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Medizinische Fakultät Mannheim
der Universität Heidelberg

Universitätsklinikum Mannheim

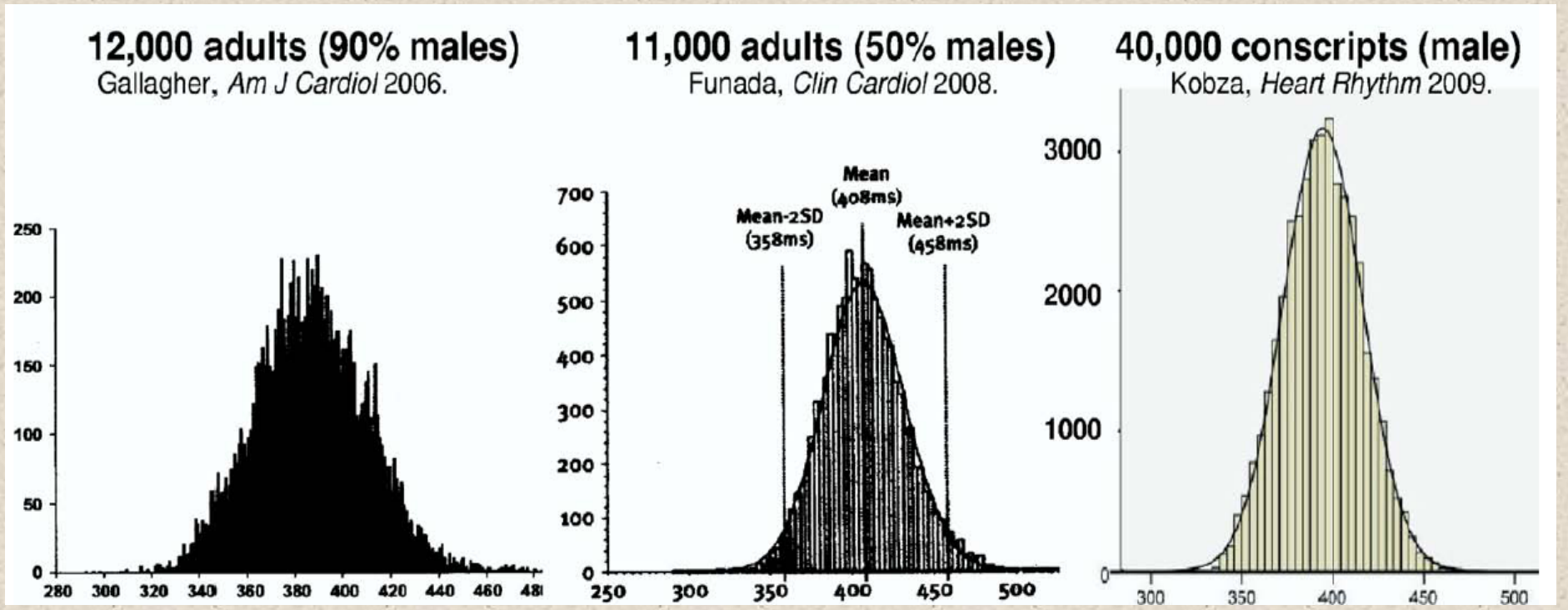
Asymptomatic Long QT

Prof. Dr. Martin Borggrefe

Mannheim

QT interval

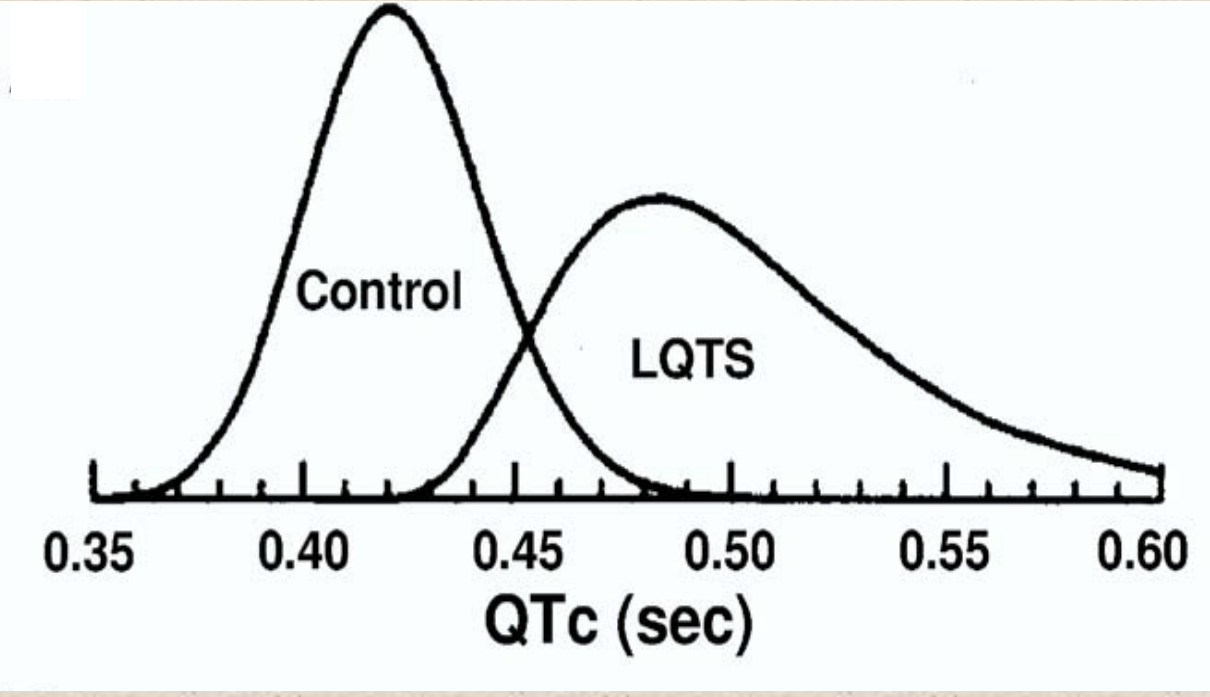
Distribution of QTc intervals in large population-based studies



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

QT interval

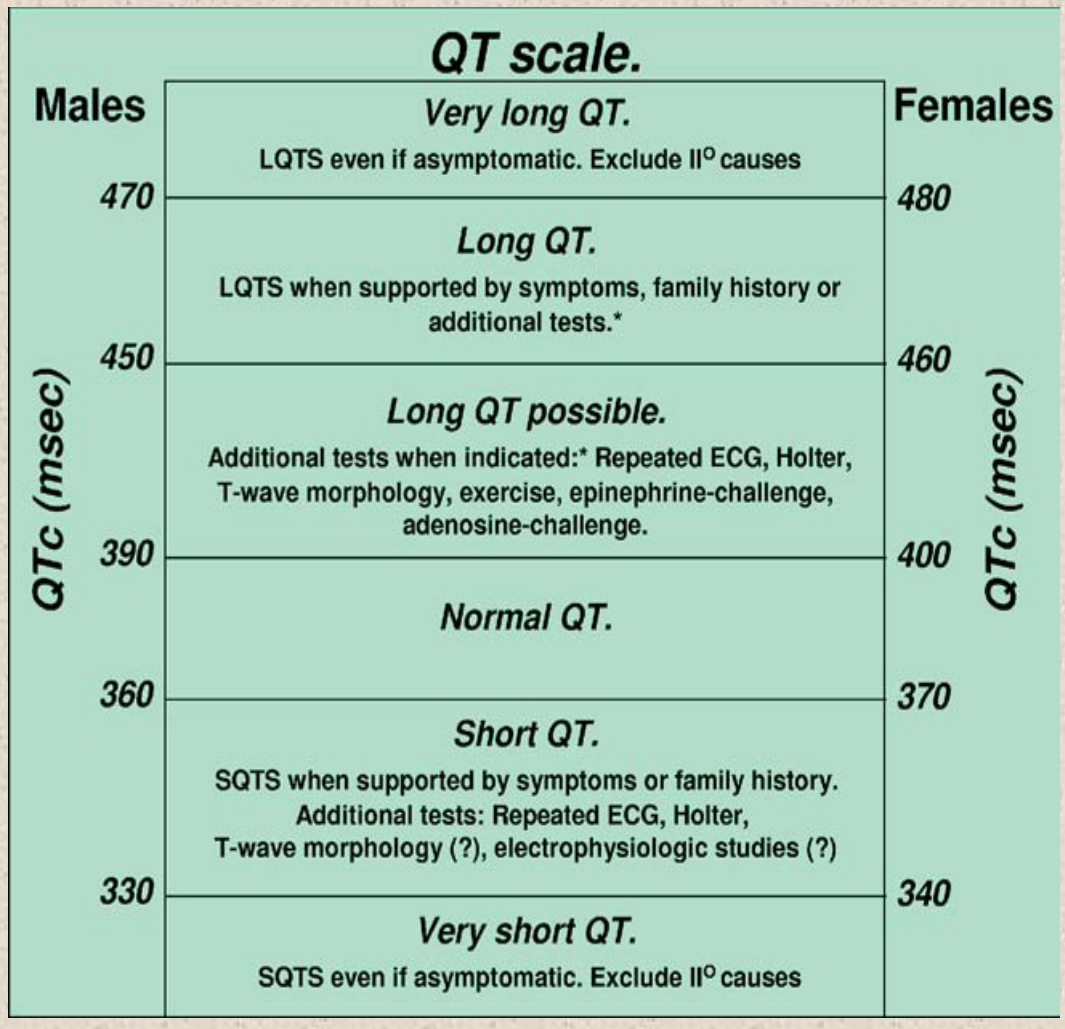
Distribution of QTc intervals of 117 LQTS mutation carriers and 113 healthy relatives (noncarriers) as reported by Vincent's group



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

QT interval

Spectrum of QT intervals



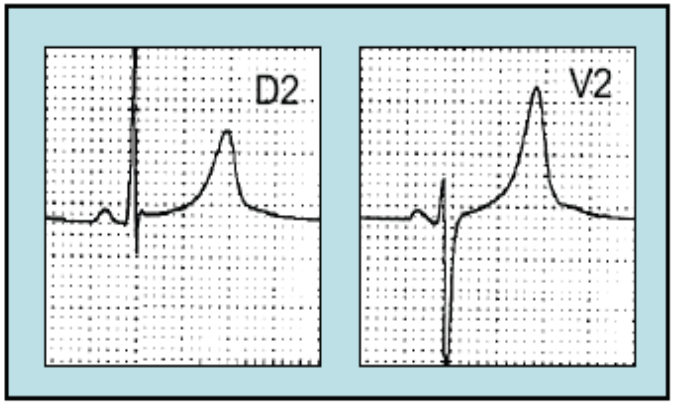
Viskin S, Heart Rhythm 2009; 6: 711-715

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)	↓ Iks	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)	↓ Ikr	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)	↑ INa	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)	↓ Iks	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)	↓ Ikr	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)	↓ IK1	Dominant negative suppression, nonfunctional channels, trafficking defect, abnormal gating	None proposed
LQT8/Timothy	12p13.3	*CACNA1c*	Voltage-gated calcium channel, CaV1.2	↑ ICa	Loss of inactivation	Calcium channel blockers†
LQT9	3p25	*CAV3*	Caveolin-3	↑ INa	Increased late Ina	Sodium channel blockers (mexiletine)
LQT10	11q23	*SCN4B*	Cardiac sodium channel β-4 subunit	↑ INa	Increased late Ina	Sodium channel blockers (mexiletine)
LQT11	7q21–22	*mAKAP*	A-kinase anchoring proteins	↓ Iks	Reduced phosphorylation of the IKs channel	β-blockers
LQT12	20q11.2	*SNTA1*	Syntrophin	↑ INa	Increased late INa	Sodium channel blockers (mexiletine)

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

The Long QT Syndromes: LQT1



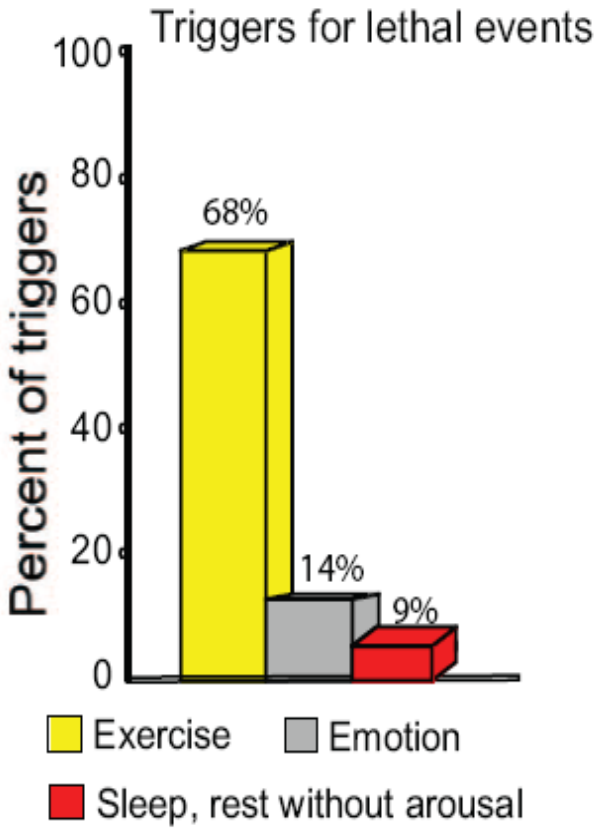
- QTc: 457±38ms
- Mean Penetrance: 55%
- Events: 30%
- CA or LQTS-death: 10%
- **Beta blockers:**

  All events

  Pre Rx: 39% Post Rx: 10%

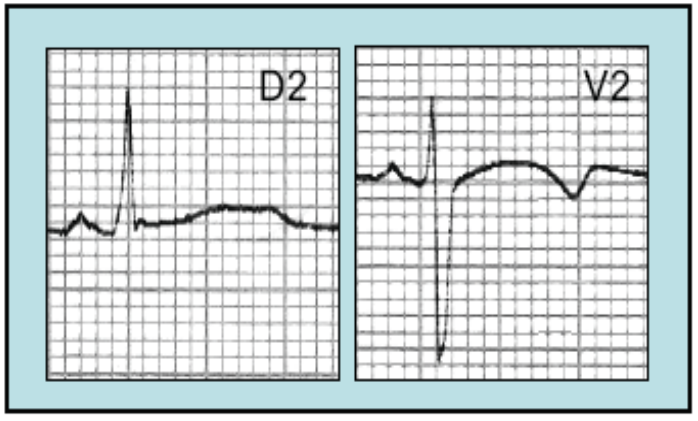
  Cardiac arrest

  Pre Rx:2% Post Rx: 1%

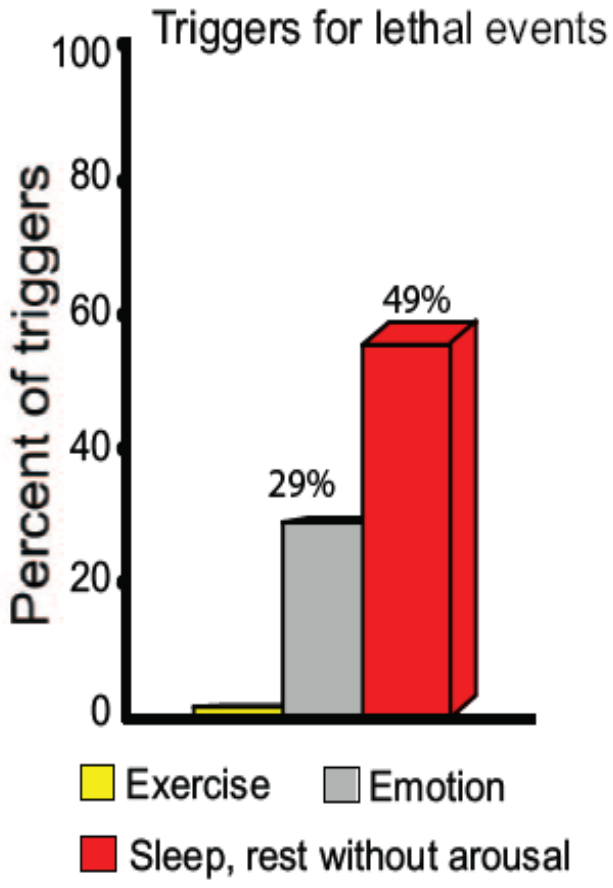


Ruan et al, Circ Arrhythmia Electrophysiol 2008; 1:290-297

The Long QT Syndromes: LQT2

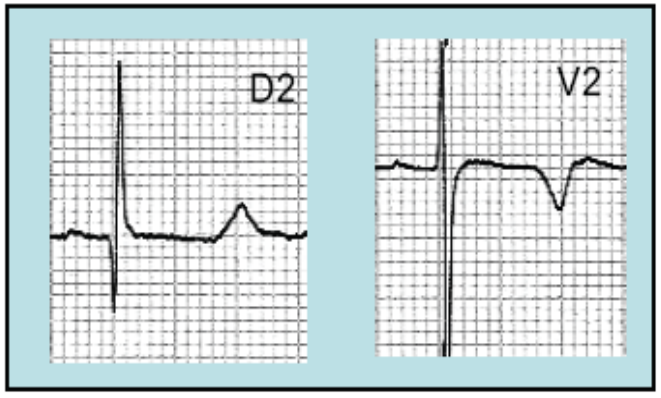


- QTc: 467±36ms
- Mean Penetrance: 70%
- Events: 46%
- CA or LQTS-death: 20%
- **Beta blockers:**
  All events
  Pre Rx: 58% Post Rx: 32%
  Cardiac arrest
  Pre Rx: 8% Post Rx: 6%



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

The Long QT Syndromes: LQT3



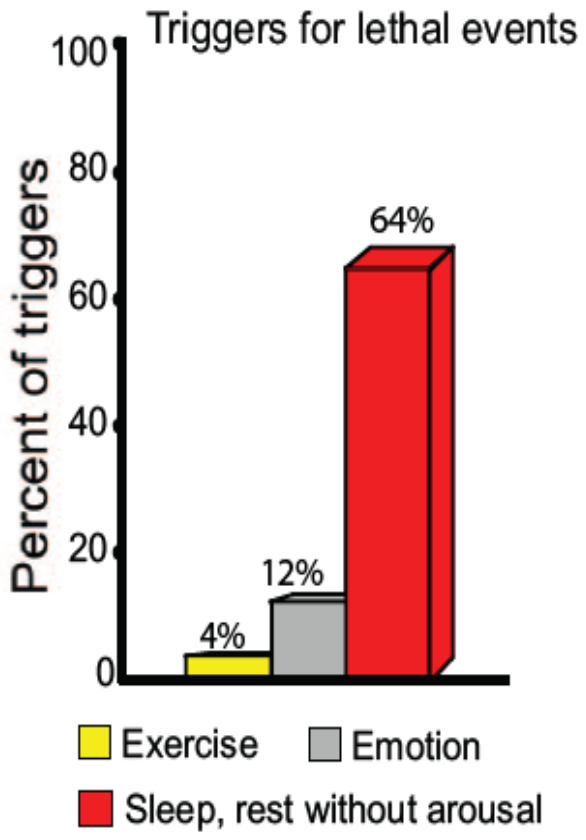
- QTc: 478±52ms
- Mean Penetrance: 79%
- Events: 46%
- CA or LQTS-death: 16%
- **Beta blockers:**

  All events

  Pre Rx: 57% Post Rx: 32%

  Cardiac arrest

  Pre Rx:18% Post Rx: 14%



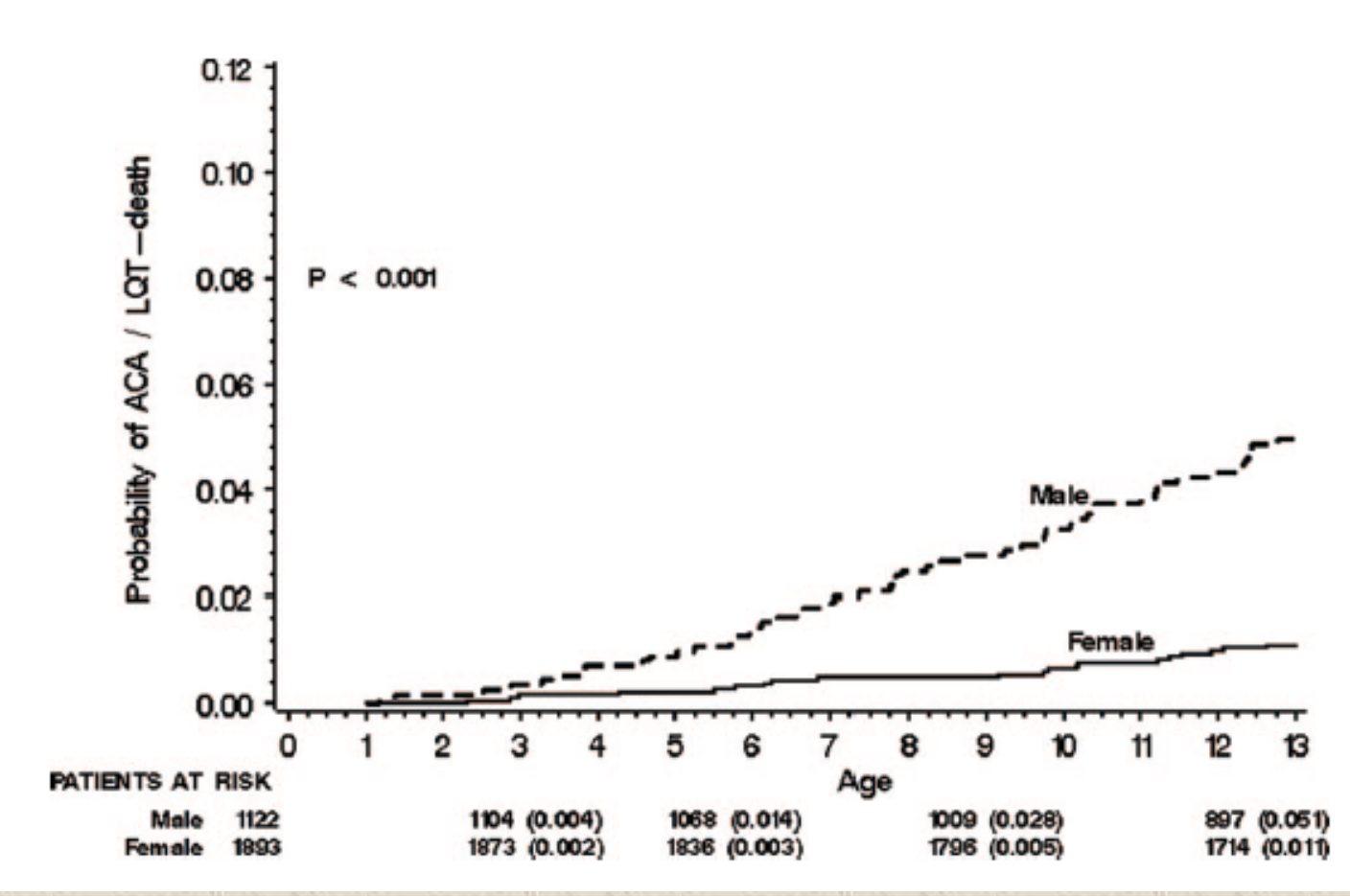
Ruan et al, Circ Arrhythmia Electrophysiol 2008; 1:290-297

Risk Factors for ACA or SCD During Childhood: Male Versus Female HR in Risk Subsets

	Male vs Female Risk	
Risk Subset	HR (95% CI)	*P*
No prior syncope and		
QTc >500 ms	12.11 (3.73–39.31)	<0.001
QTc ≤500 ms	4.23 (1.47–12.19)	0.008
Prior syncope and		
QTc >500 ms	2.68 (1.22–5.91)	0.01
QTc ≤500 ms	0.94 (0.38–2.30)	0.88

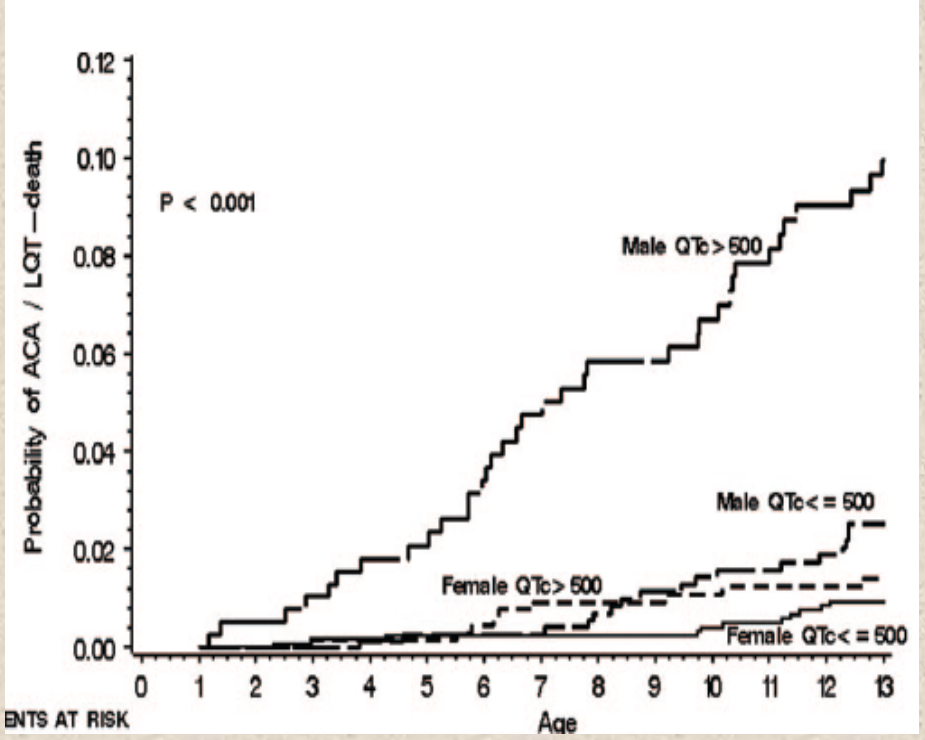
Goldenberg et al, Circulation, 2008; 117: 2184-2192

Probability of ACA or SCD by gender

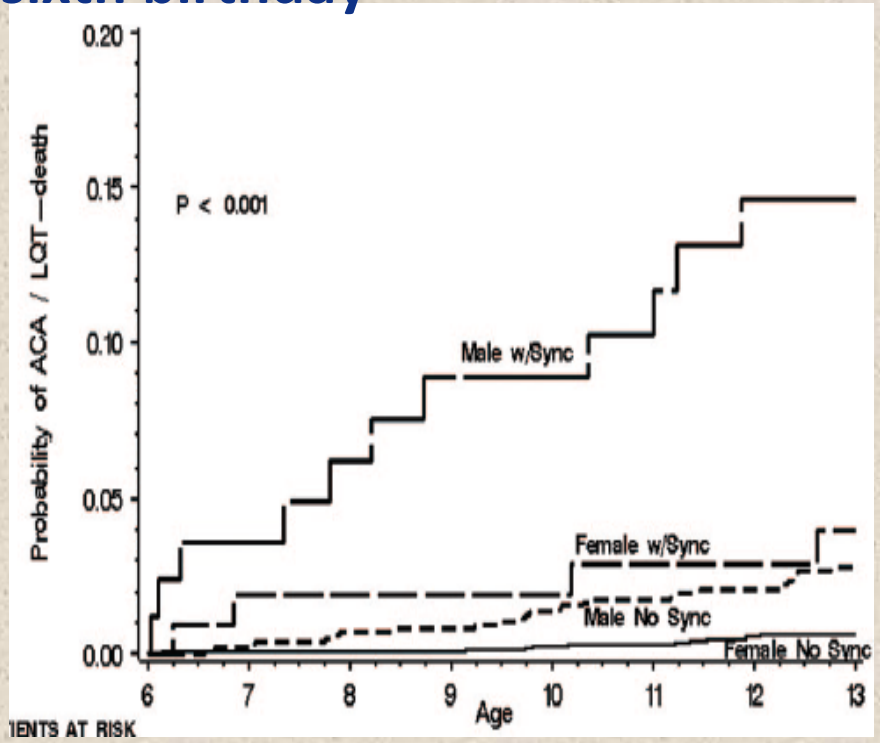


Goldenberg et al, Circulation, 2008; 117: 2184-2192

Probability of ACA or SCD by gender and QTc subgropus

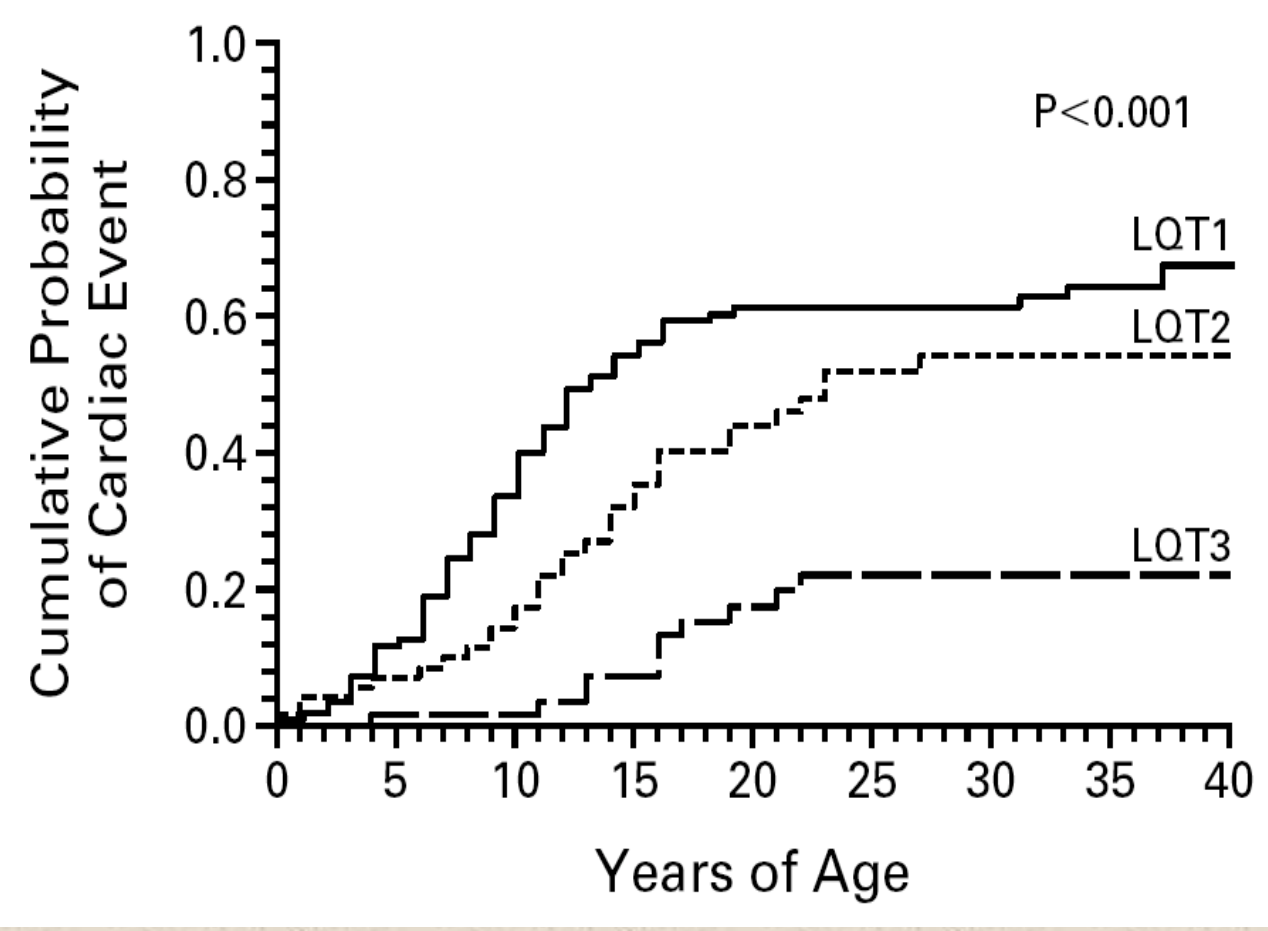


Probability of ACA or SCD after 6 years of age by gender and a history of syncope before the sixth birthday



Goldenberg et al, Circulation, 2008; 117: 2184-2192

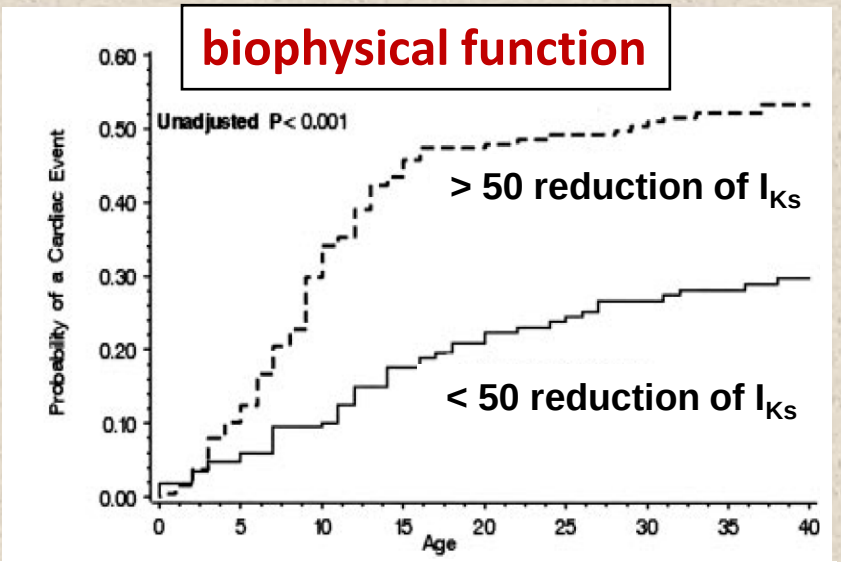
Risk in LQT according to genotype and age

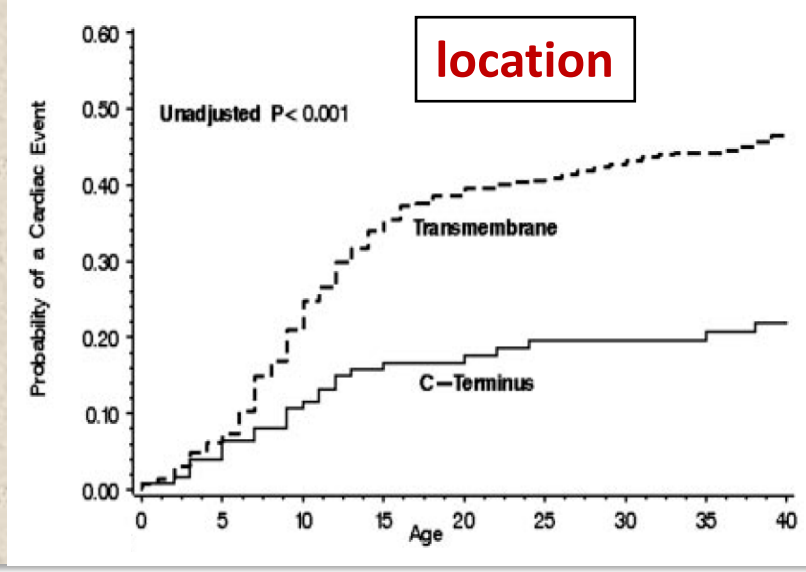


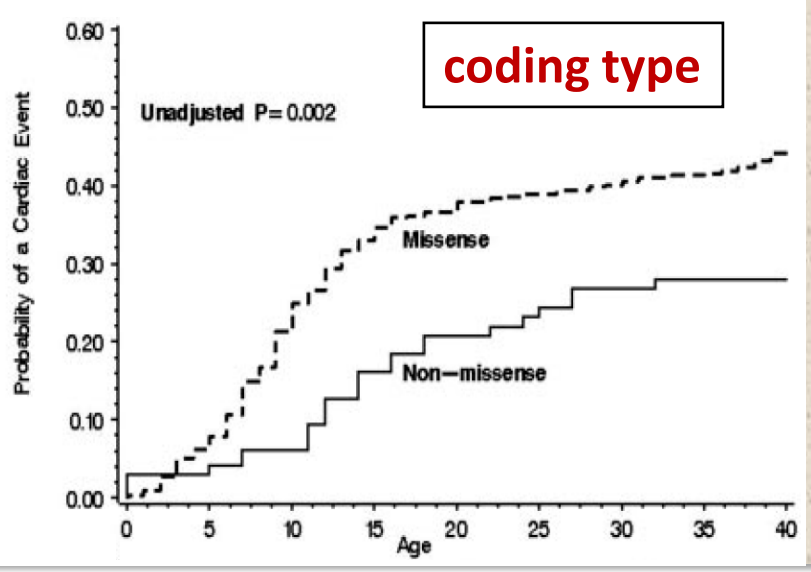
Zareba et al NEJM 1996

Type of LQT1 mutation and outcome

- 600 patients with LQT 1
- Outcome regarding:
  - location
  - coding type
  - biophysical function







Moss et al Circulation 2007

Location of mutation and prognosis in LQT 2

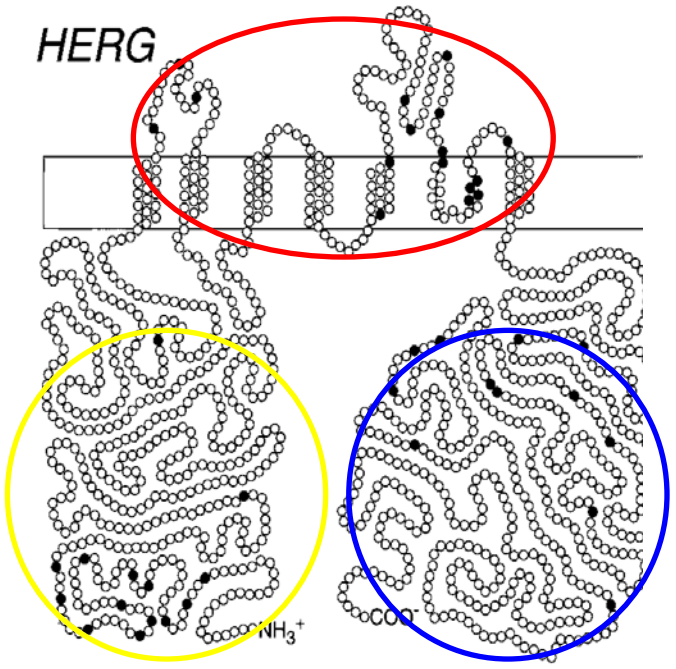
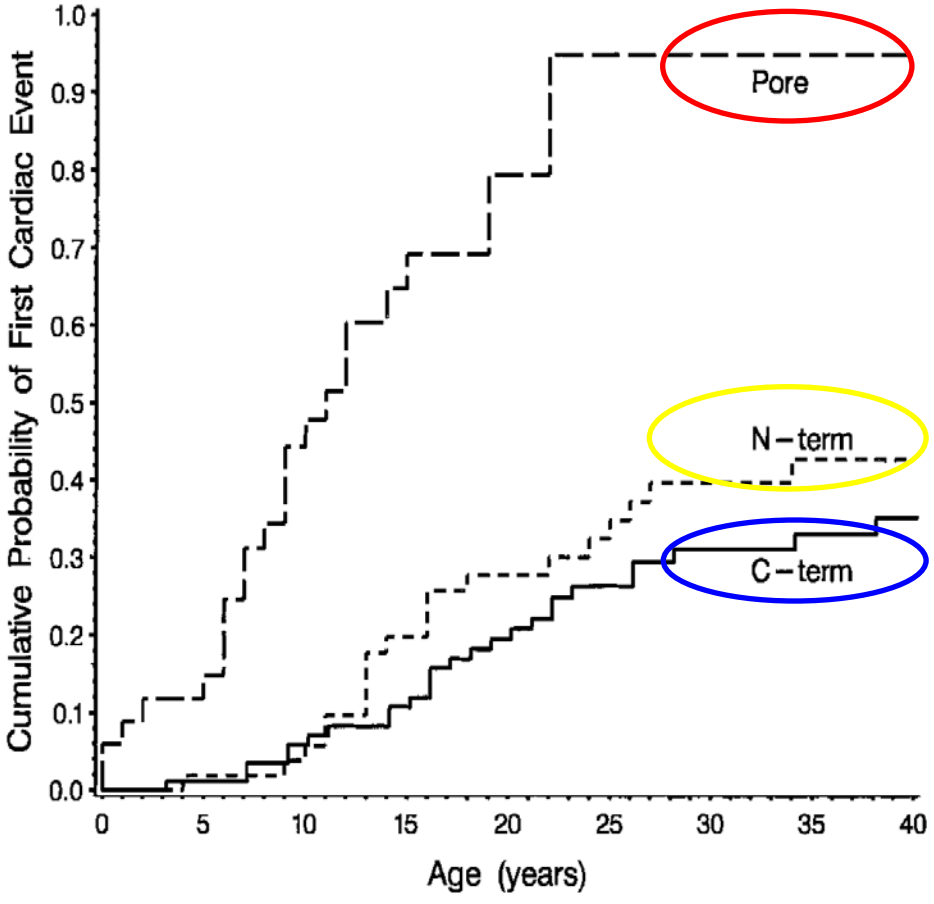


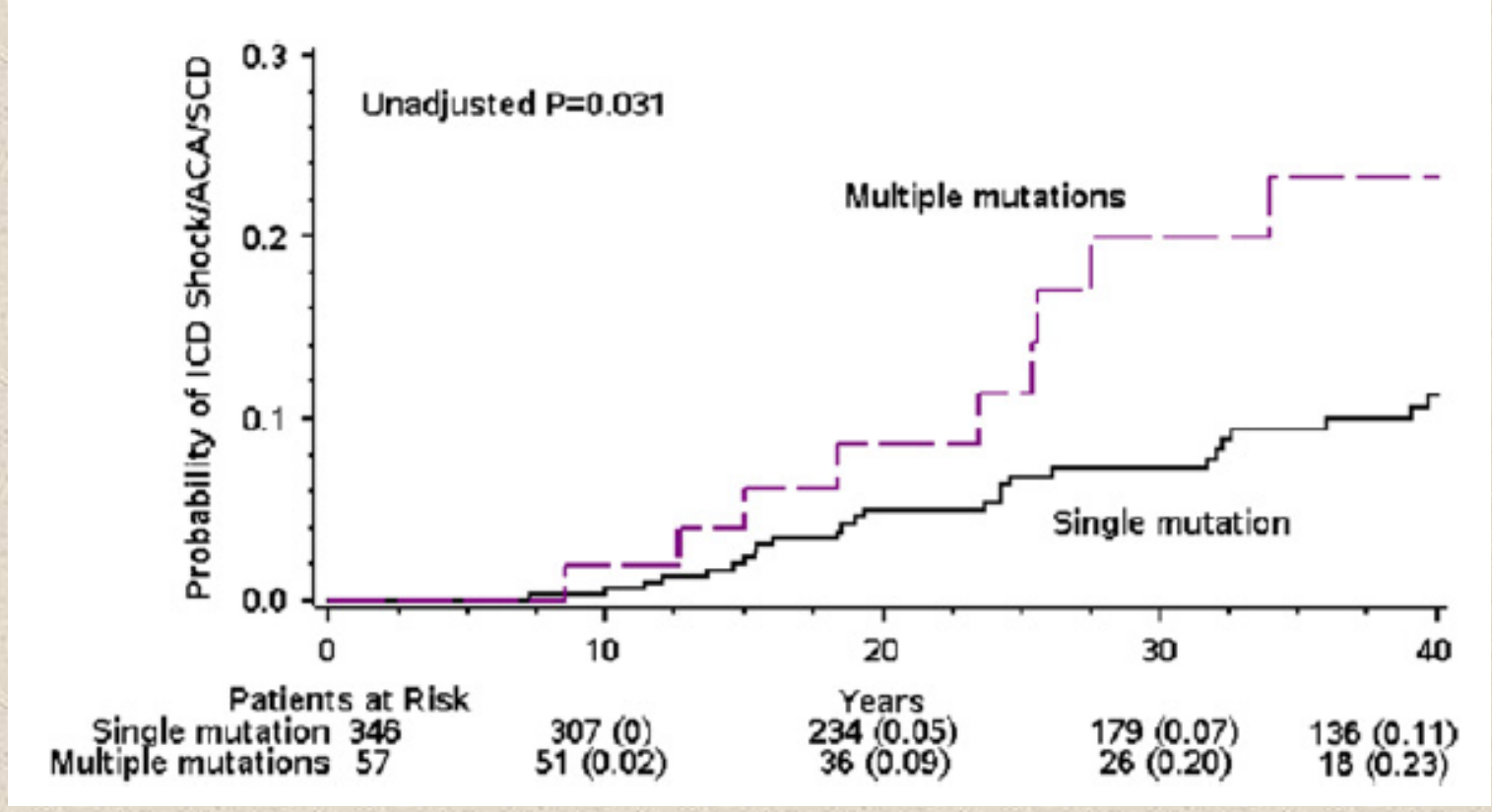
Figure 1. Schematic representation of HERG potassiur channel-α subunit involving the N-terminus portion (NH membrane-spanning segments with the pore region ex from segments S_5 to S_6, and the C-terminus portion (C Mutational locations are indicated by black dots.



Moss et al Circulation 2007

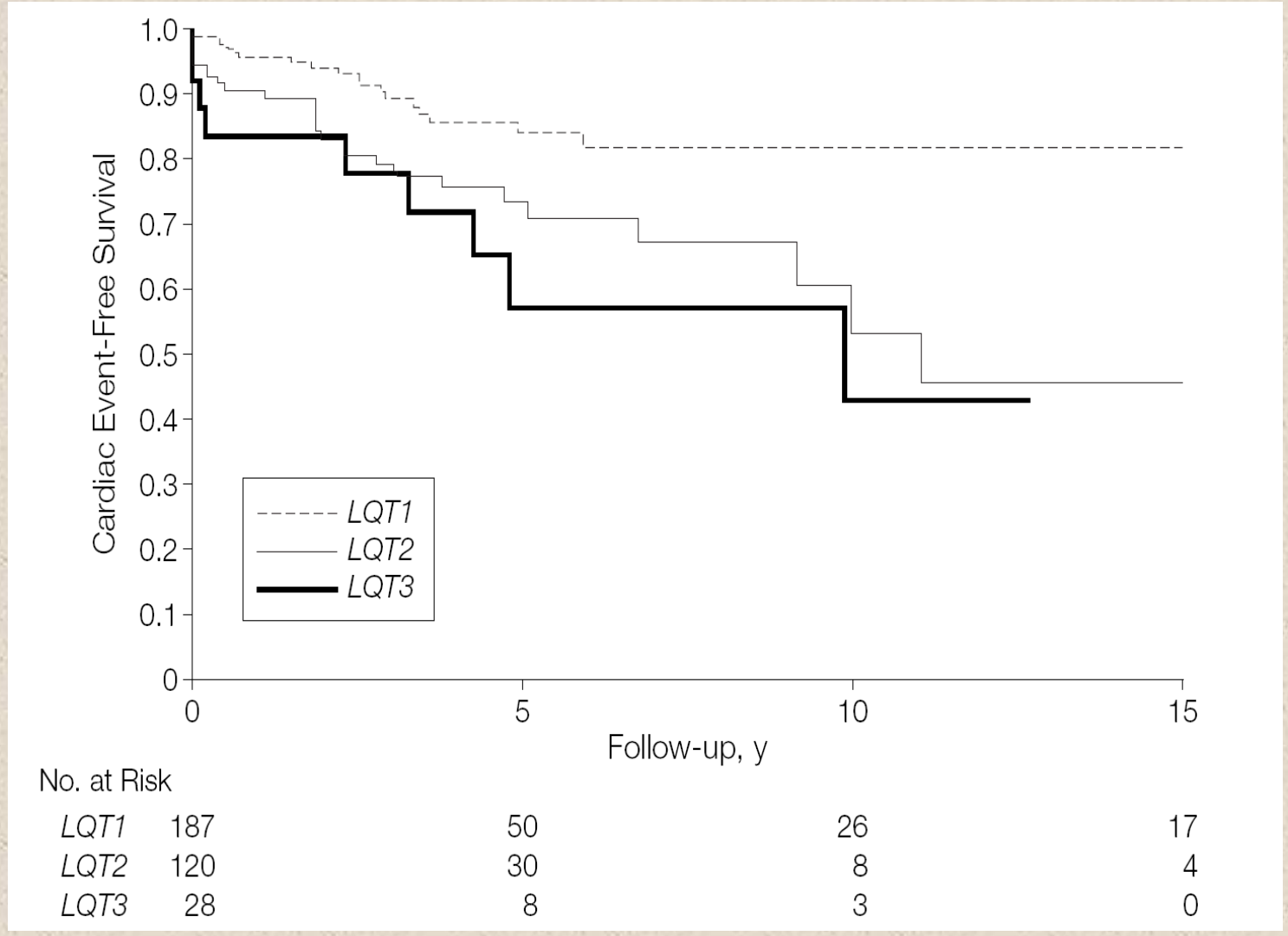
Long QT Syndrome and Multiple Mutations

Cumulative probability of life-threatening cardiac events by mutation subgroup

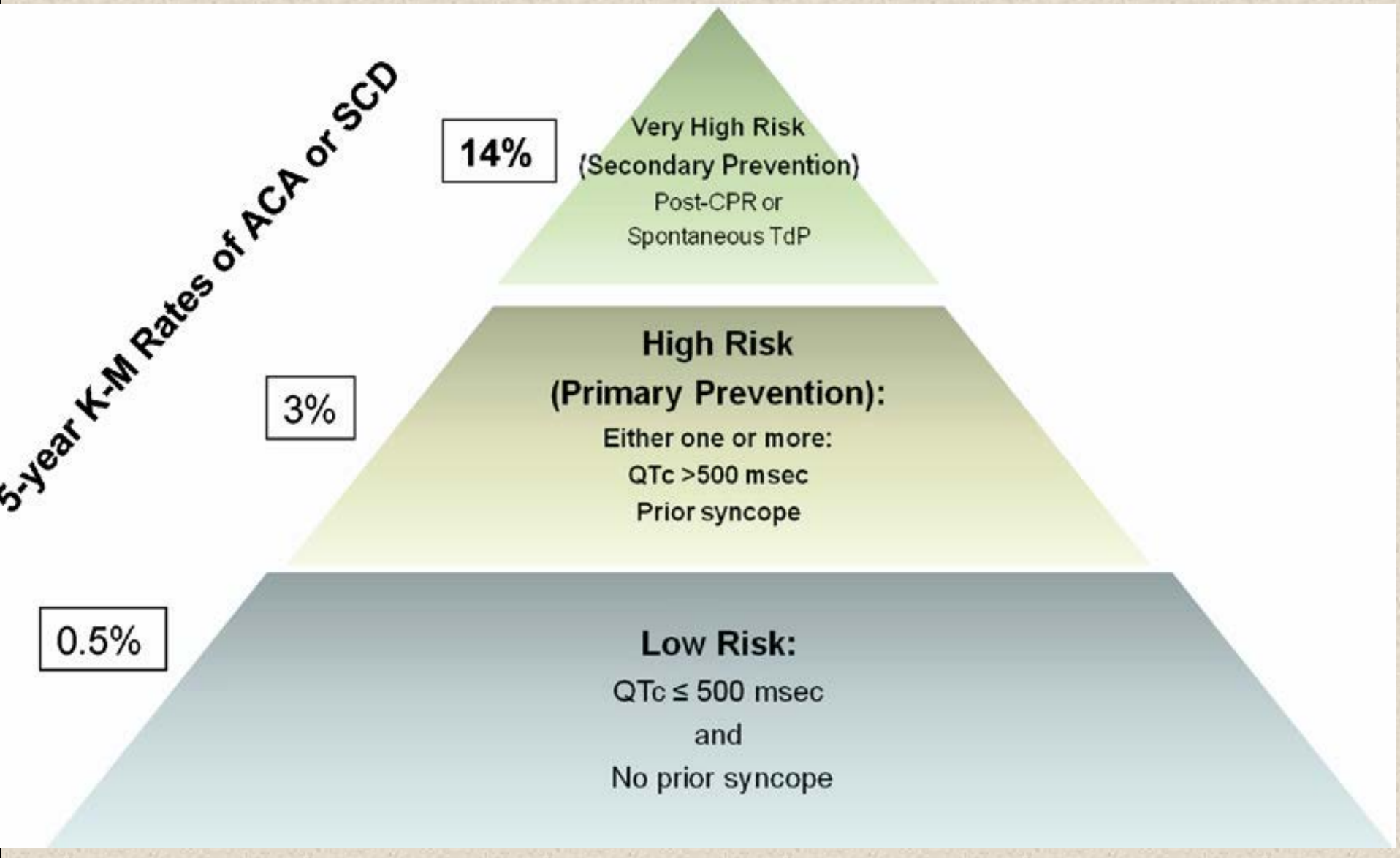


Mullally et al. Heart Rhythm 2013;10:378-382

Betablocker response and genotype



Priori et al. Jama 2004



Goldenberg et al, JACC 2008

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%

Goldenberg et al Circulation 2008;

Hobbs et al JAMA 2006;

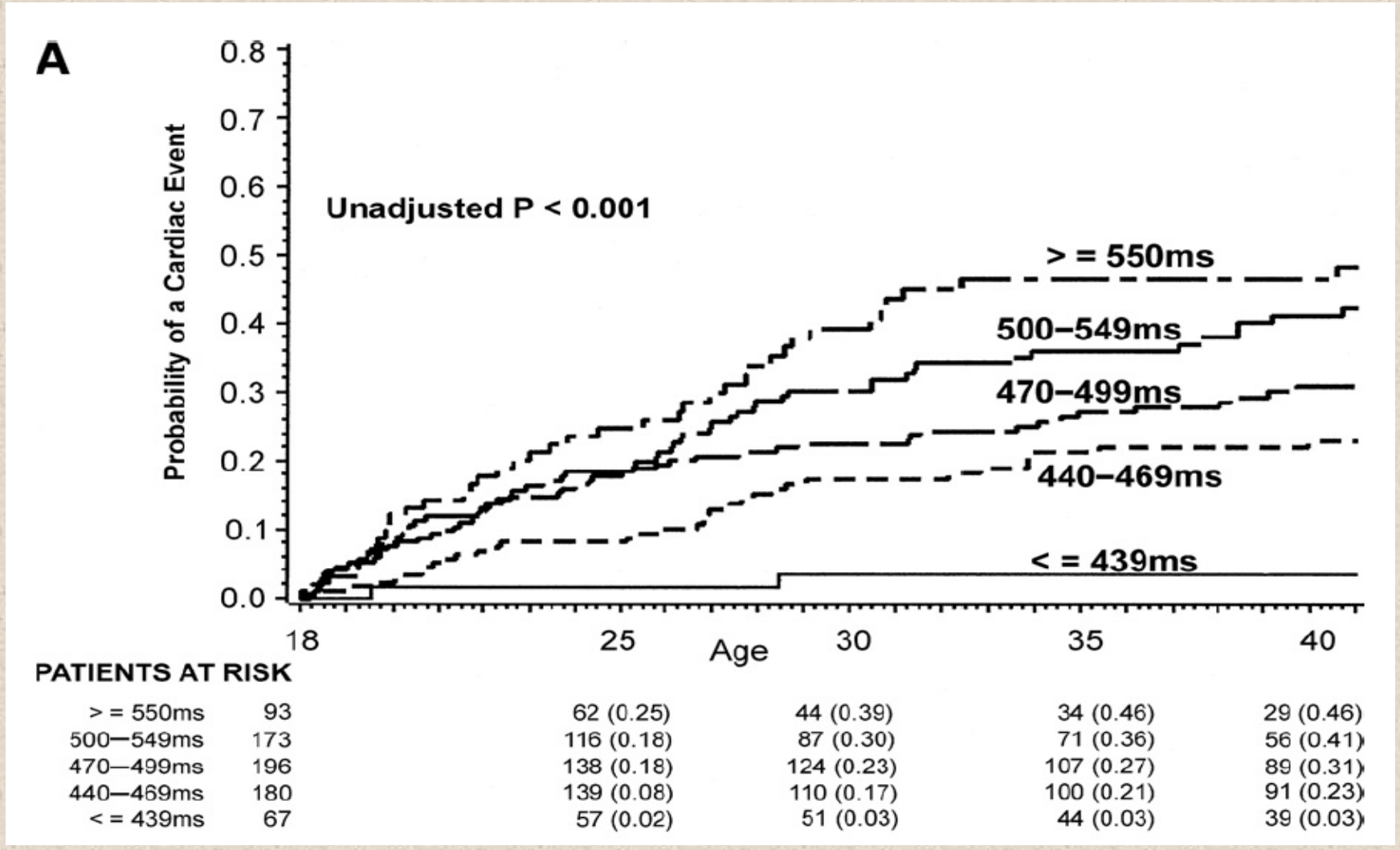
Sauer et al JACC 2007

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



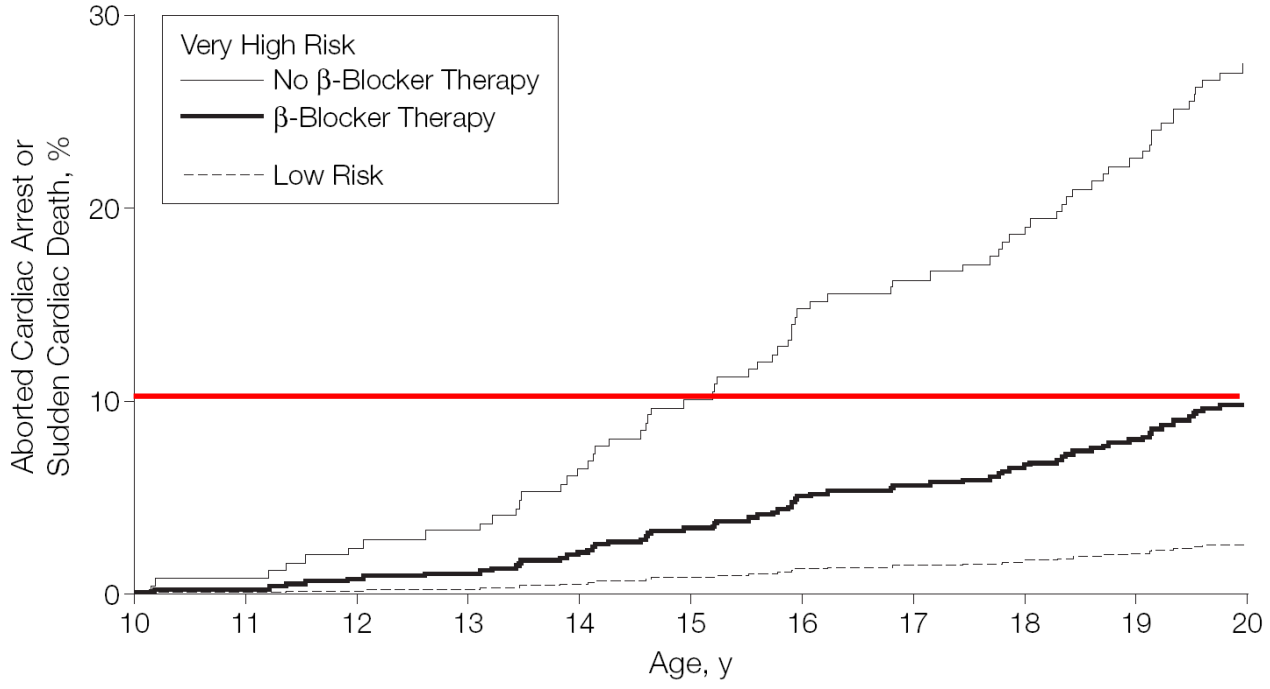
PATIENTS AT RISK

> = 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)

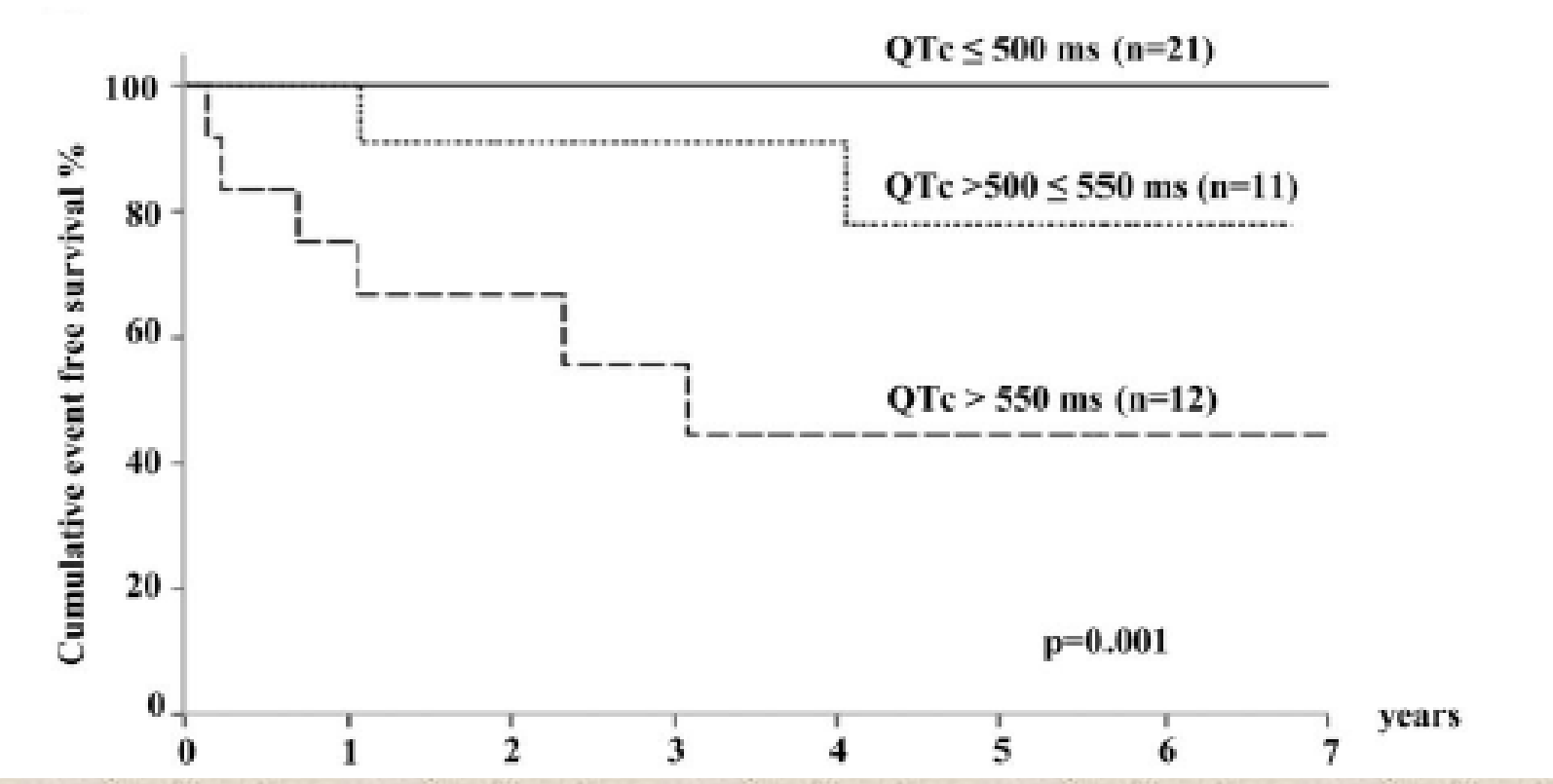
Sauer et al, JACC 2007

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



Cumulative event-free survival for a first appropriate ICD shock is shown according to the degree of QT interval prolongation



Schwartz et al. Circulation 2010;122:1272-1282

Multivariate Risk Predictors of Appropriate Shock During Follow-Up in Patients With an ICD

Clinical Variables	Hazard Ratio (95% CI)	P
Prior ACA	1.81 (1.09 –3.0)	0.023
Events on therapy	1.81 (1.08–3.0)	0.025
Age at implantation <20 y	2.3 (1.38–3.8)	0.001
QTc	1.41 (1.03–1.92)	0.03

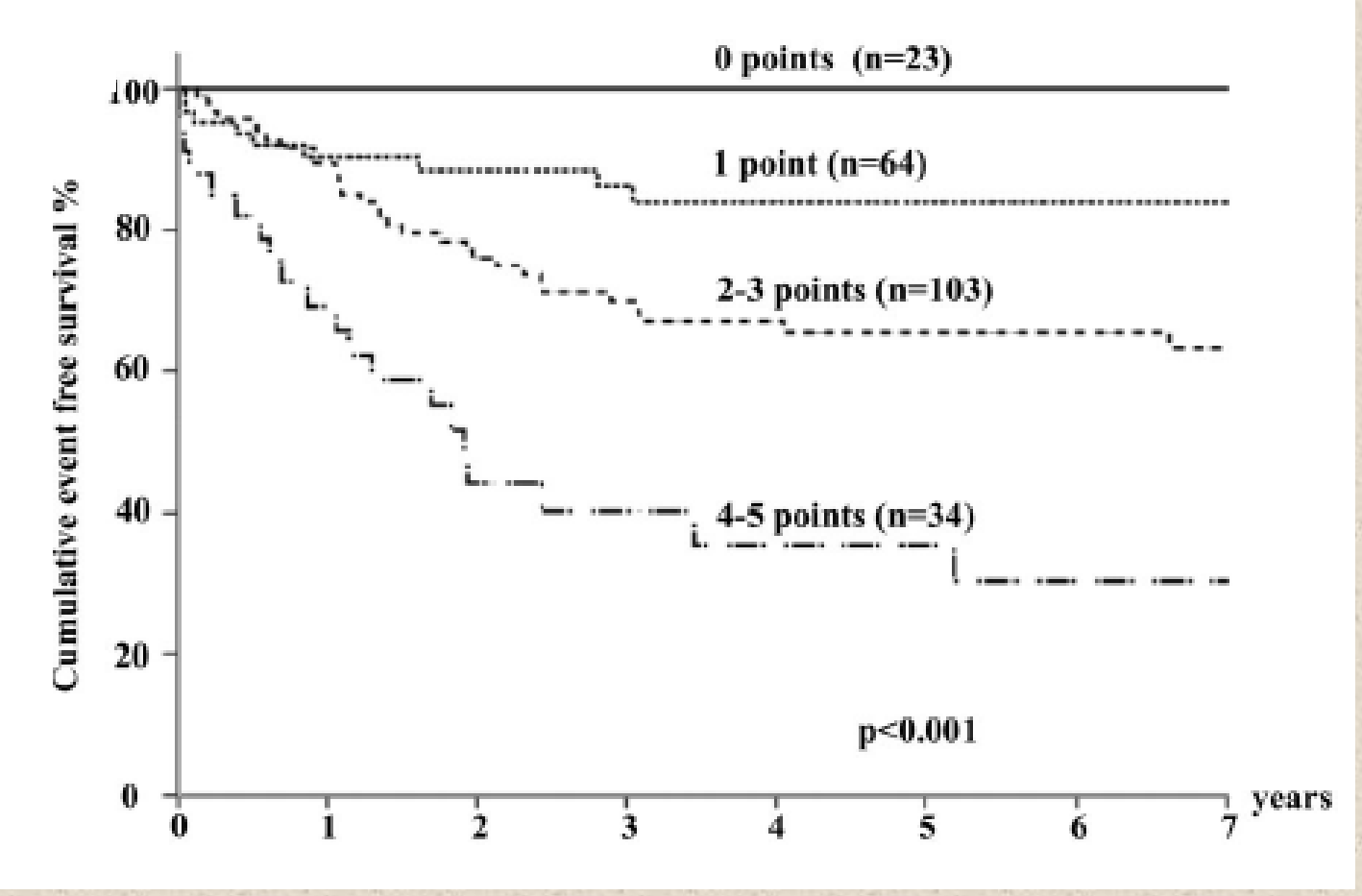
Schwartz et al. Circulation 2010;122:1272-1282

M-FACT* Risk Score

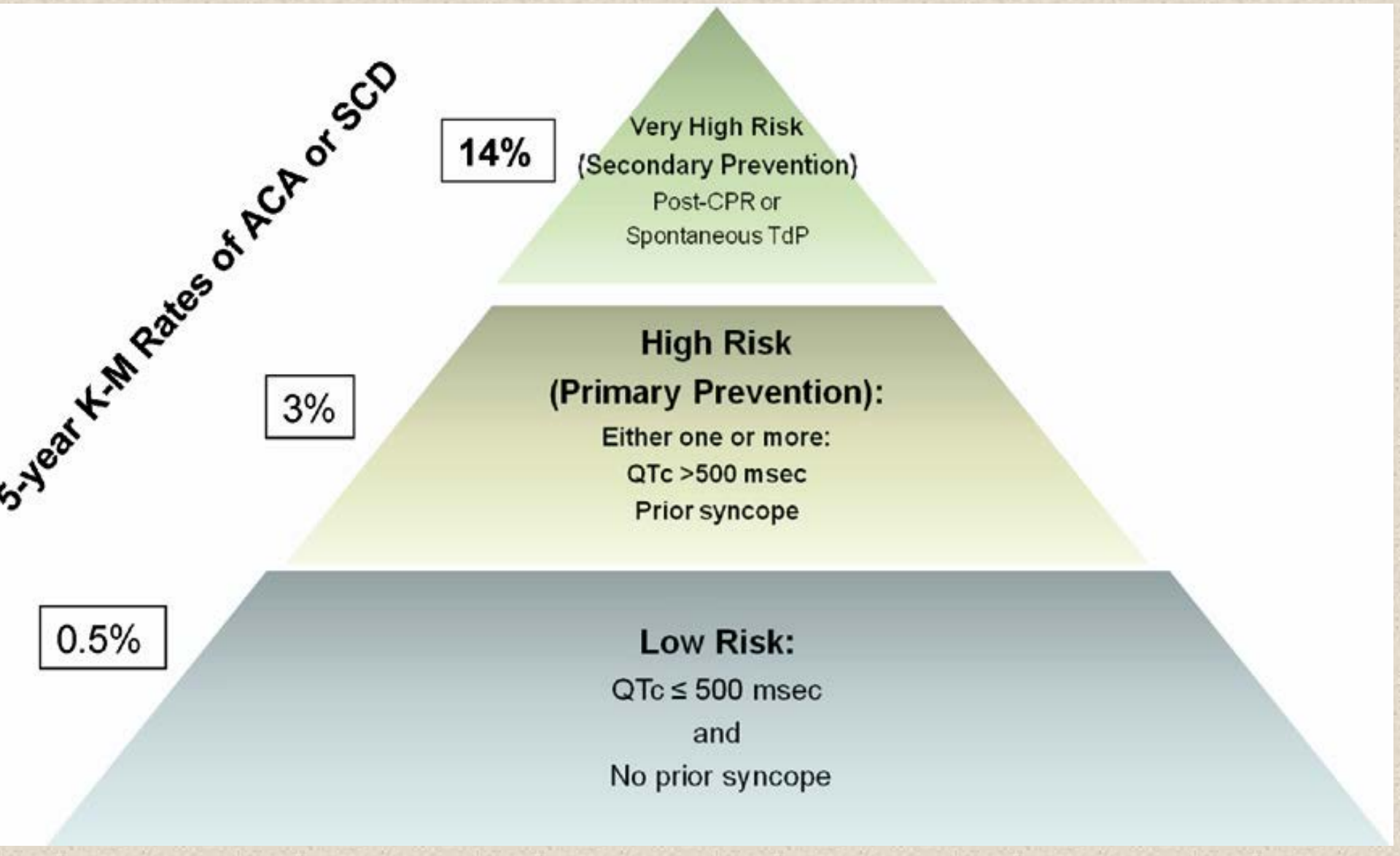
	-1 point	0 points	1 point	2 points
Event-free on therapy for 10 y	yes			
QTc, ms		≤500	>500–≤550	>550
Prior ACA		No	Yes	
Events on therapy		No	Yes	
Age at implantation, y	>20	≤20		

Schwartz et al. Circulation 2010;122:1272-1282

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



Schwartz et al. Circulation 2010;122:1272-1282



Goldenberg et al, JACC 2008

Long QT Syndrome

Class I

1. Lifestyle modification is recommended for patients with an LQTS diagnosis (clinical and/or molecular). *(Level of Evidence: B)*
2. Beta blockers are recommended for patients with an LQTS clinical diagnosis (i.e., in the presence of prolonged QT interval). *(Level of Evidence: B)*
3. Implantation of an ICD along with use of beta blockers is recommended for LQTS patients with previous cardiac arrest and who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: A)*

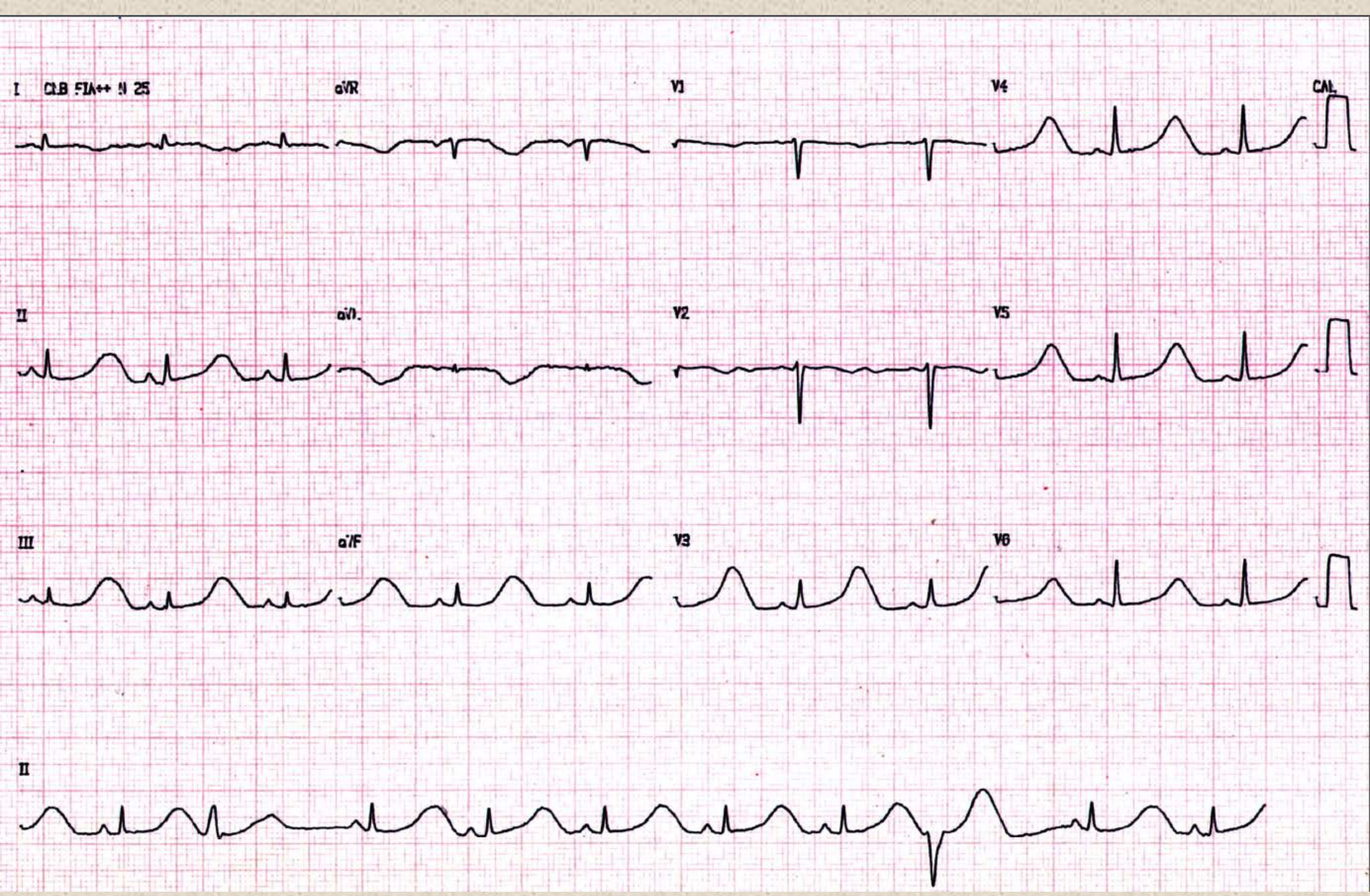
Zipes et al, JACC 2006; 48:e247-e346

Long QT Syndrome

Class IIa

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

Zipes et al, JACC 2006; 48:e247-e346


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II