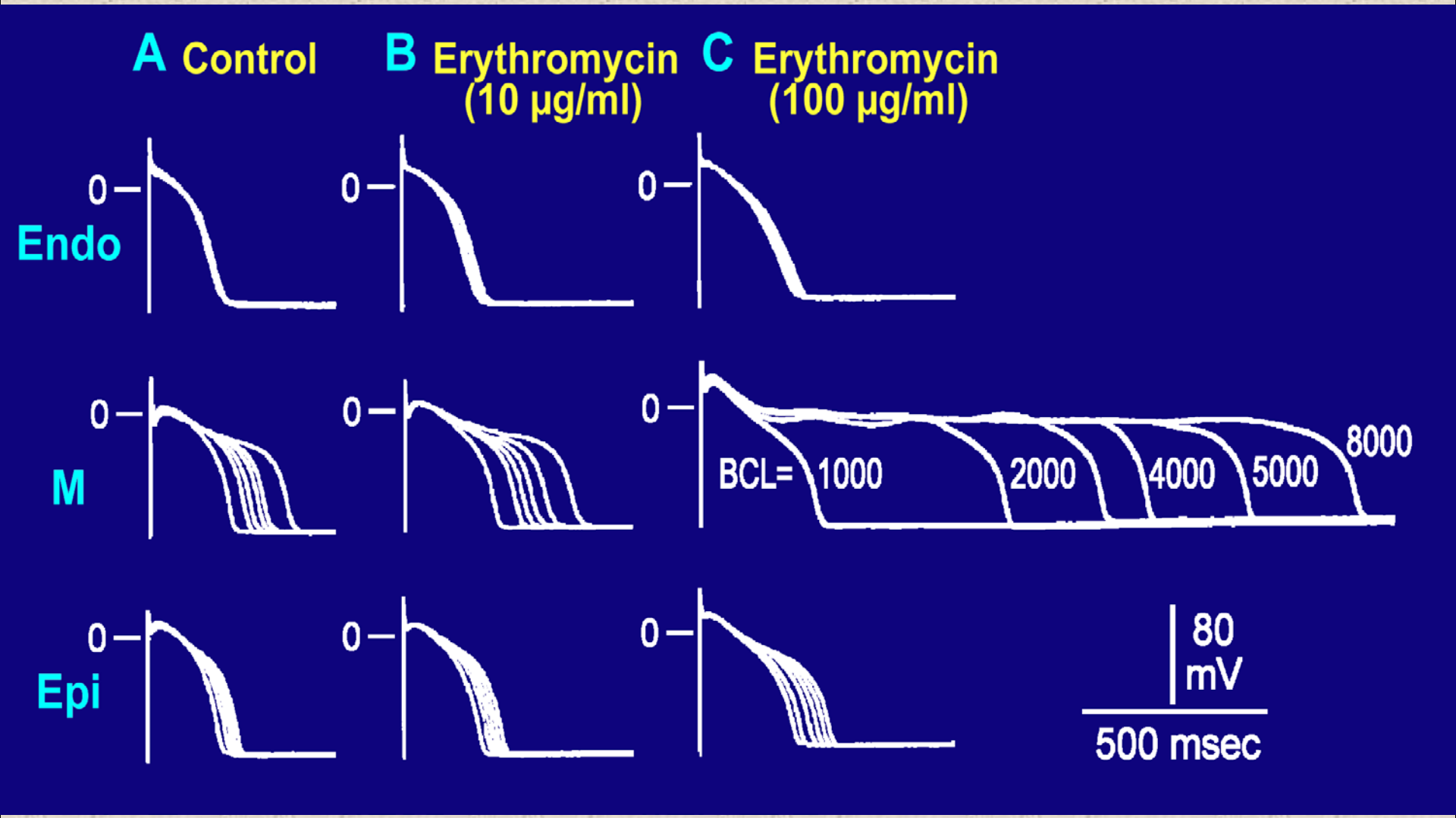
Veratricline

Arsenic

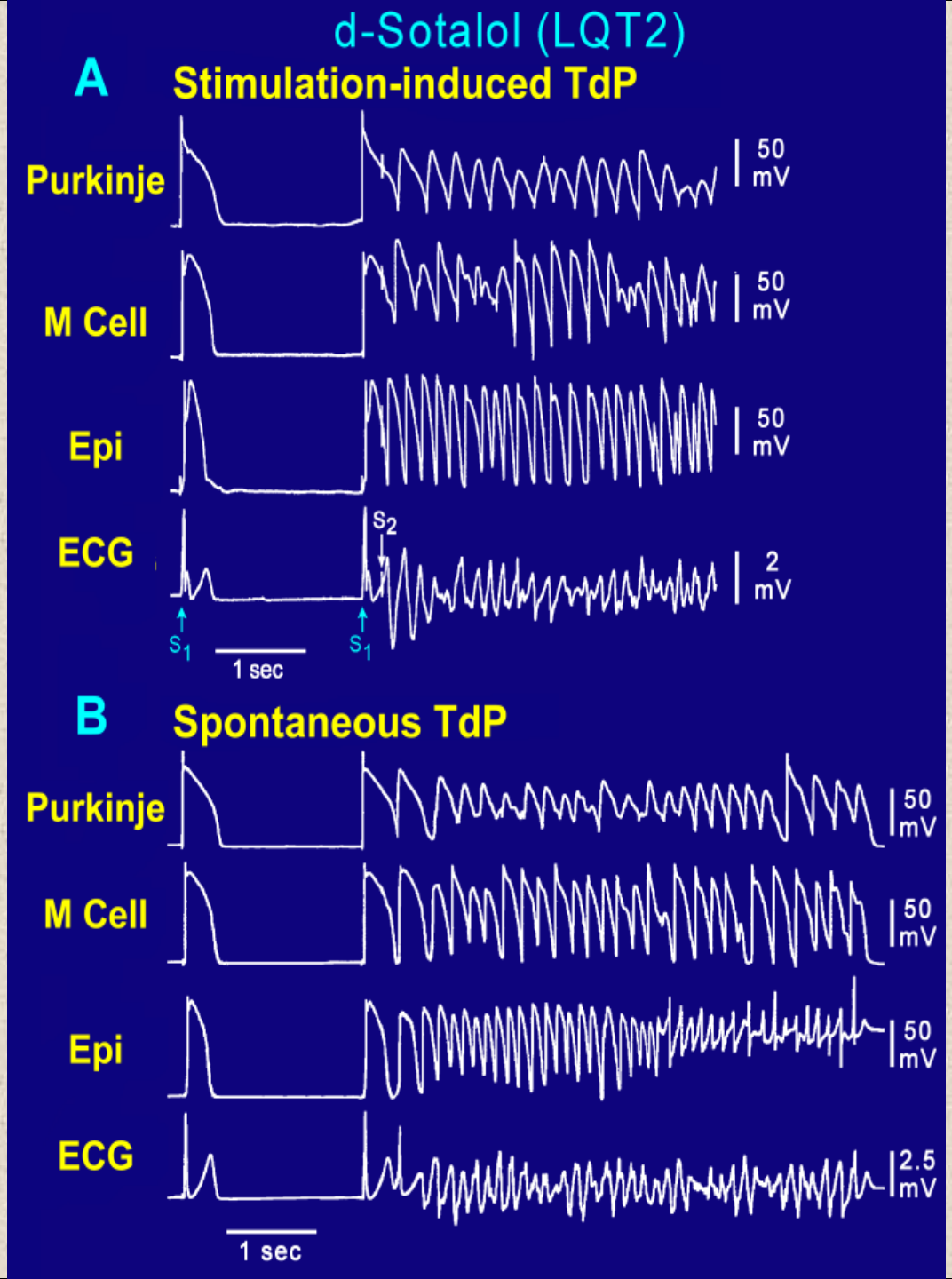
Organophosphate insecticides

Liquid protein diets

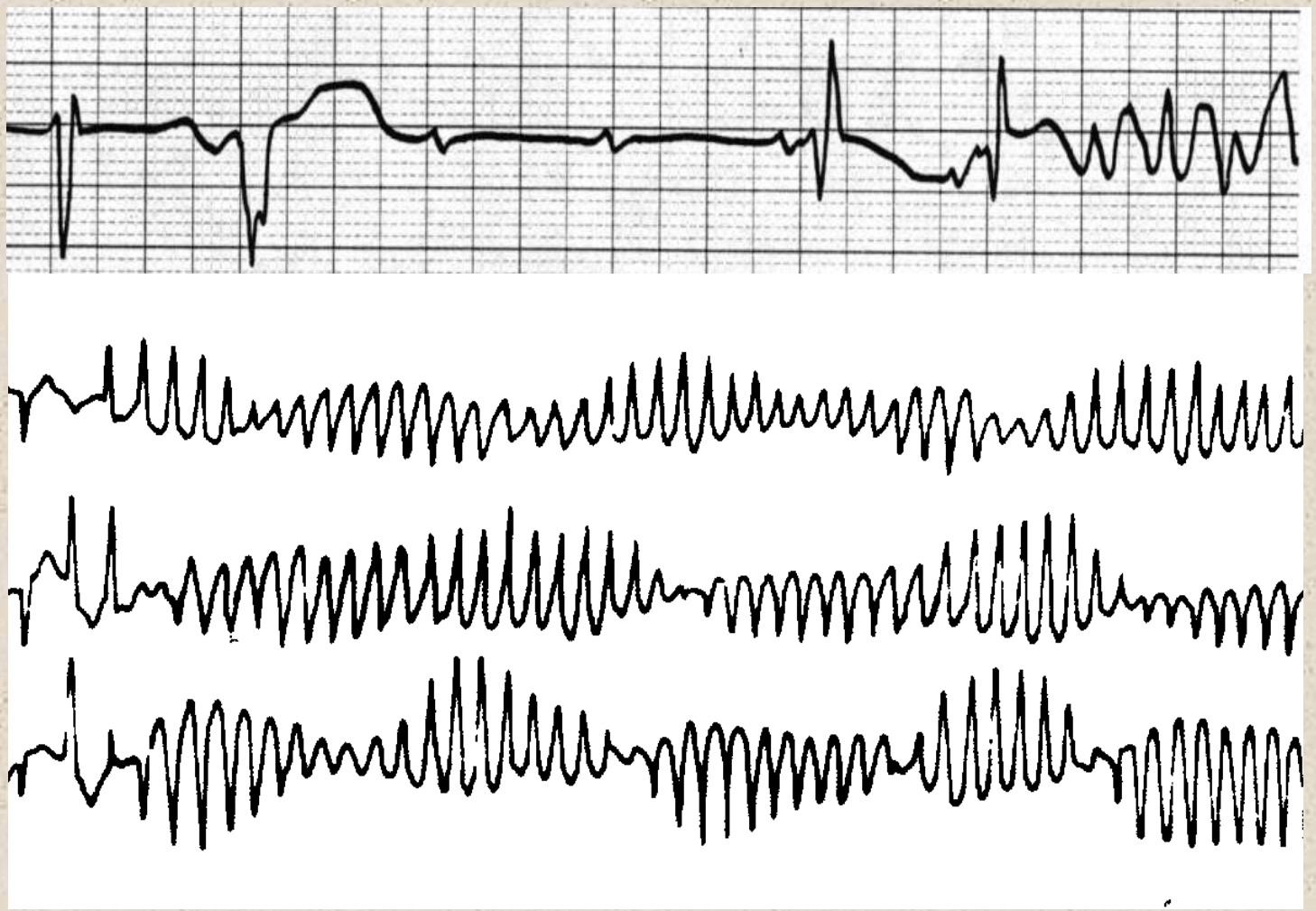
Hypokalemia

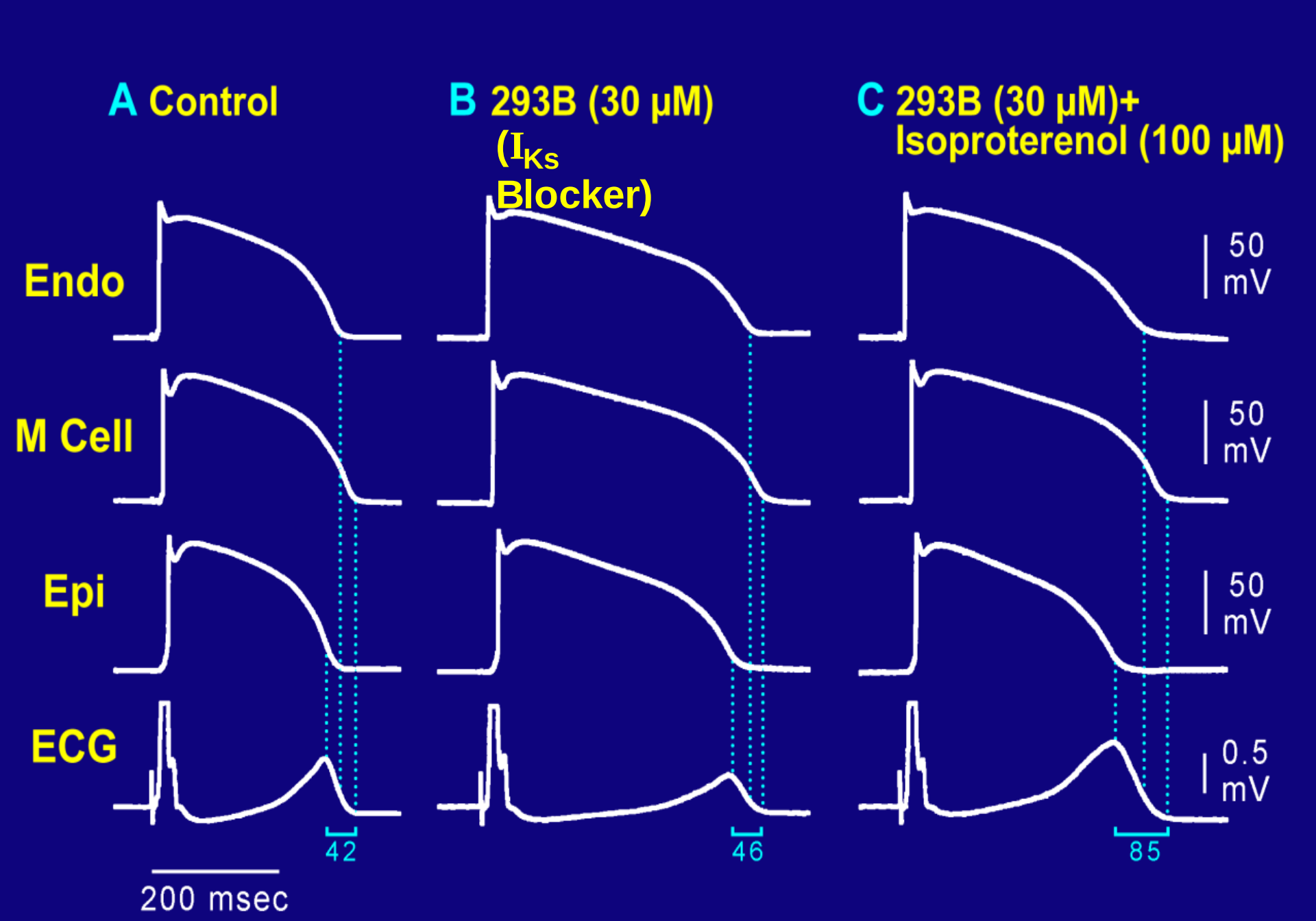


Antzelevitch et al, JACC 28:1836-1848, 1996


d-Sotalol (LQT2)
A
Stimulation-induced TdP
Purkinje
M Cell
Epi
ECG
50 mV
50 mV
50 mV
2 mV
S2
S1
S1
1 sec
B
Spontaneous TdP
Purkinje
M Cell
Epi
ECG
50 mV
50 mV
50 mV
2.5 mV
1 sec

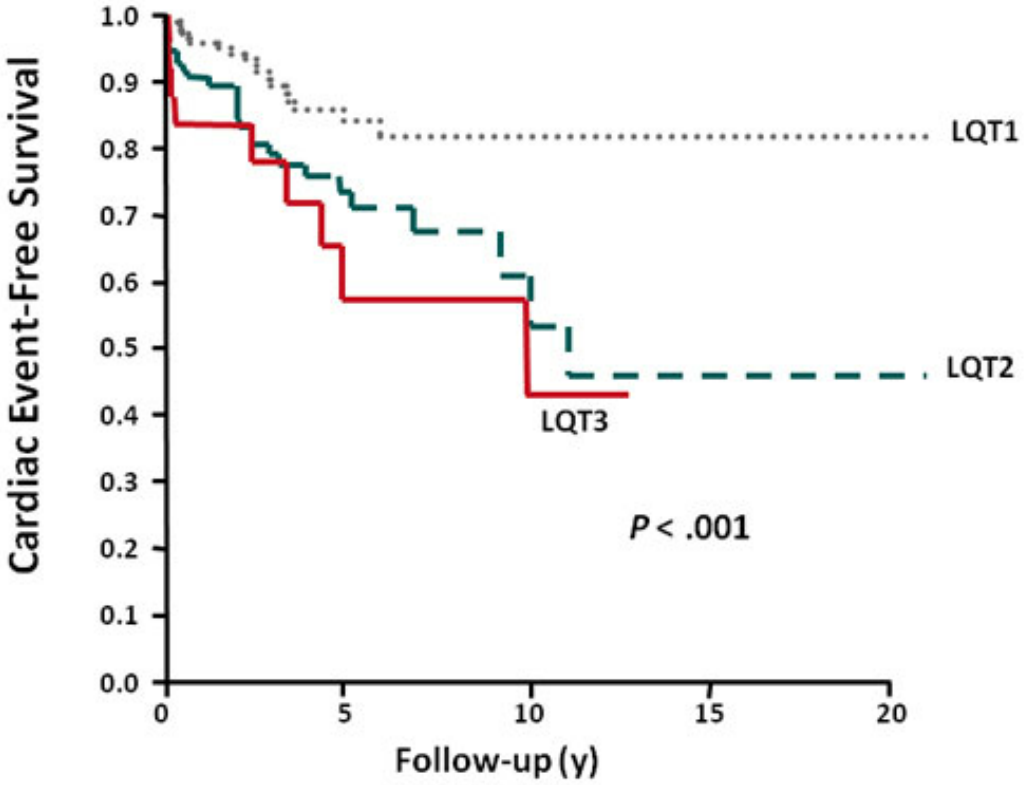
QT Syndrom (LQTS)





Shimizu and Antzelevitch. Circulation 98: 2314-22, 1998

Cardiac Events While on Beta-blockers in LQTS



Adapted from Priori SG, et al. *JAMA*. 2004;292:1341-1344.

International LQT Registry - Outcome

Age	No. of Patients	Symptoms	No. (%) SCD/ACA	Annual event rate
1–12y	3015	21 %	53 (1.8%)	0.15%
10–20y	824	21 %	26 (3.2%)	0.31%
18–40y	812	23 %	50 (6.1%)	0.28%
40–75y	2759	21 %	246 8.9%	0.47%

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Goldenberg et al Circulation 2008;
Hobbs et al JAMA 2006;
Sauer et al JACC 2007

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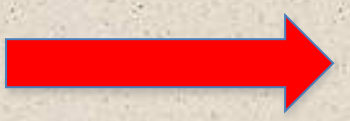
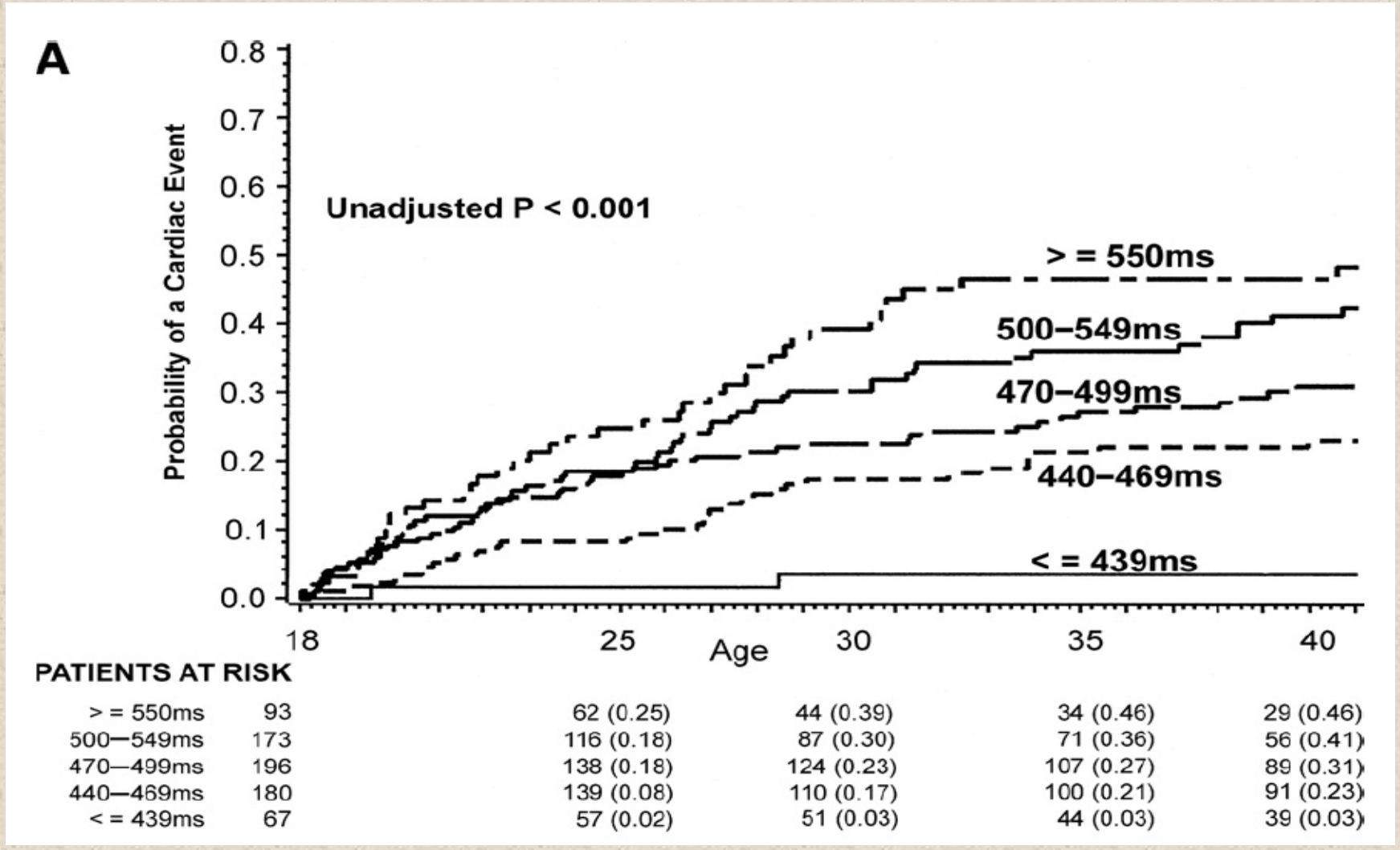
Beta-Blockers in Long QT syndrome

Age	Reduction of ACA/SCD	Patients on beta-blockers
1 – 12y	53 %	21 %
10 – 20y	64 %	14 %
18 – 40y	60 %	18 %
40 - 75y	42 %	31 %
MEAN	55 %	21 %



Mean event rate 0.32 SCD/SCA /year

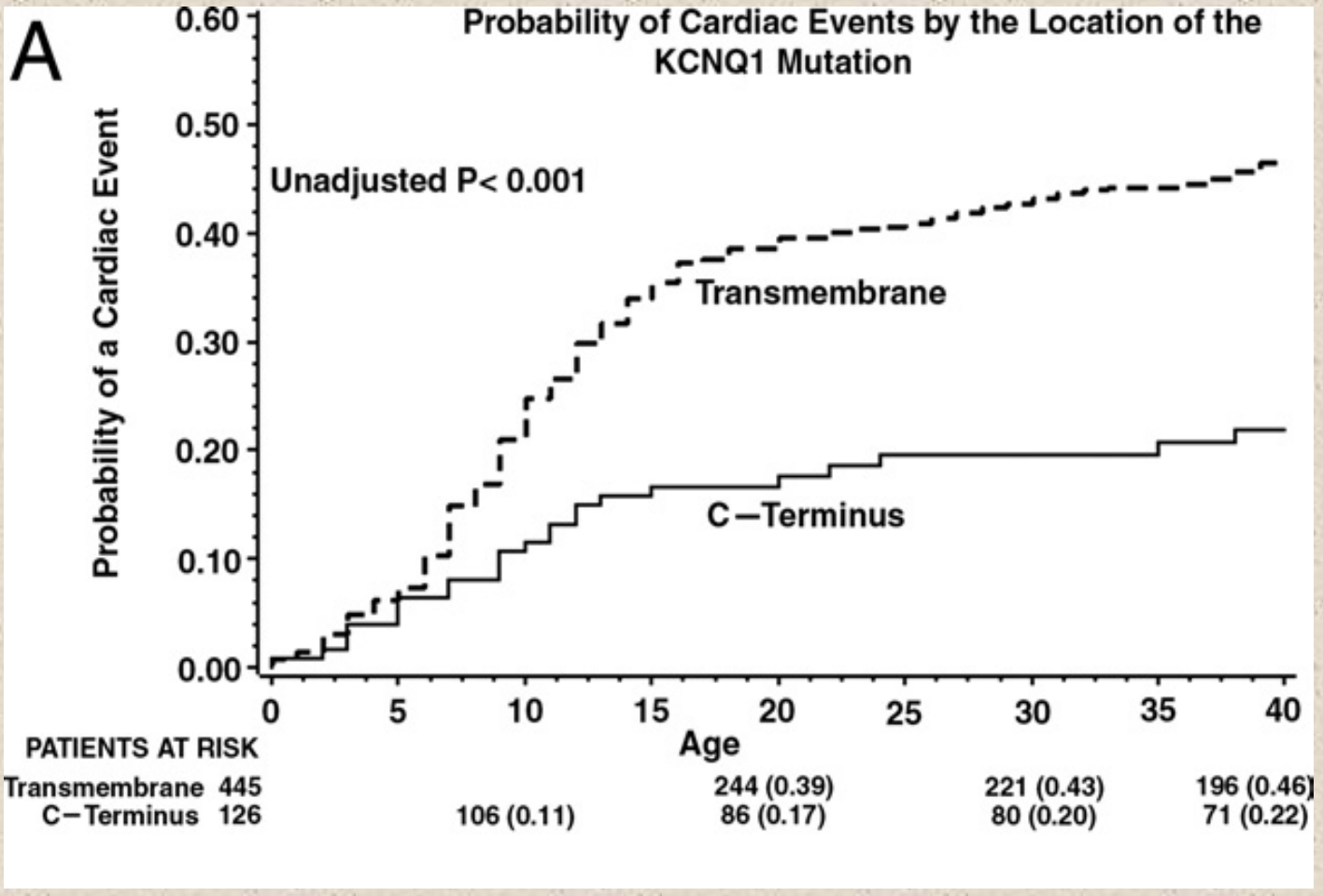
Patients 18-40 years of age not stratified for symptoms



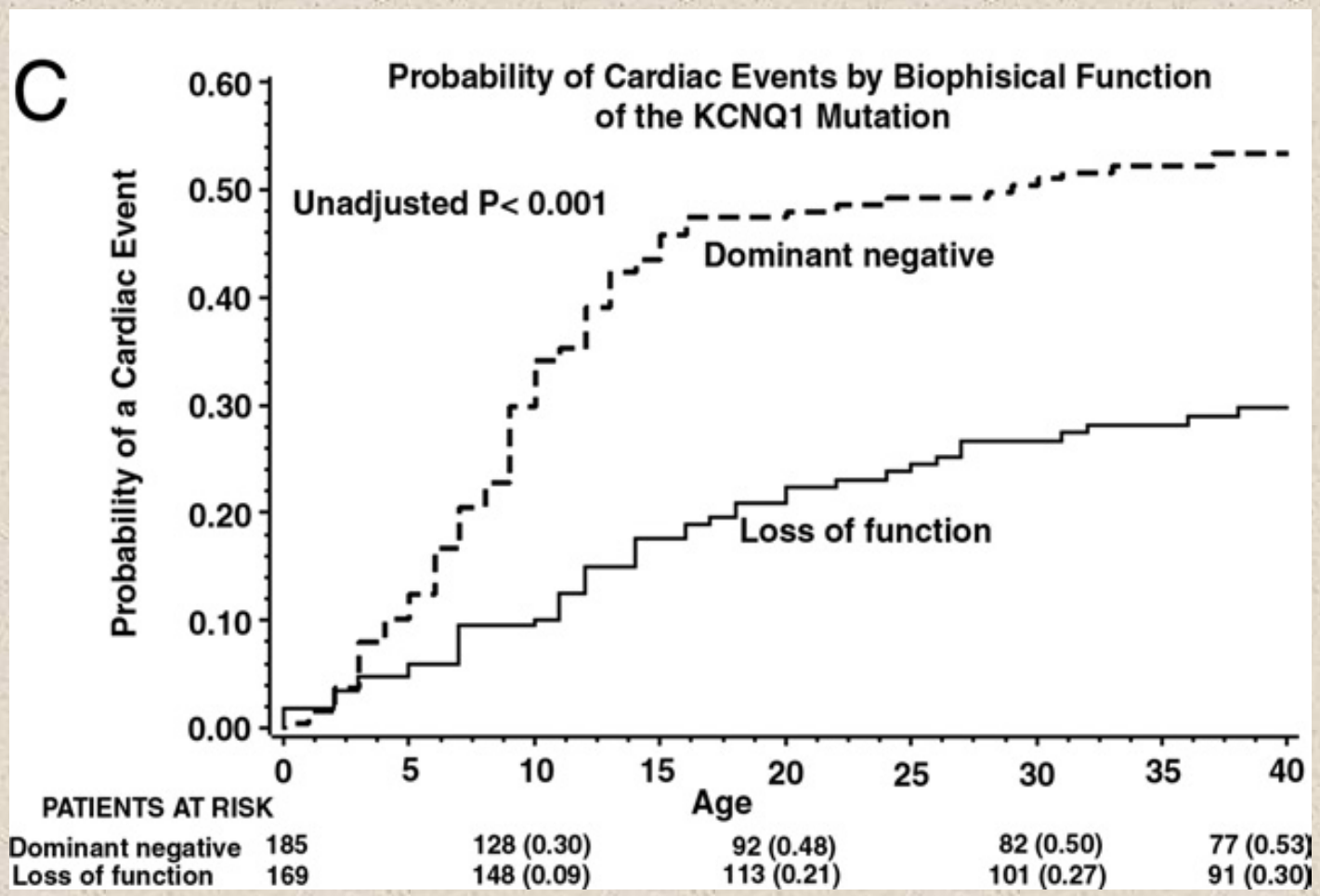
PATIENTS AT RISK

> = 550ms	93	62 (0.25)	44 (0.39)	34 (0.46)	29 (0.46)
500—549ms	173	116 (0.18)	87 (0.30)	71 (0.36)	56 (0.41)
470—499ms	196	138 (0.18)	124 (0.23)	107 (0.27)	89 (0.31)
440—469ms	180	139 (0.08)	110 (0.17)	100 (0.21)	91 (0.23)
< = 439ms	67	57 (0.02)	51 (0.03)	44 (0.03)	39 (0.03)

Sauer et al, JACC 2007



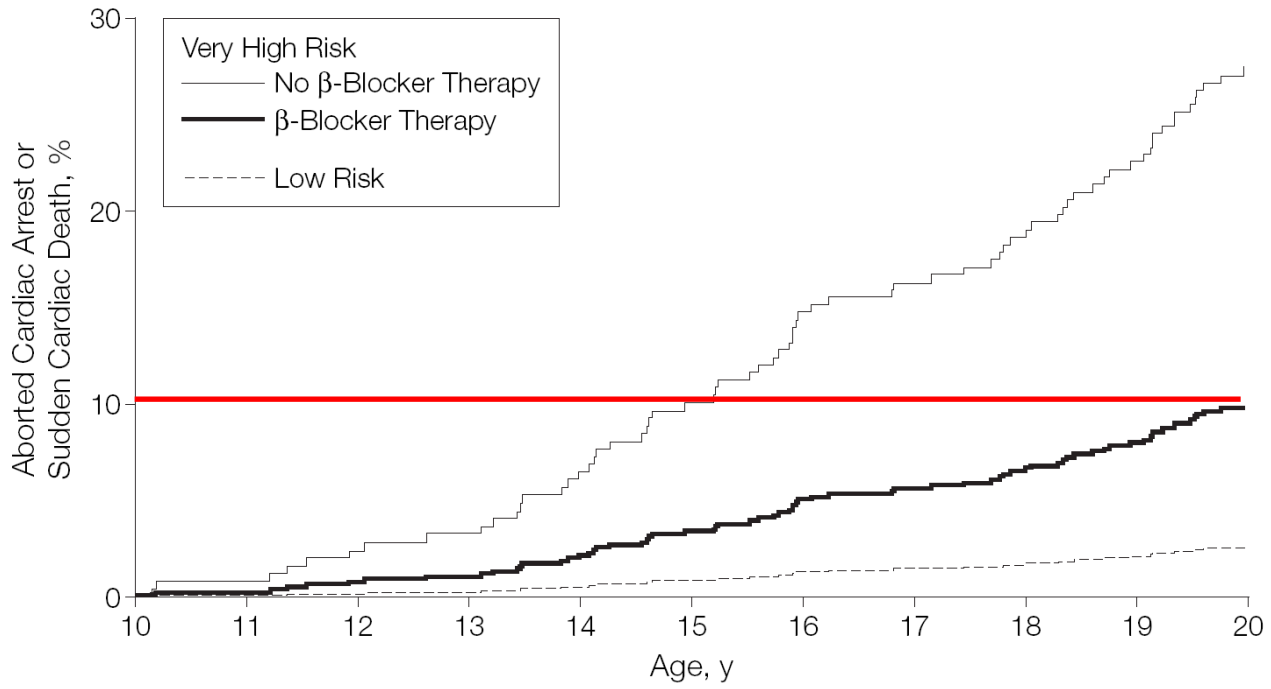
Goldenberg and Moss, JACC, 2008; 51: 2291-2300



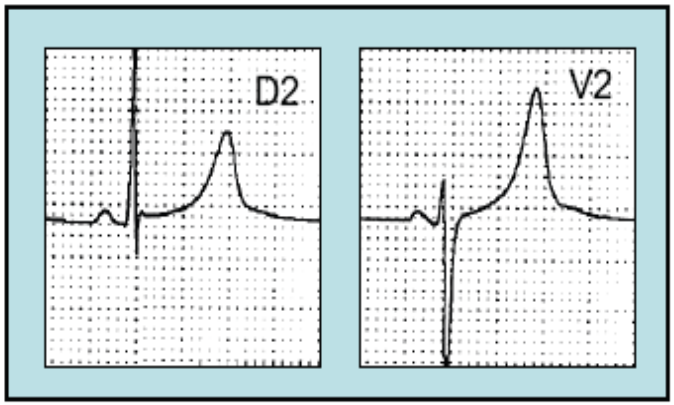
Goldenberg and Moss, JACC, 2008; 51: 2291-2300

Morts subites pendant adolescence

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



The Long QT Syndromes: LQT1



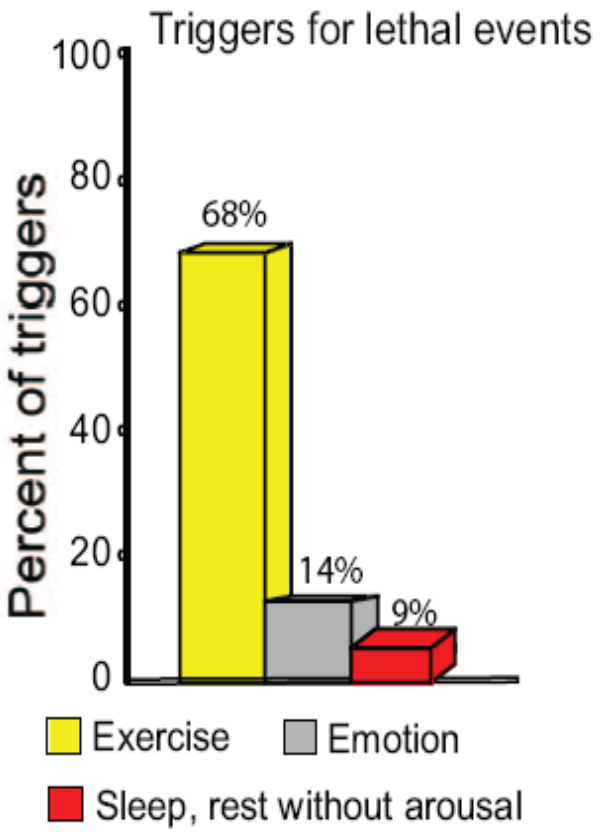
- QTc: 457±38ms
- Mean Penetrance: 55%
- Events: 30%
- CA or LQTS-death: 10%
- **Beta blockers:**

  All events

  Pre Rx: 39% Post Rx: 10%

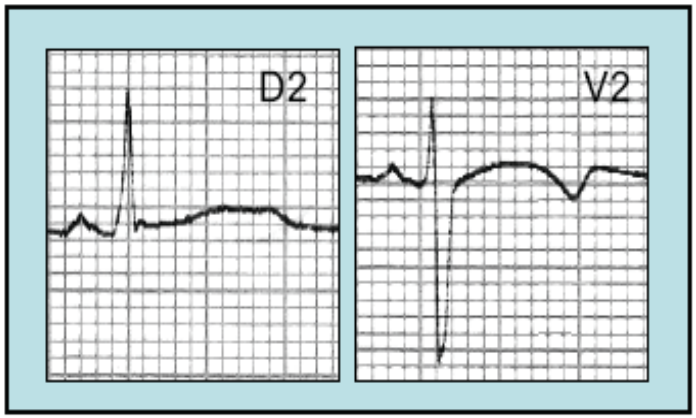
  Cardiac arrest

  Pre Rx:2% Post Rx: 1%



Ruan et al, Circ Arrhythmia Electrophysiol 2008; 1:290-297

The Long QT Syndromes: LQT2



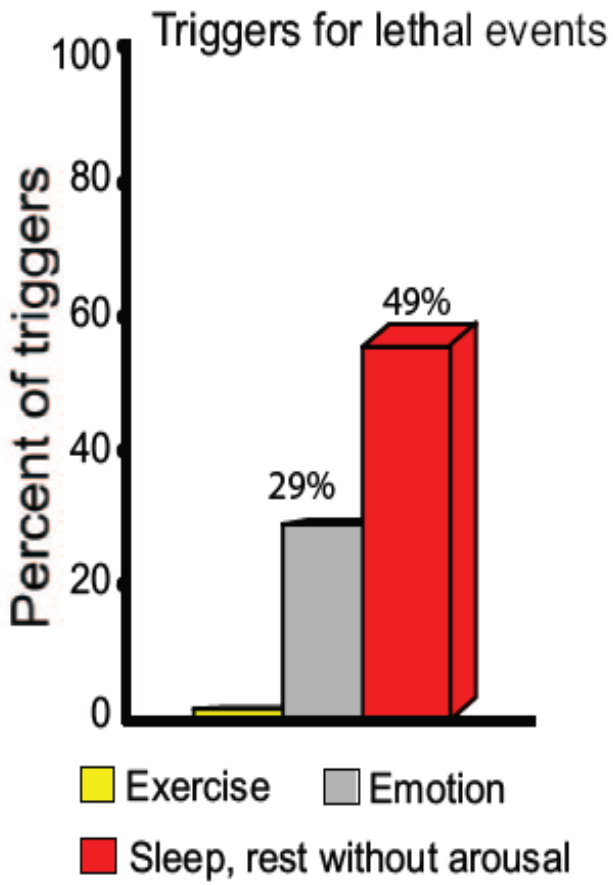
- QTc: 467±36ms
- Mean Penetrance: 70%
- Events: 46%
- CA or LQTS-death: 20%
- **Beta blockers:**

  All events

  Pre Rx: 58% Post Rx: 32%

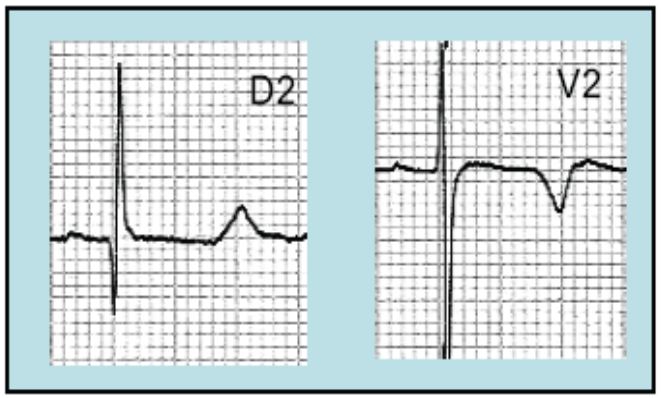
  Cardiac arrest

  Pre Rx: 8% Post Rx: 6%



Ruan et al, Circ Arrhythmia Electrophysiol 2008; 1:290-297

The Long QT Syndromes: LQT3



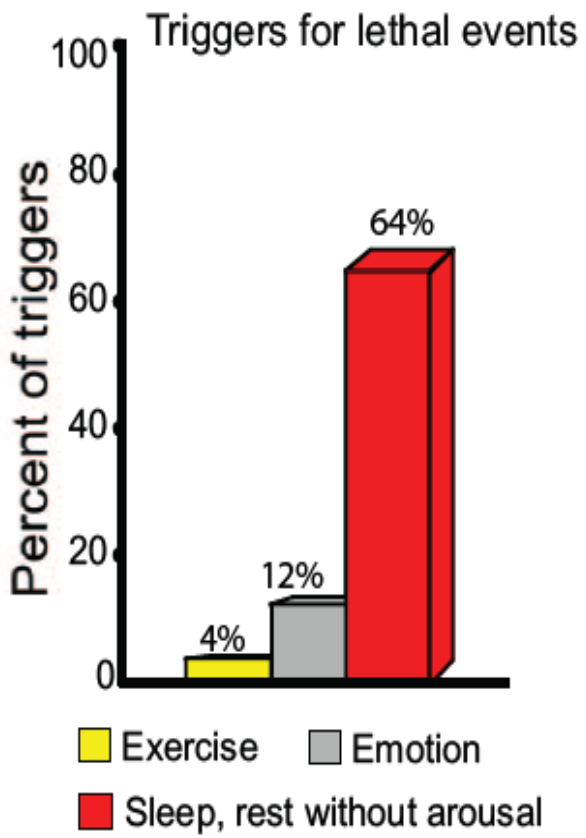
- QTc: 478±52ms
- Mean Penetrance: 79%
- Events: 46%
- CA or LQTS-death: 16%
- **Beta blockers:**

  All events

  Pre Rx: 57% Post Rx: 32%

  Cardiac arrest

  Pre Rx:18% Post Rx: 14%

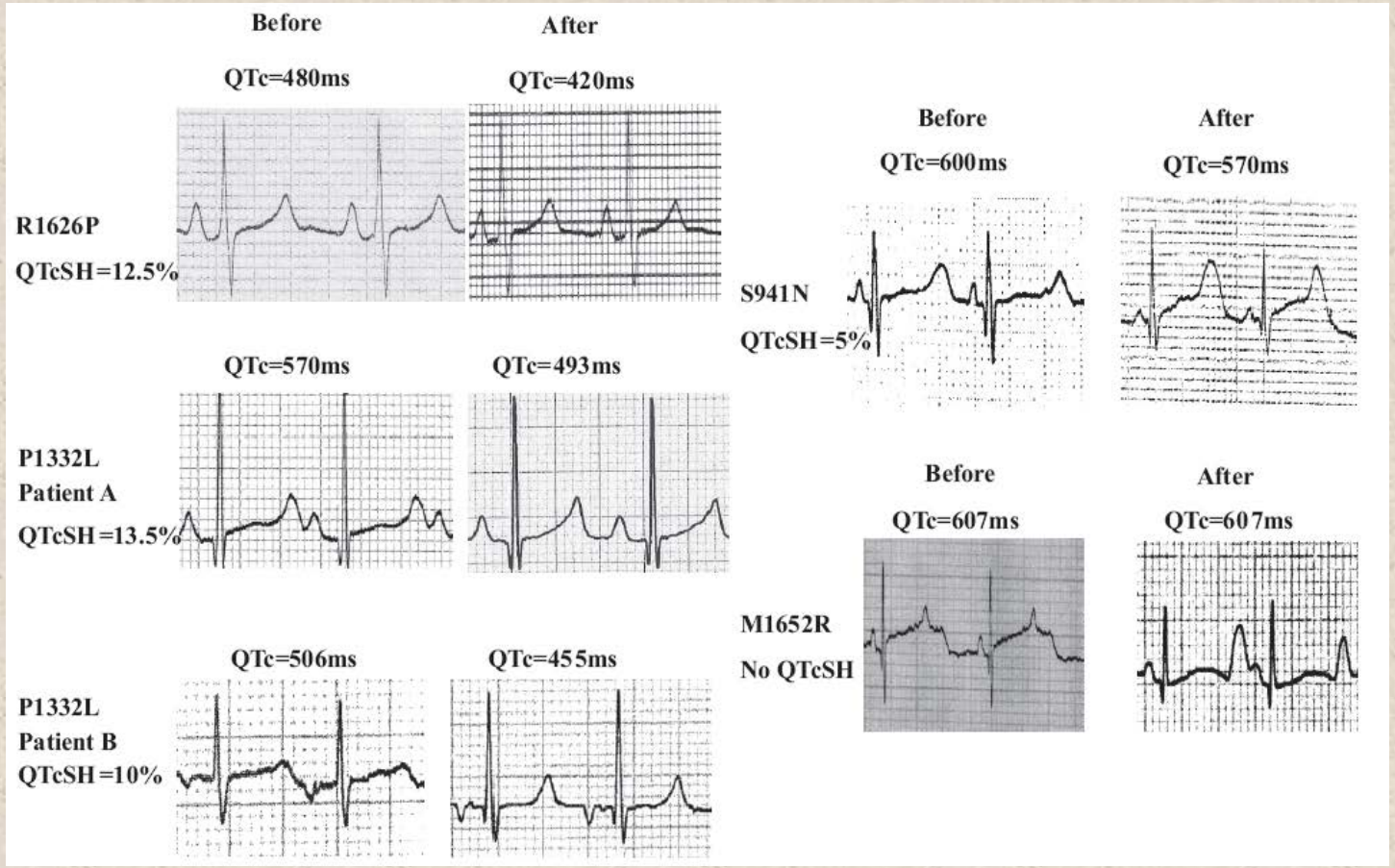


Ruan et al, Circ Arrhythmia Electrophysiol 2008; 1:290-297

Long QT Syndromes: LQT3

Sensitive to Mexiletine

Insensitive to Mexiletine



Ruan et al, Circ Arrhythmia Electrophysiol 2008; 1:290-297

Inherited Long QT Syndromes

Locus Name	Chromosomal Locus	Gene Symbol	Protein (Symbol)	Current	In Vitro Characterization	Gene-Specific Therapy*
LQT1	11p15.5	*KCNQ1*	I_{Ks} potassium channel α-subunit (KvLQT1)	↓ Ks	Dominant negative suppression, trafficking defect, abnormal gating, reduced response to β-AR signal	β-blockers,† potassium channel openers†
LQT2	7q35-q36	*KCNH2*	I_{Kr} potassium channel α-subunit (HERG)	↓ Kr	Dominant negative suppression, trafficking defect, abnormal gating	β-blockers,† potassium supplement,† potassium channel openers, fexofenadine and thapsigargin
LQT3	3p21	*SCN5A*	Cardiac sodium channel α-subunit (Nav 1.5)	↑ Na	Abnormal gating: sustained current, slower inactivation, faster recovery, increased window current	Sodium channel blockers (mexiletine)†
LQT4	4q25-q27	*ANK2*	Ankyrin B, (ANKB)	↓ Ncx1, Na/K ATPase, InsP3	Loss of expression and mislocalization	None proposed
LQT5	21q22.1-q22.2	*KCNE1*	I_{Ks} potassium channel β-subunit (MinK)	↓ Ks	Dominant negative suppression, abnormal gating, reduced response to β-AR signal	β-blockers, potassium supplement, potassium channel openers
LQT6	21q22.1-q22.2	*KCNE2*	I_{K} potassium channel beta subunit (MiRP)	↓ Kr	Reduced current density and abnormal channel gating	β-blockers, potassium supplement, potassium channel openers, fexofenadine and thapsigargin
LQT7/Andersen	17q23.1-q24.2	*KCNJ2*	I_{K1} potassium channel (Kir2.1)	↓ K1	Dominant negative suppression, nonfunctional channels, trafficking defect, abnormal gating	None proposed
LQT8/Timothy	12p13.3	*CACNA1c*	Voltage-gated calcium channel, CaV1.2	↑ Ca	Loss of inactivation	Calcium channel blockers†
LQT9	3p25	*CAV3*	Caveolin-3	↑ Na	Increased late Ina	Sodium channel blockers (mexiletine)
LQT10	11q23	*SCN4B*	Cardiac sodium channel β-4 subunit	↑ Na	Increased late Ina	Sodium channel blockers (mexiletine)
LQT11	7q21–22	*mAKAP*	A-kinase anchoring proteins	↓ Ks	Reduced phosphorylation of the IKs channel	β-blockers
LQT12	20q11.2	*SNTA1*	Syntrophin	↑ Na	Increased late INa	Sodium channel blockers (mexiletine)

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