

Prolonged QT Syndromes: Congenital and Acquired

April 30, 2014

Elizabeth S. Kaufman, MD

I have no financial disclosures.



MetroHealth Campus,
Case Western Reserve University

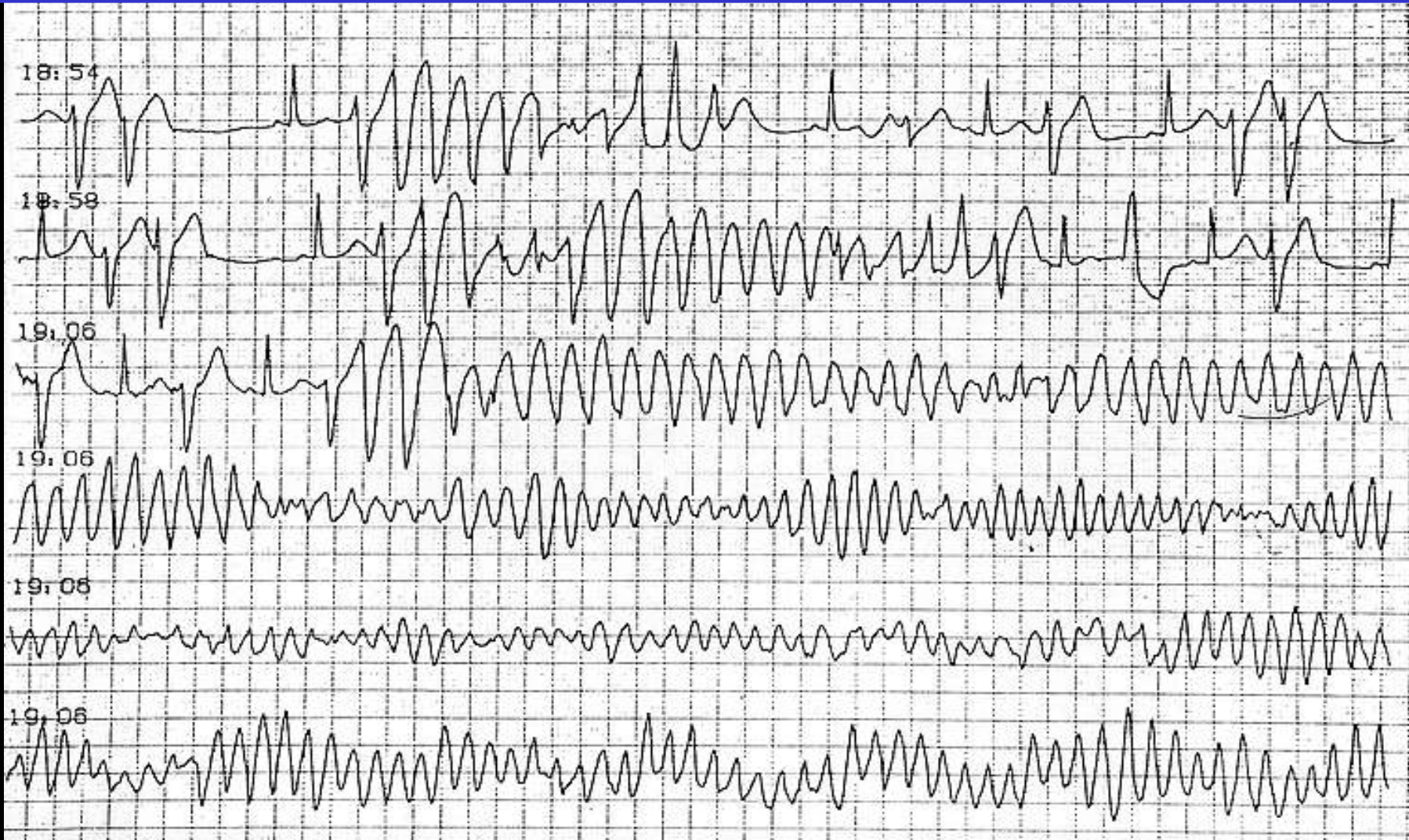


- Congenital LQTS
 - Genetic basis
 - Diagnosis
 - Risk assessment
 - Treatment
 - Role of genetic testing
- Acquired LQTS
 - Risk factors for torsades
 - Medications that prolong QT
 - How to keep patients safe

Congenital Long QT Syndrome

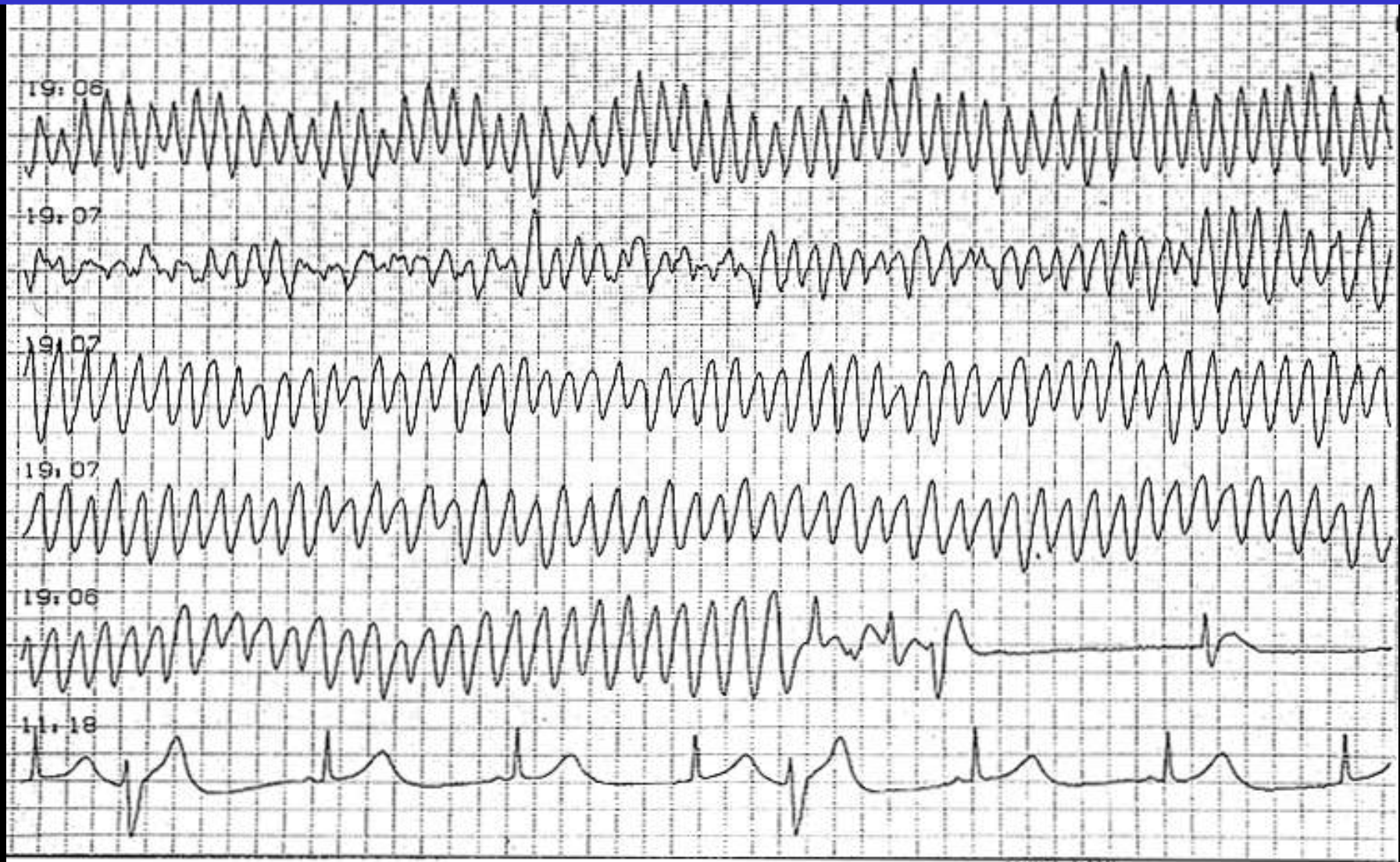
- Genetic disorder (autosomal dominant)
- QT interval prolonged
 - >440 ms in males
 - >460 ms in females
- Torsades de pointes VT
- Syncope and sudden cardiac death
- Congenital deafness in Jervell and Lange-Nielsen syndrome (autosomal recessive)

Holter ECG Recording in LQTS Patient with Syncope (representative strips of ECG recording, part 1 of 2)



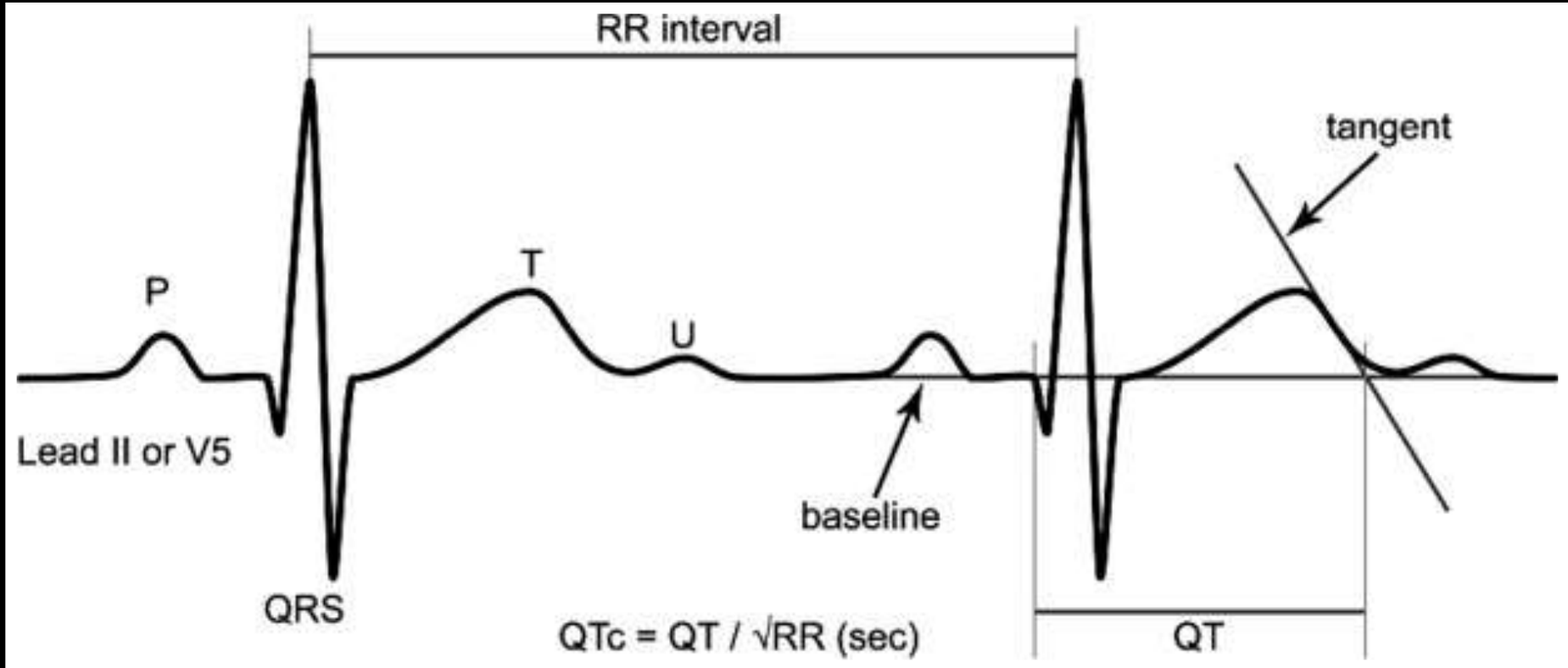
From Moss AJ with the C.A.R.E. Foundation, 2002

Holter ECG Recording in LQTS Patient with Syncope (representative strips of ECG recording, part 2 of 2)

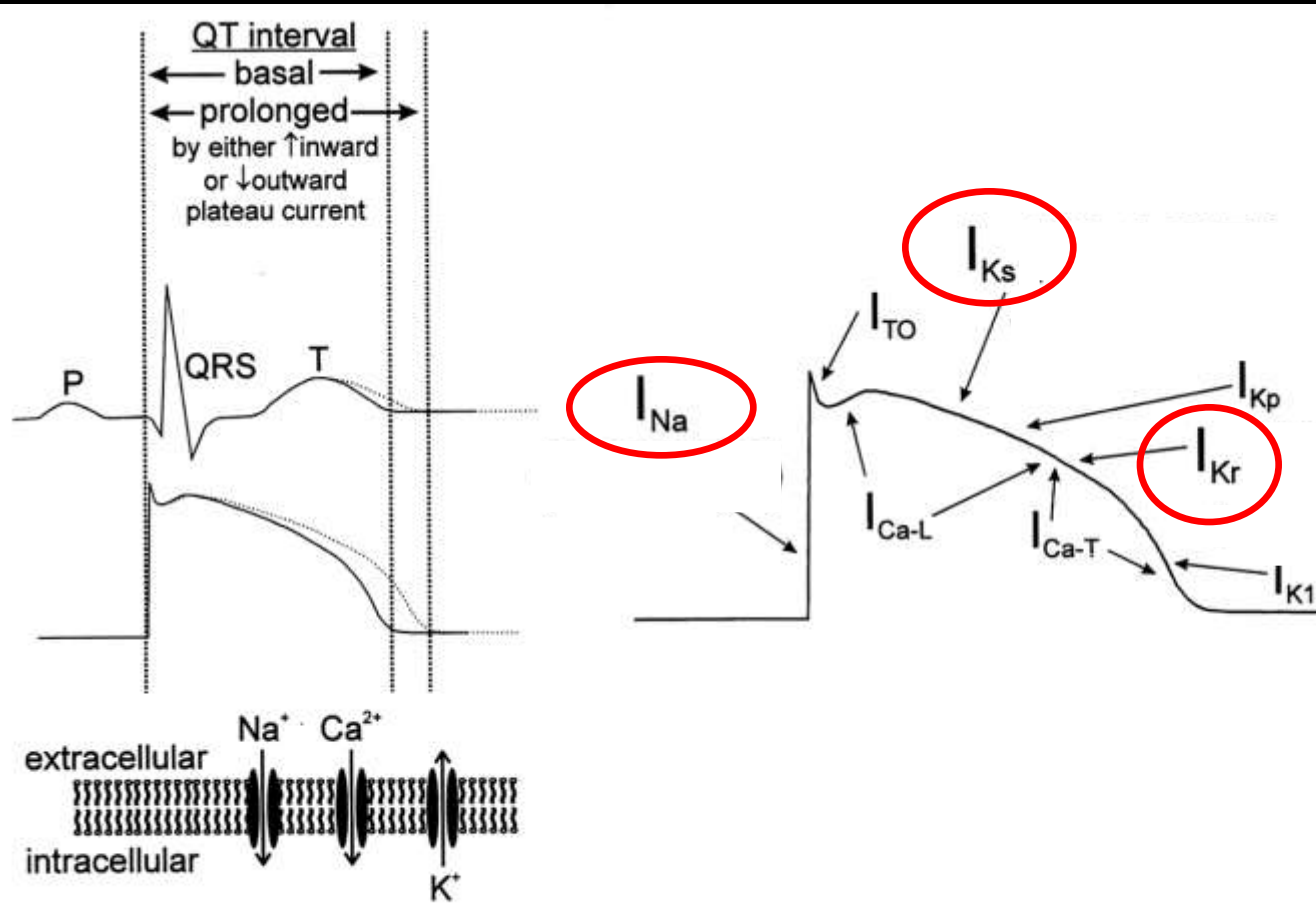


From Moss AJ with the C.A.R.E. Foundation, 2002

Measuring QT: Tangent Method



Postema et al. Heart Rhythm 2008;5:1015-1018



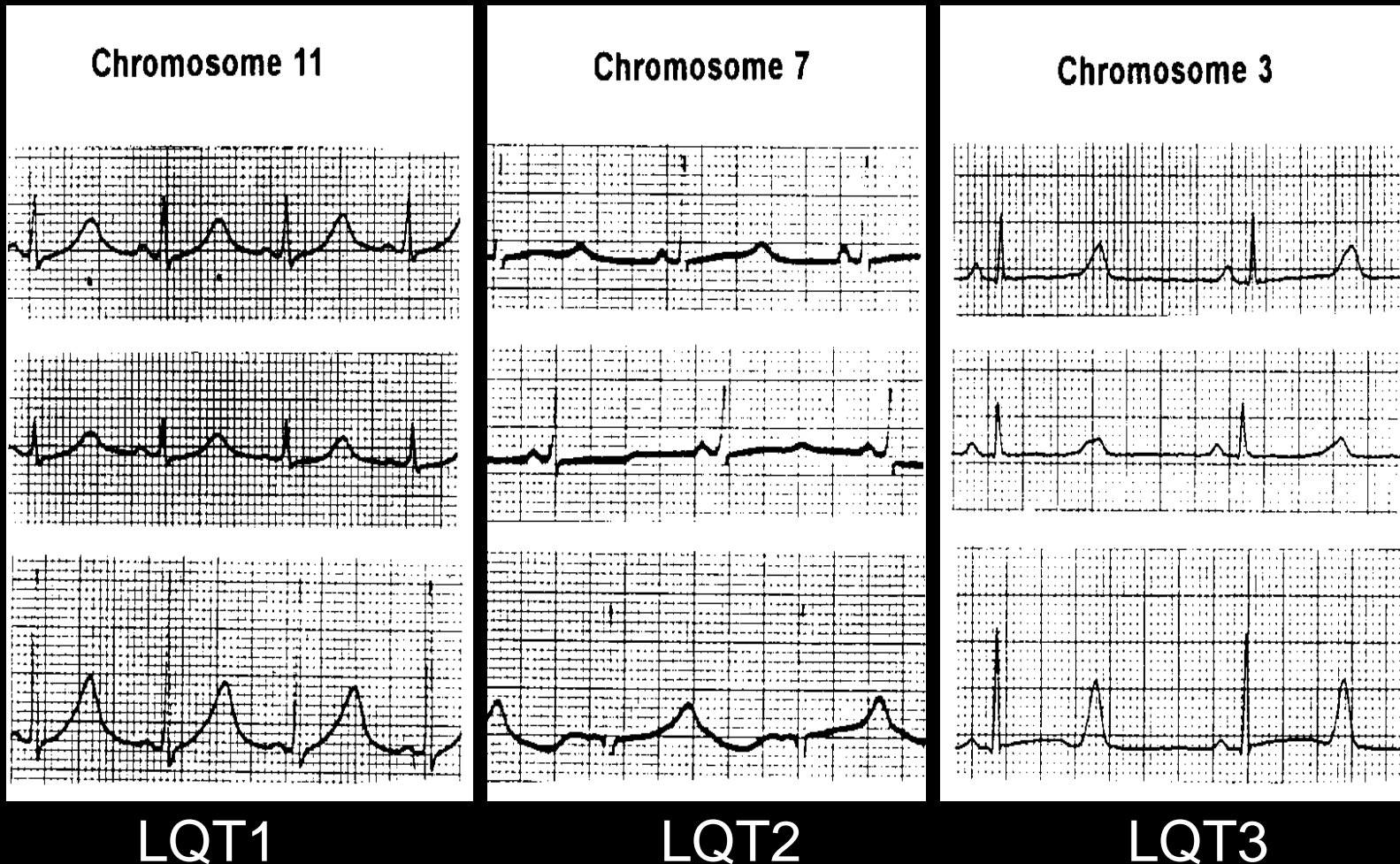
Basis for the Long QT Syndrome

Genetic Basis for Congenital LQTS

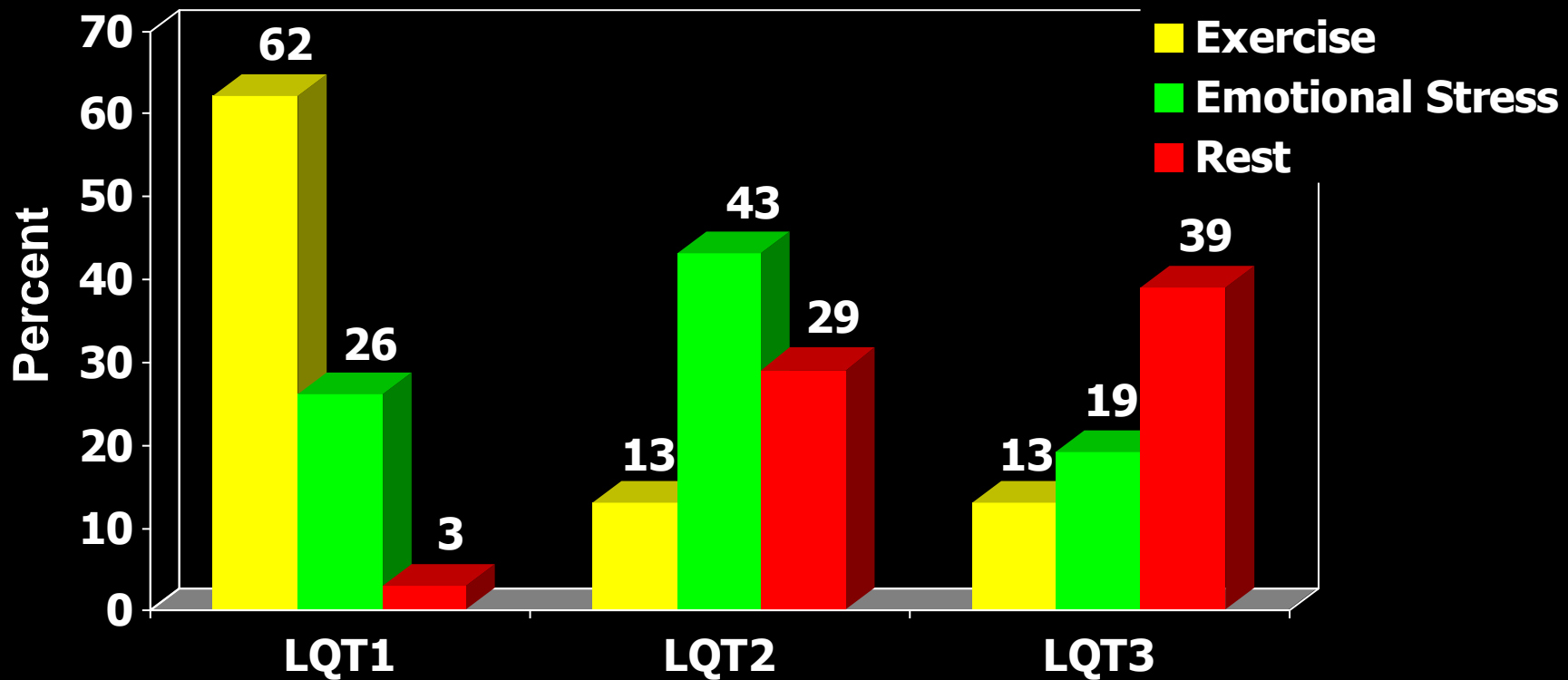


Type	Locus	Gene	Protein	Function	Frequency
LQT1	11p15.5	KCNQ1	K _V 7.1 α	I _{Ks} ↓	30-35%
LQT2	7q35	KCNH2	K _V 11.1 α	I _{Kr} ↓	25-30%
LQT3	3p21	SCN5A	Na _v 1.5α	I _{Na} ↑	5-10%
LQT4	4q25	ANK2	Ankyrin-B	I _{Na,K} ↓ I _{NCX} ↓	rare
LQT5	21q22.1	KCNE1	minK β	I _{Ks} ↓	1%
LQT6	21q22.1	KCNE2	MiRP1 β	I _{Kr} ↓	rare
LQT7*	17q23	KCNJ2	Kir2.1 α	I _{K1} ↓	rare
LQT8**	12p13.3	CACNA1C	Ca _v 1.2 α _{1c}	I _{Ca,L} ↑	rare
LQT9	3p25	CAV3	Caveolin-3	I _{Na} ↑	rare
LQT10	11q23	SCN4B	Na _v 1.5 β4	I _{Na} ↑	rare
LQT11	7q21	AKAP9	Yotiao	I _{Ks} ↓	rare
LQT12	20q11.2	SNTA1	A1-syntrophin	I _{Na} ↑	rare
LQT13	11q24	KCNJ5	Kir3.4/GIRK4	I _{KACh} ↑	rare

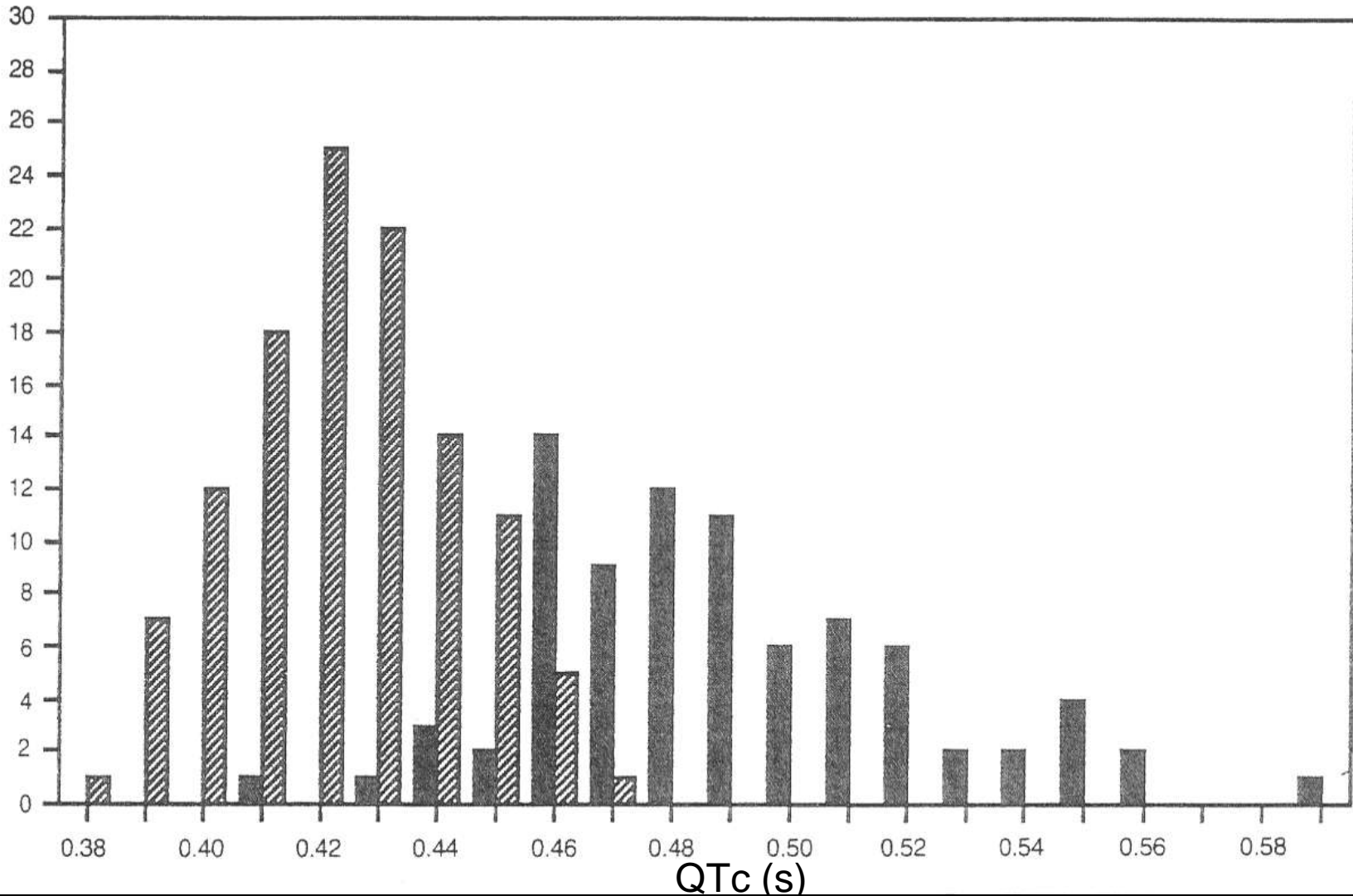
T-wave Morphology in LQTS by Genotype



Occurrence of Gene-Specific Triggers



Making the Diagnosis



Phenotype/Genotype Mismatch



- Genetic variations!
- Environmental factors

- **Diagnostic Dilemma**
 - Accurate diagnosis and treatment saves lives.
 - Even individuals with normal phenotype at baseline may be at risk for sudden death **during adrenergic stimulation.**
- Which patients should be treated, and how should they be treated?

Diagnosis



- ECG (QT interval) at baseline
- ECG with exercise, 24-hour monitor
- Symptoms
- Family history
- Genetic testing

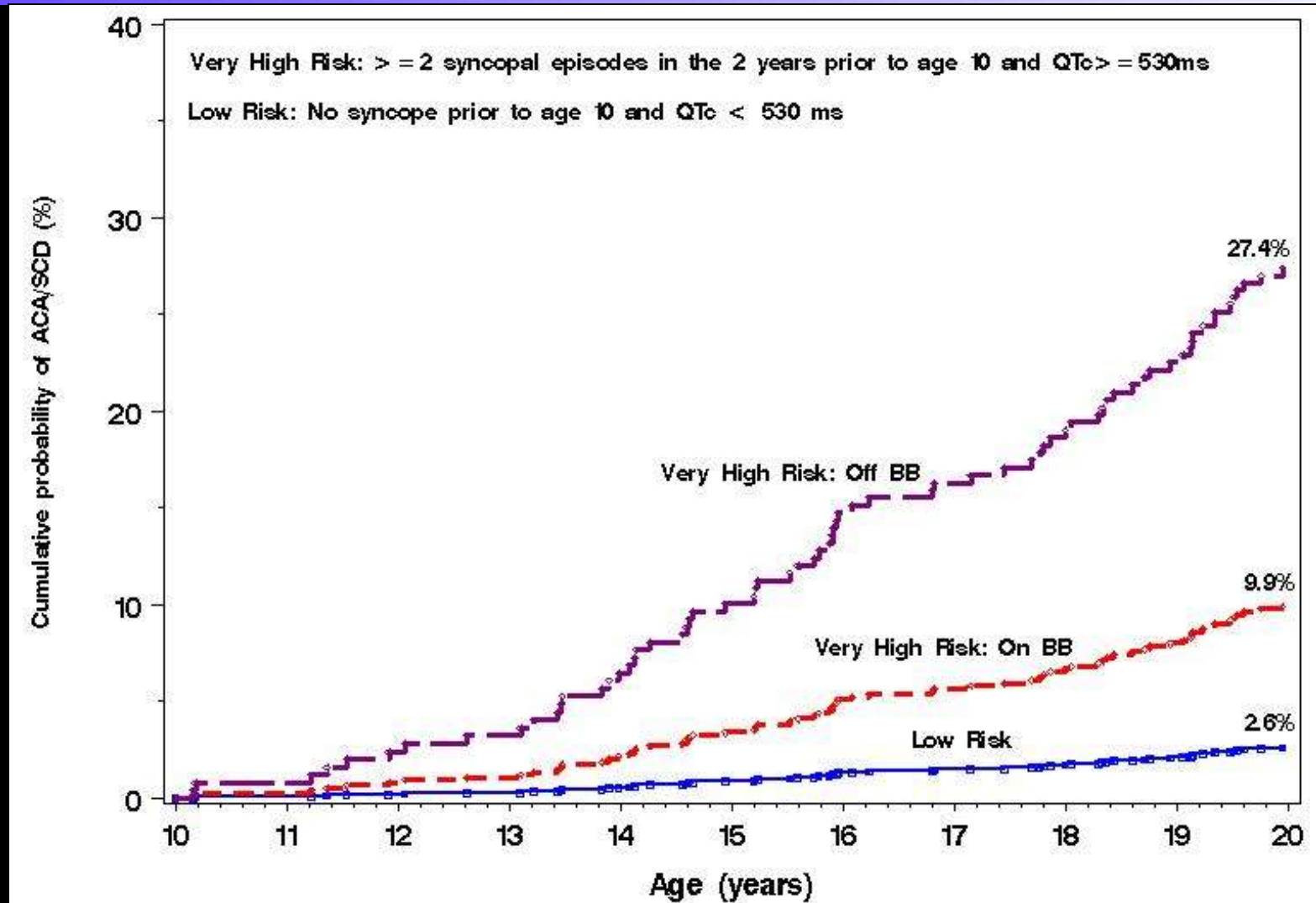
- Avoidance of QT-prolonging drugs
- Restriction from competitive sports
- Antiadrenergic therapy
 - >53% 15-year mortality for LQTS patients presenting with syncope
 - 9% after antiadrenergic therapy
 - (1985 Schwartz and Locati)
 - Choice of beta blocker matters!
- ICD

Which subgroups of LQTS patients are inadequately protected by beta blocker therapy?

Markers of High Risk

- Symptoms in the first year of life
- Aborted cardiac arrest
- Syncope (on beta-blockers)
- Excessive QT prolongation
- Gender, age
- LQTS genetic subtype
- Specific mutation

Excessive QT Prolongation and Syncope

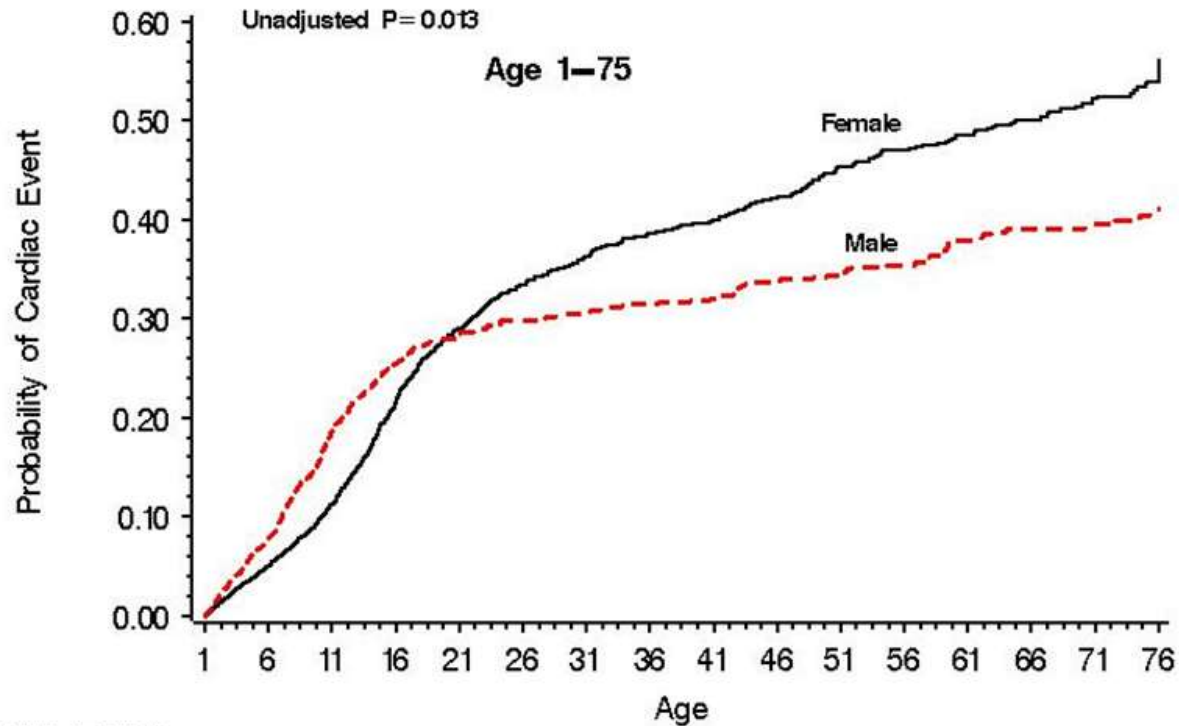


Hobbs et al. for the International LQT Registry, JAMA 2006;296:1252

Age and Gender Interaction: Any symptom

Fig. 1A

Probability of a First Cardiac Event from age 1 through 75 years by Gender

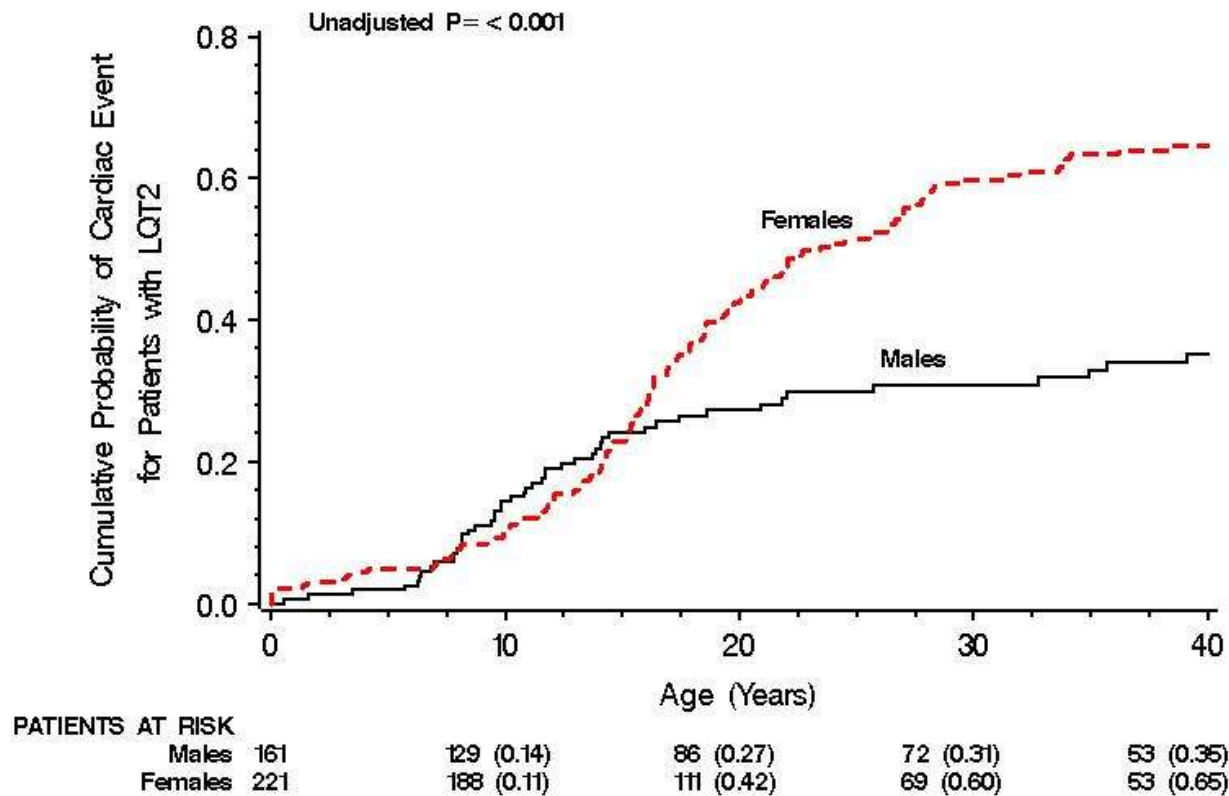


PATIENTS AT RISK

Female	2319	1506 (0.22)	919 (0.36)	587 (0.42)	305 (0.48)	87 (0.56)
Male	1450	786 (0.26)	530 (0.31)	383 (0.34)	222 (0.38)	73 (0.41)

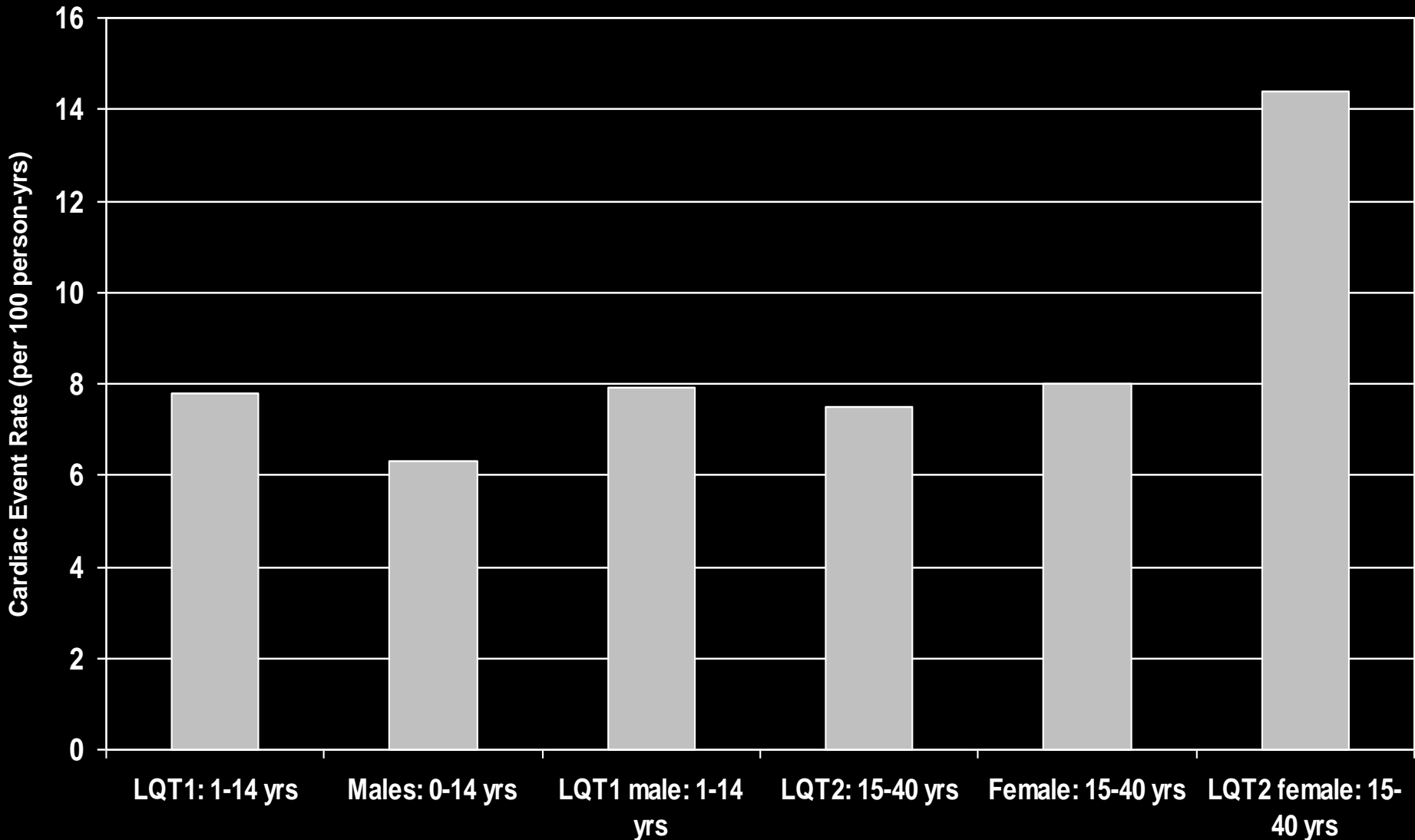
Courtesy of Ilan Goldenberg

LQT2: Cardiac Event Rate by Gender

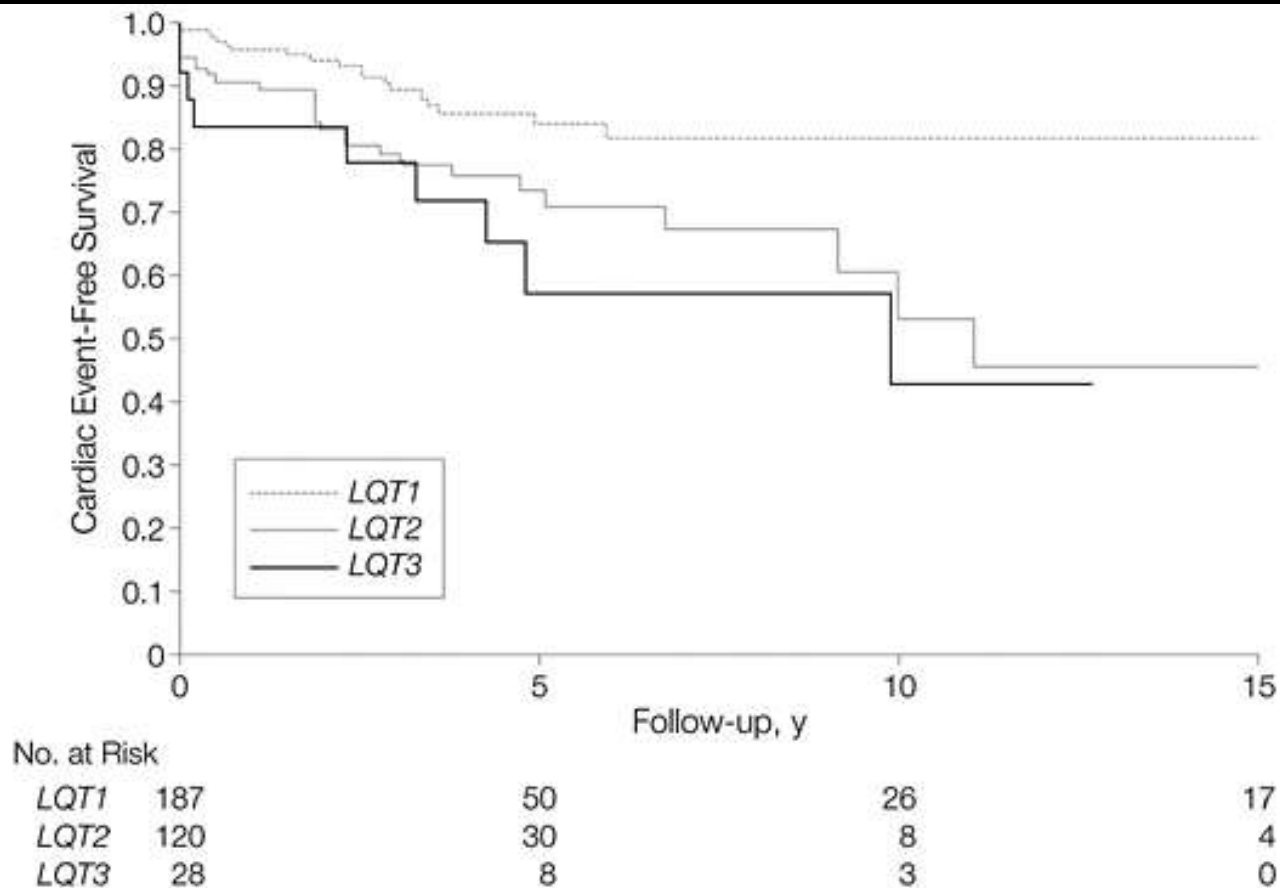


Courtesy of Ilan Goldenberg

Residual Rate of First Cardiac Events during β -Blocker Therapy

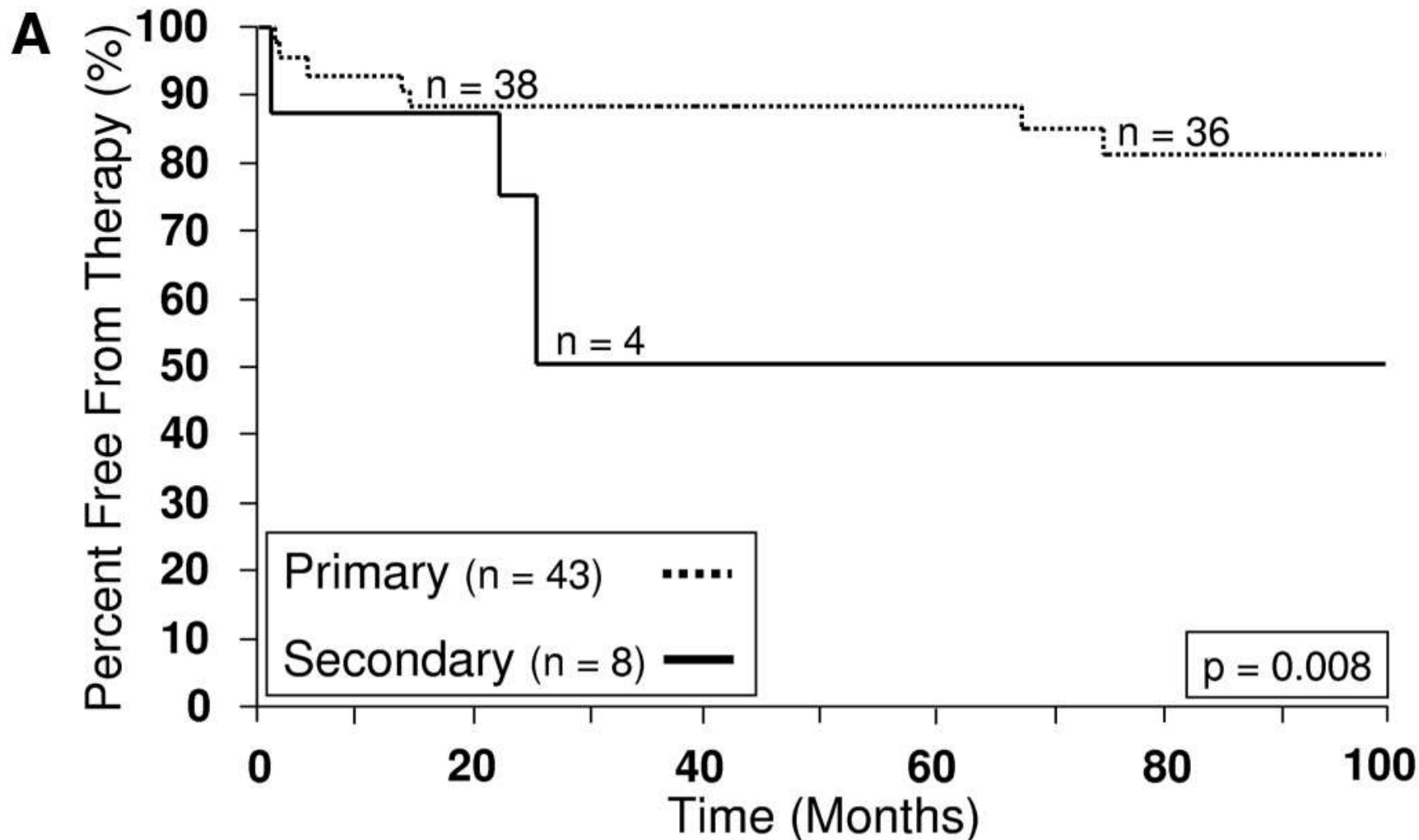


Event-free survival on beta-blockers

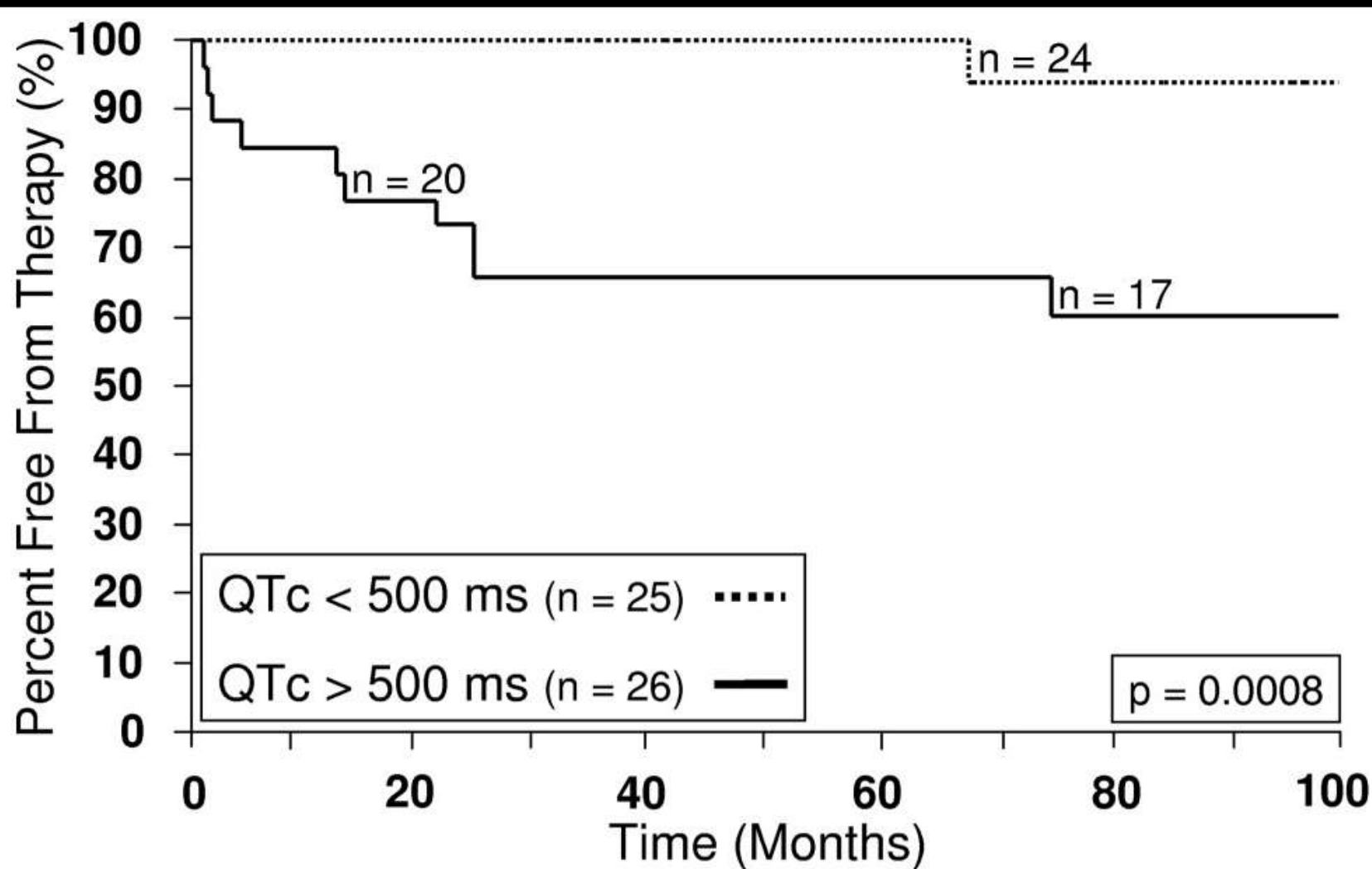


Priori et al. JAMA 2004;292:1341-1344

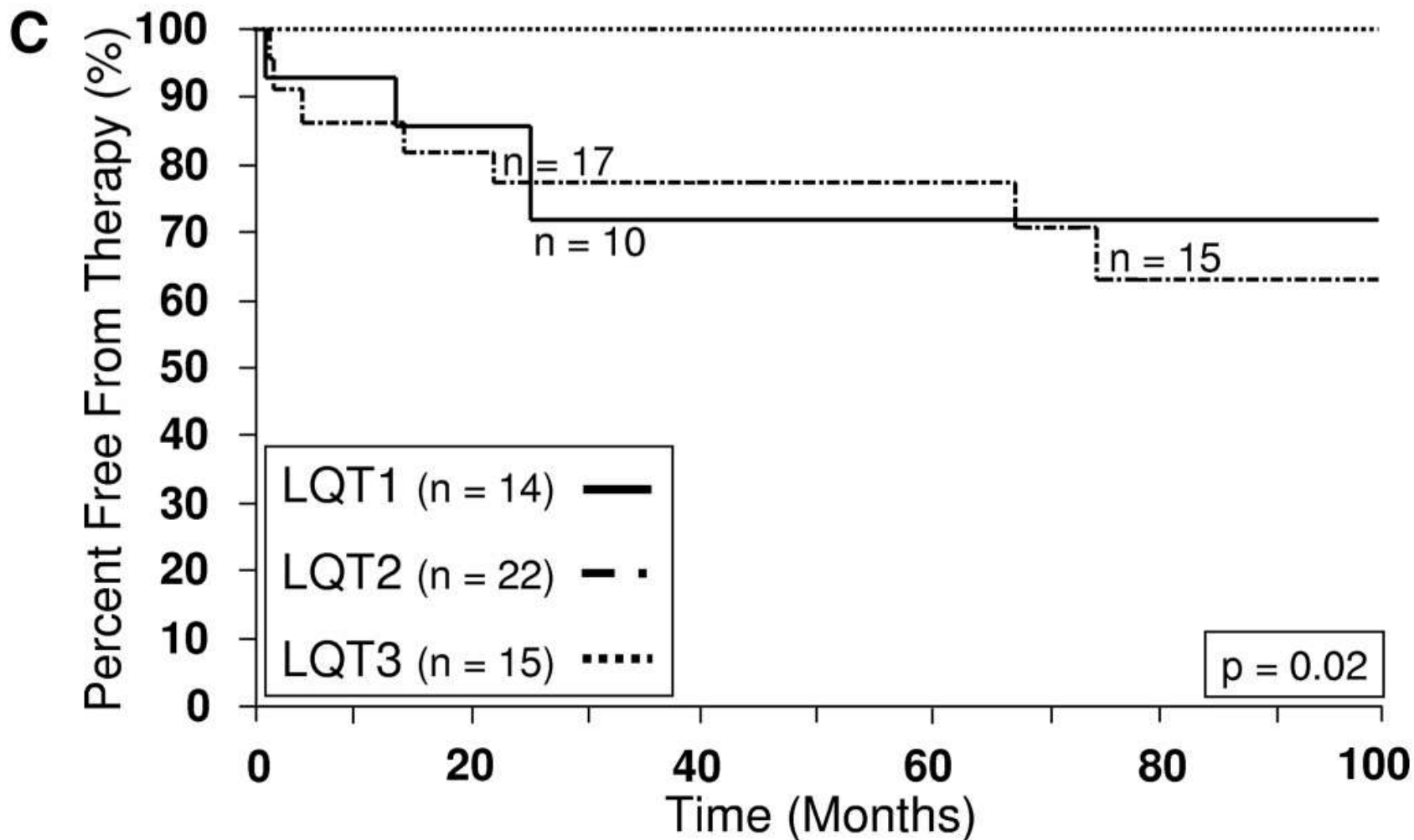
Appropriate ICD shocks by history



Appropriate ICD shocks by QTc



Appropriate ICD shocks by genotype

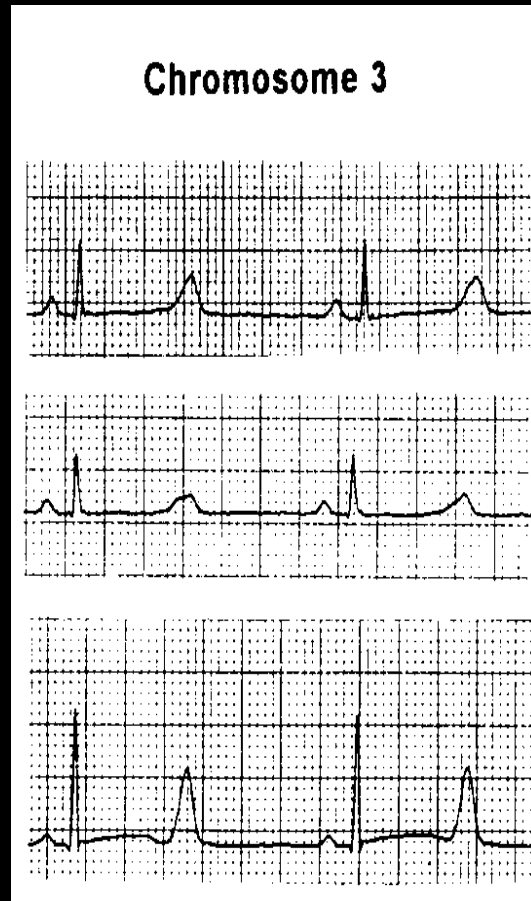


LQT3 Dogma until recently



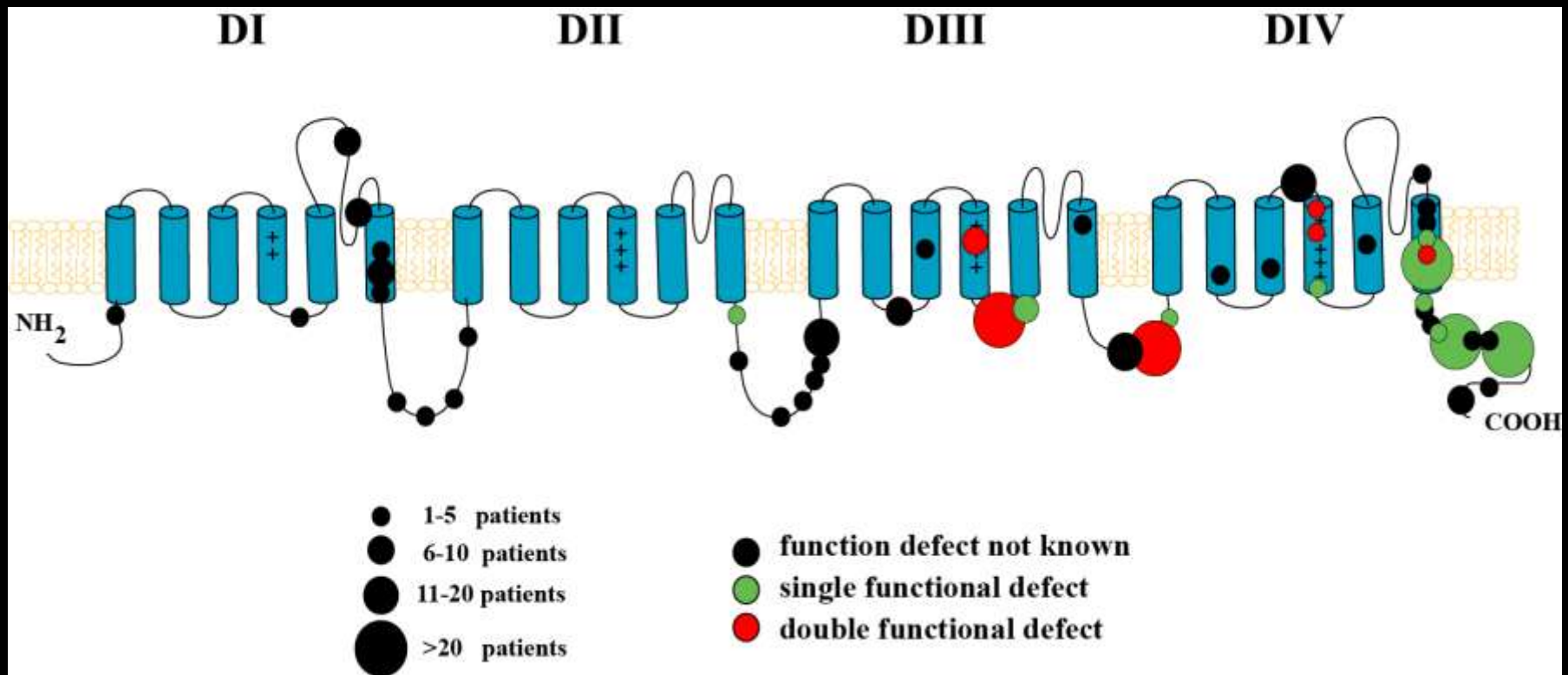
- Outcomes in LQT3 are unpredictable.
- No evident protective effect of beta blocker therapy in LQT3
- High-risk patients with LQT3 should receive an ICD.

LQT3, gain-of-function sodium channel mutation

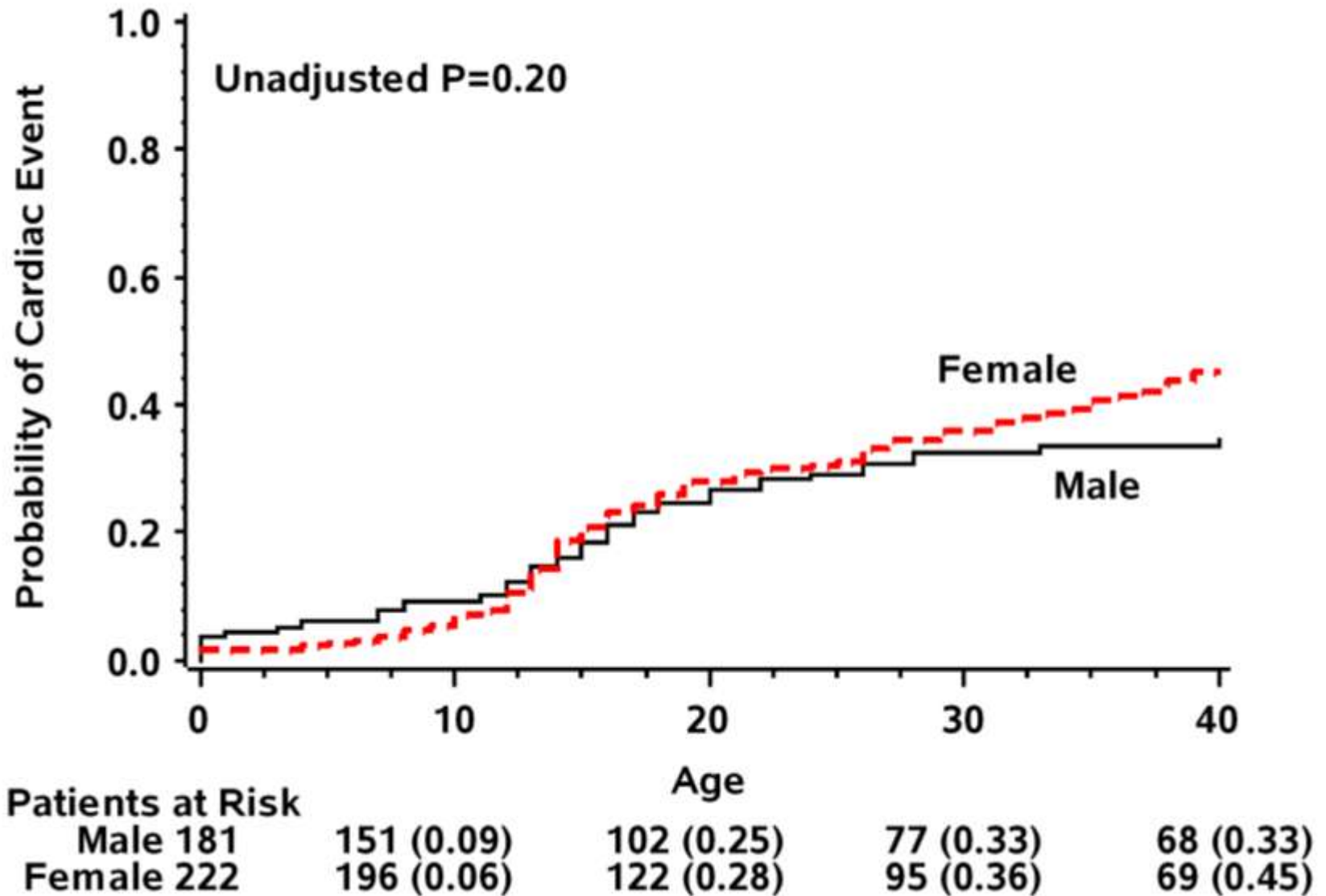


5-10% of genotyped LQTS

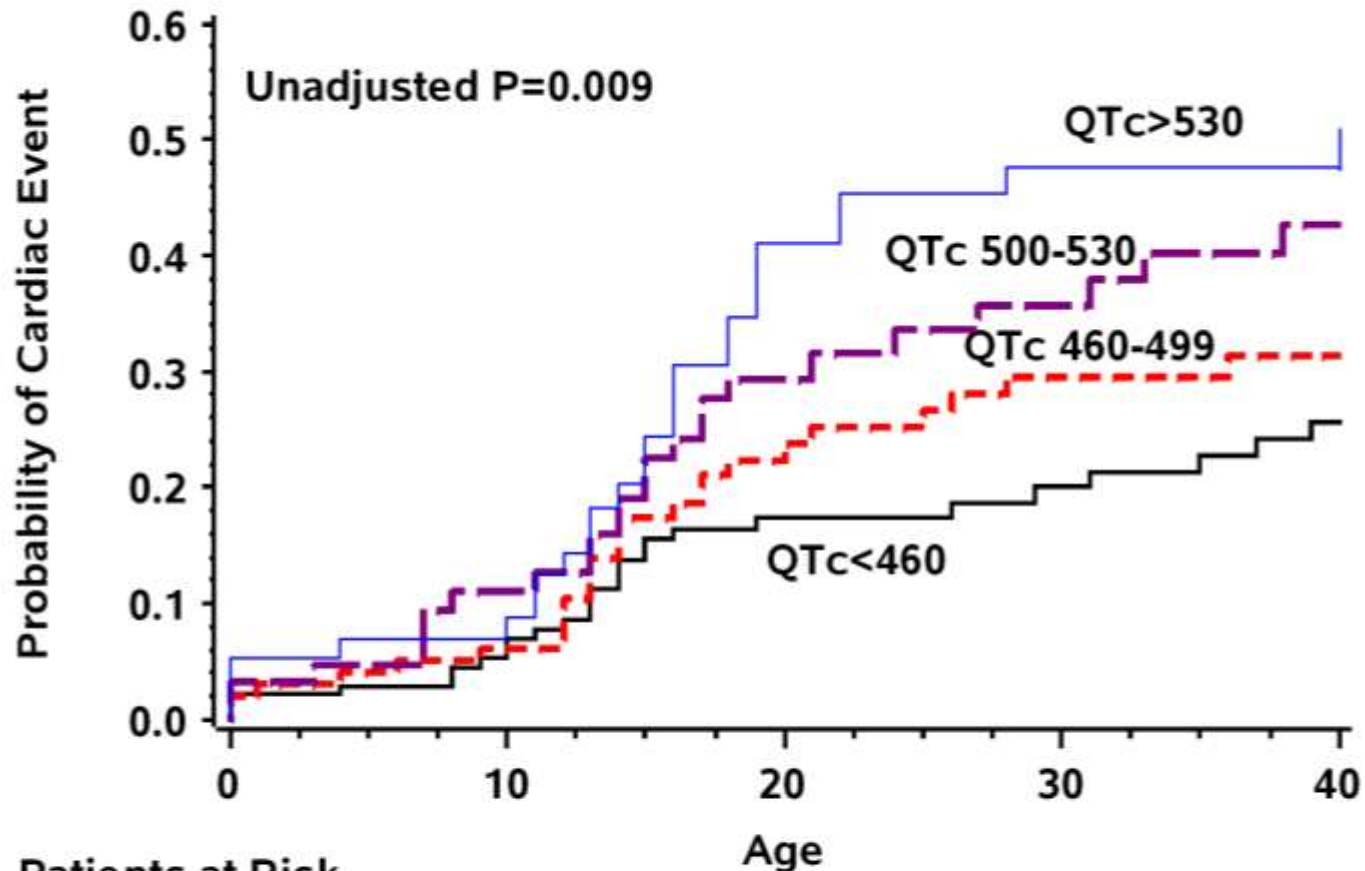
403 Patients with 53 Different SCN5a Mutations



Gender and Risk in LQT3

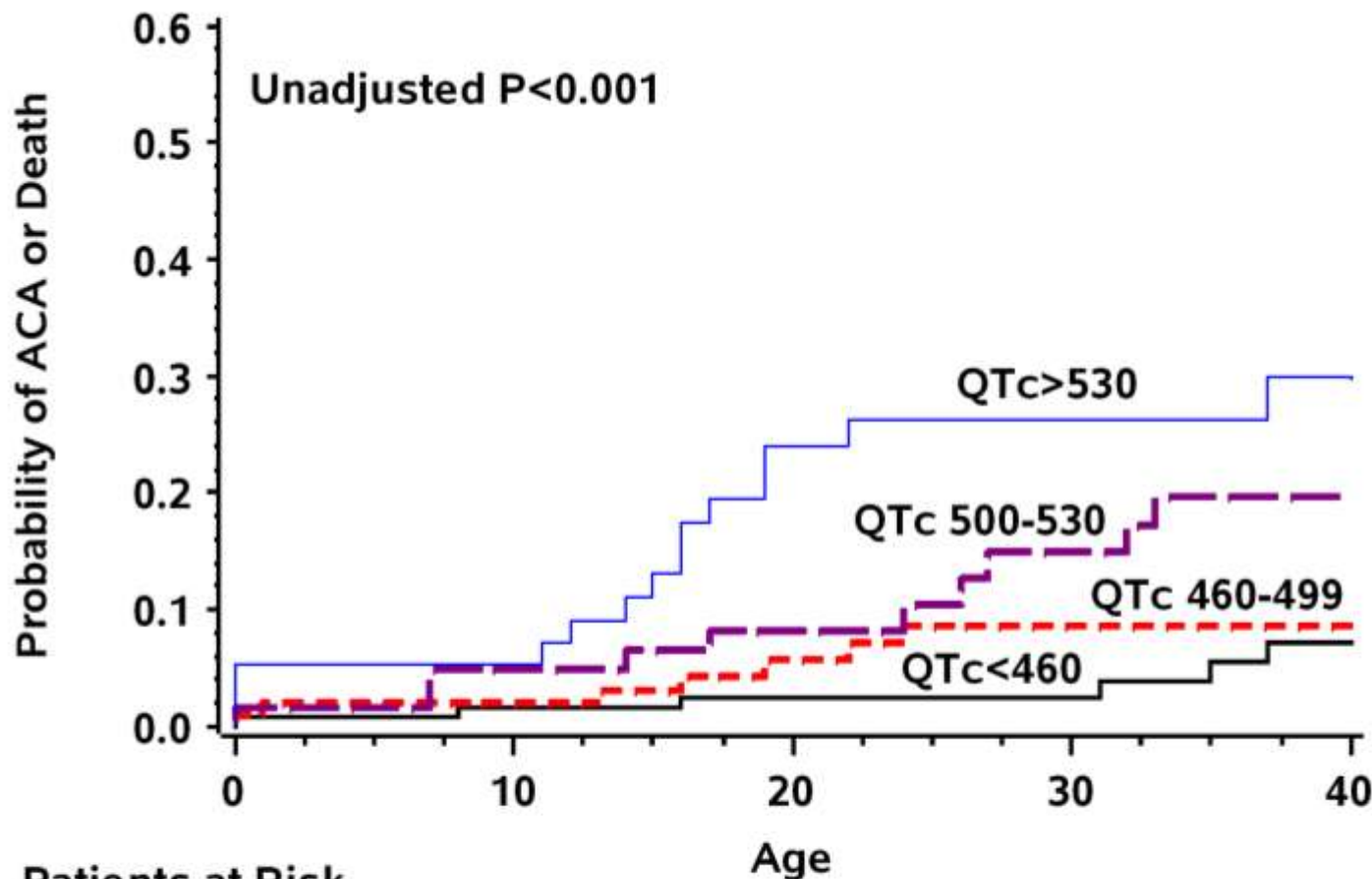


QT interval and risk in LQT3



	Patients at Risk				
	0	10	20	30	40
QTc < 460	138	115 (0.05)	79 (0.17)	61 (0.20)	47 (0.26)
QTc 460-499	100	87 (0.06)	56 (0.22)	45 (0.30)	41 (0.31)
QTc 500-530	63	56 (0.11)	36 (0.29)	29 (0.36)	24 (0.43)
QTc > 530	57	51 (0.07)	28 (0.41)	21 (0.48)	16 (0.48)

QTc and risk of lethal event in LQT3



	Patients at Risk	0	10	20	30	40
$QTc < 460$	138	119 (0.02)	86 (0.02)	67 (0.02)	53 (0.07)	
$QTc 460-499$	100	91 (0.02)	68 (0.06)	56 (0.09)	49 (0.09)	
$QTc 500-530$	63	59 (0.05)	45 (0.08)	36 (0.15)	31 (0.20)	
$QTc > 530$	57	52 (0.05)	33 (0.24)	27 (0.26)	16 (0.30)	

LQT3, Study of 403 Patients



- 130 (32%) had a first cardiac event, of which 40 were ACA/SCD
- Risk directly related to QT interval
- No gender difference in risk
- Higher risk in symptomatic patients
- Very high risk among those symptomatic during first year of life
- Beta blockers are protective!

Roles for Genetic Testing in LQTS



1. To stratify risk and guide therapy, by defining the subtype of LQTS
2. To make or exclude the diagnosis in a borderline-phenotype individual, when the family's mutation is known

Case #1, Genetic testing



- 20-year-old male student presents with syncope.
- QTc interval is 0.50 seconds.
- Genetic testing is performed.

Genetic Basis for Congenital LQTS



Type	Locus	Gene	Protein	Function	Frequency
LQT1	11p15.5	KCNQ1	K _v 7.1 α	I _{Ks} ↓	30-35%
LQT2	7q35	KCNH2	K _v 11.1 α	I _{Kr} ↓	25-30%
LQT3	3p21	SCN5A	Na _v 1.5α	I _{Na} ↑	5-10%
LQT4	4q25	ANK2	Ankyrin-B	I _{Na,K} ↓ I _{NCX} ↓	rare
LQT5	21q22.1	KCNF4	minK β	I _{K1} ↓	1%
LQT6	21q22.1	KCNK9	hKv1.8	I _{K1} ↓	rare
LQT7*	17q23	KCNJ2	Kir2.1 α	I _{K1} ↓	rare
LQT8**	12p13.3	CACNA1C	Ca _v 1.2 α _{1c}	I _{Ca,L} ↑	rare
LQT9	3p25	CAV3	Caveolin-3	I _{Na} ↑	rare
LQT10	11q23	SCN4B	Na _v 1.5 β4	I _{Na} ↑	rare
LQT11	7q21	AKAP9	Yotiao	I _{Ks} ↓	rare
LQT12	20q11.2	SNTA1	A1-syntrophin	I _{Na} ↑	rare
LQT13	11q24	KCNJ5	Kir3.4/GIRK4	I _{KACh} ↑	rare

Sensitivity about 70%

Example of Test Results

Class I: Disease-causing mutation

Class II: Possible disease-causing mutation

Class III: Unlikely to be disease-causing

<u>Num</u>	<u>Gene</u>	<u>Region(G)</u>	<u>Nucl.Change</u>	<u>A.A.Change</u>	<u>Genotype</u>	<u>Region(P)</u>	<u>Region Type(P)</u>	<u>Class</u>
1	KCNQ1	exon 15	1760 C>T	Thr 587 Met	C/T	C-Terminal	C-Terminal	II
2	KCNE1	exon 4	112 G>A	Gly 38 Ser	A/A	N-Terminal	N-Terminal	III

TEST RESULTS

Possible Deleterious Mutation Detected

This individual is positive for a **Class II** mutation, which is likely associated with disease.

- 20-year-old male student presents with syncope.
- QTc interval is 0.50 seconds.
- Genetic testing reveals a LQT1 mutation.
- Patient is treated with beta blocker therapy and modification of exercise.

Limitations of genetic testing



- In a normal/borderline phenotype individual, when a family's mutation is not known,
 - Sensitivity low
 - Specificity low
- A genetic result must be interpreted in clinical context.

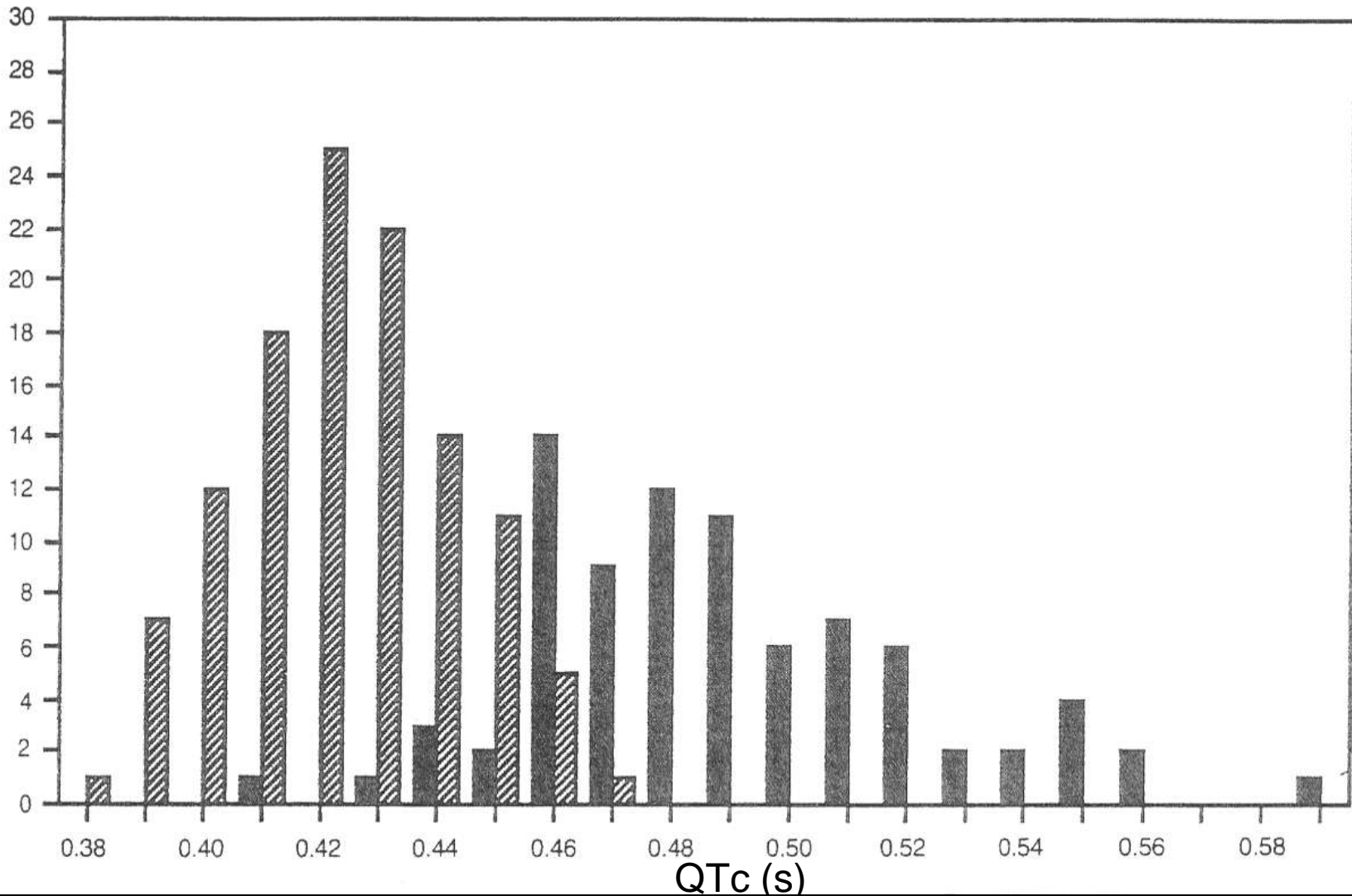
1. To stratify risk and guide therapy, by defining the subtype of LQTS
2. To make or exclude the diagnosis in a borderline-phenotype individual, when the family's mutation is known

Case 2: Genetic testing



- A 14-year-old girl wants to play on the school basketball team.
- Brother died suddenly while running and was found to have a LQT1 mutation.
- No syncope
- QTc 0.46 seconds

Making the Diagnosis



Gene-positive.....Or not



- Avoidance of high-intensity sports?
- Beta blocker
- Surveillance, serial ECGs, exercise tests, Holters
- Can play sports
- No beta blocker
- No cardiologist

If positive, would she need an ICD?



- Probably not!
- Variable penetrance
- A positive genotype is only weakly predictive of risk and must be interpreted in the context of clinical risk markers.

Why make the diagnosis?



- Appropriate treatment saves lives.
- Avoiding inappropriate treatment saves money, quality of life.

Genetic testing can “rule in” or “rule out” the diagnosis, in a borderline-phenotype individual, when the family’s mutation is known.

Why is Sensitivity Low?



- We haven't discovered other major ion channel genes(?)
- The genetic substrate for LQTS is more complex!

- Patients with **abnormal genotype but normal phenotype** may demonstrate LQTS with further provocation (drugs, electrolyte disorders, bradycardia).
- Patients with “acquired” LQTS when exposed to drugs, etc. might have underlying “silent” genetic mutation.

- Small minority have underlying mutation in major LQTS genes.
- A disproportionately high number of ALQTS patients have certain “benign” LQTS polymorphisms.

Implications

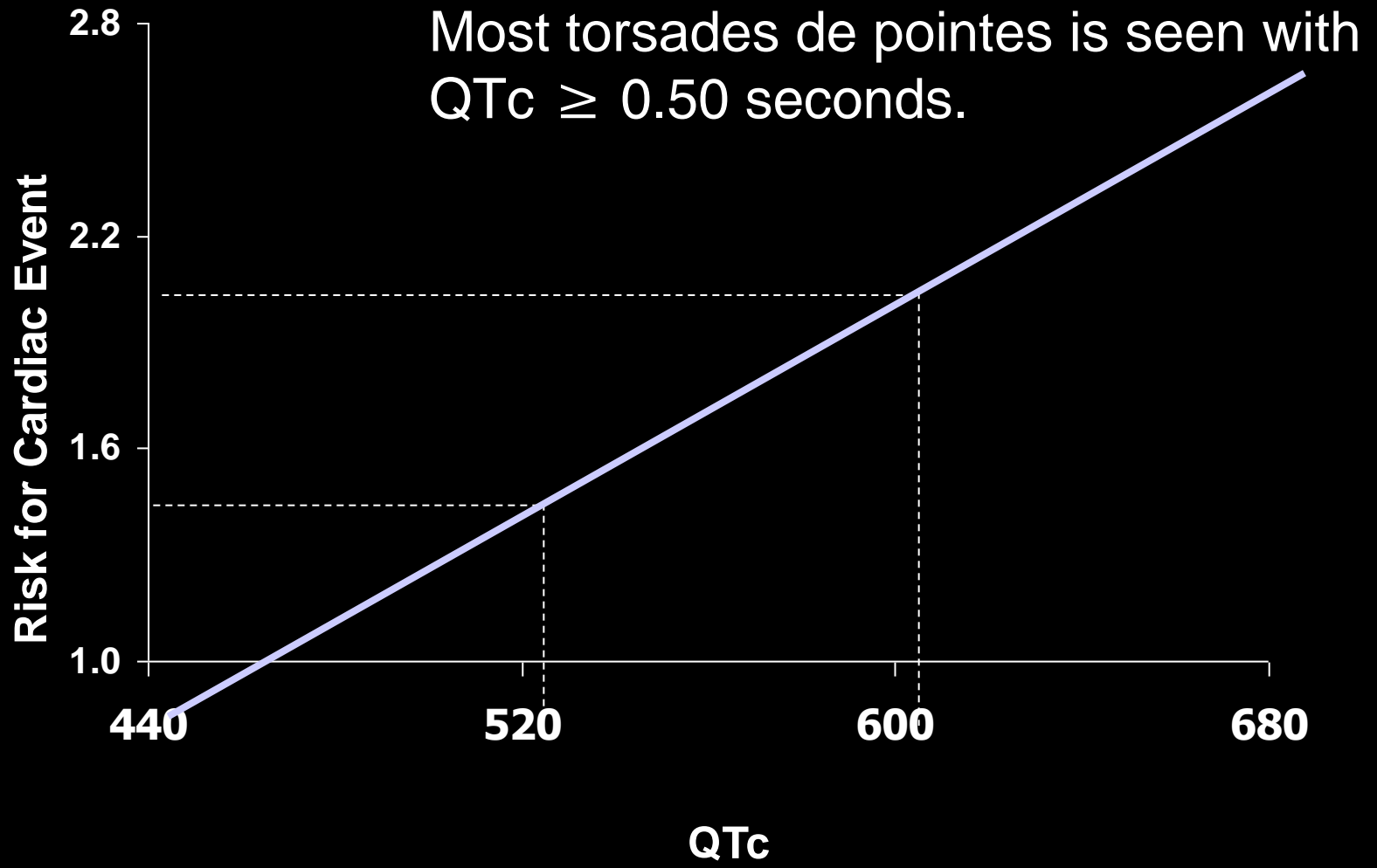
- Genotype (or our current understanding of it) incompletely predicts phenotype
- Clinical risk stratification still essential for guiding therapy.

Risk Factors for Torsades

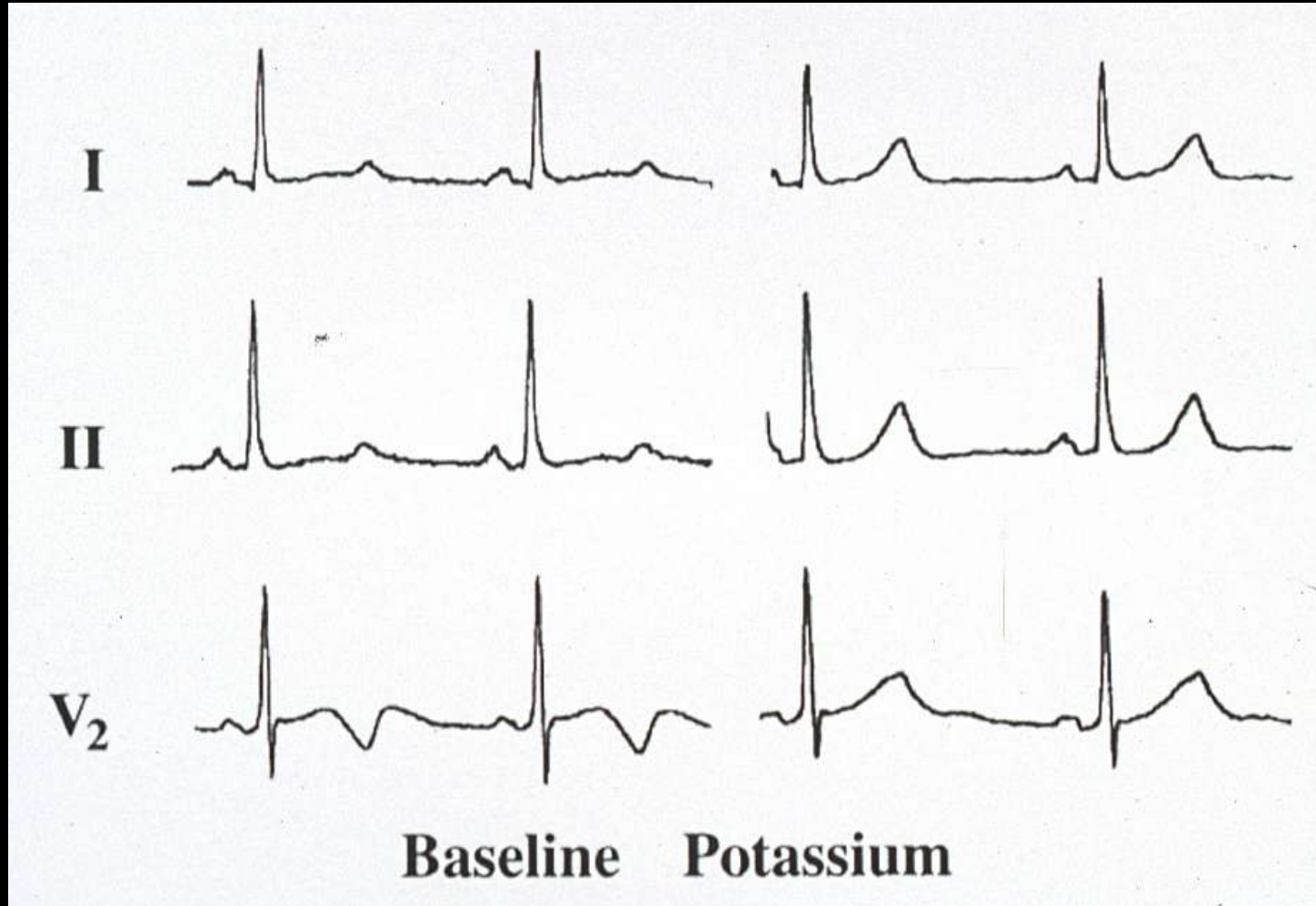


- Female gender
- Age over 65 years
- Bradycardia
- Low K, Mg or diuretic use
- Structural heart disease (HF, LVH)
- Multiple drugs
- Genetic polymorphisms
- Prolonged baseline QT

QTc Interval and Risk



Electrolytes: Potassium



QT-Prolonging Drugs

- Antiarrhythmics
- Antihistamines
- Antimicrobials
- Antifungals
- Antipsychotics
- Antidepressants

Miscellaneous Drugs to Avoid



- Epinephrine
- Diuretics
- Probucol
- Cisapride
- Ephedra*
- Ma huang*
- Chloral hydrate
- Methadone

Inhibitors of CYP3A4

- Imidazole antifungals
- Macrolide antibiotics
- Cimetidine
- Fluoxetine
- Paroxetine
- Haloperidol
- Grapefruit juice

My guidelines

QTc > .44 seconds → ? initiation

QTc > .50 seconds → ? stop drug,
on drug intensify
monitoring

QT > 0.55 seconds → Stop, ? admit

Torsades → Admit, stop drug,
or syncope monitor

Summary

- Risk factors for life-threatening torsades de pointes can be identified.
- Avoid multiple drugs
- Replace electrolytes
- Continuous ECG monitoring of high-risk patients allows early recognition and treatment of serious arrhythmias.



"Hey, Lorl! Take a look at Mr. Geckler's EKG!"

CLOSE TO HOME
By John McPherson