

LESSONS FROM THE LQTS REGISTRY

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THE INTERNATIONAL LQTS REGISTRY

- **Multinational collaboration headed by URMC:**
 - **US**
 - **Europe**
 - **Israel**
 - **Japan**

- **>8000 patients and family members**
 - **Genetics**
 - **Electrocardiographic**
 - **Clinical**
 - **Yearly follow-up**



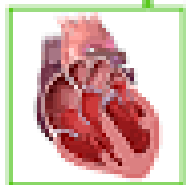
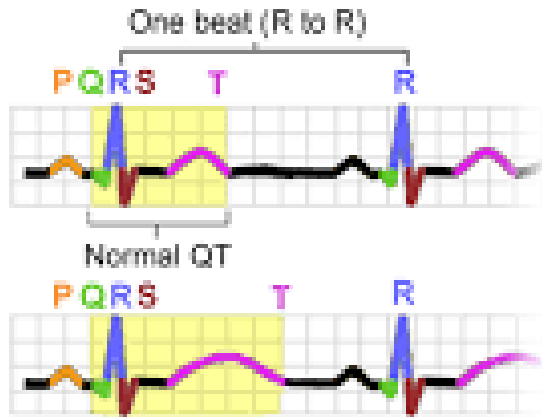
OUTLINE

- **Risk factors for sudden death in long QT syndrome:**
 - **Age**
 - **Sex**
 - **ECG: QTc duration**
 - **Clinical history**
 - **Family history**
- **Genetic markers for risk in LQTS**
 - **Genotype-specific triggers**
 - **Genotype-specific risk**
 - **Location and function of mutation within each genotype**

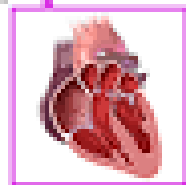


CONGENITAL LONG-QT SYNDROME

Each section of an electrocardiogram (ECG or EKG) is referred to by a letter name: Q, R, S, and T.

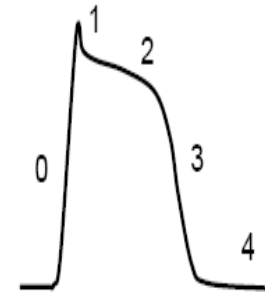


Heart is relaxed and full of blood at Q.



Heart is contracted at end of T.

© medim



Action Potential Phases	
0	= depolarization
1	= fast repolarization
2	= plateau
3	= terminal repolarization
4	= resting

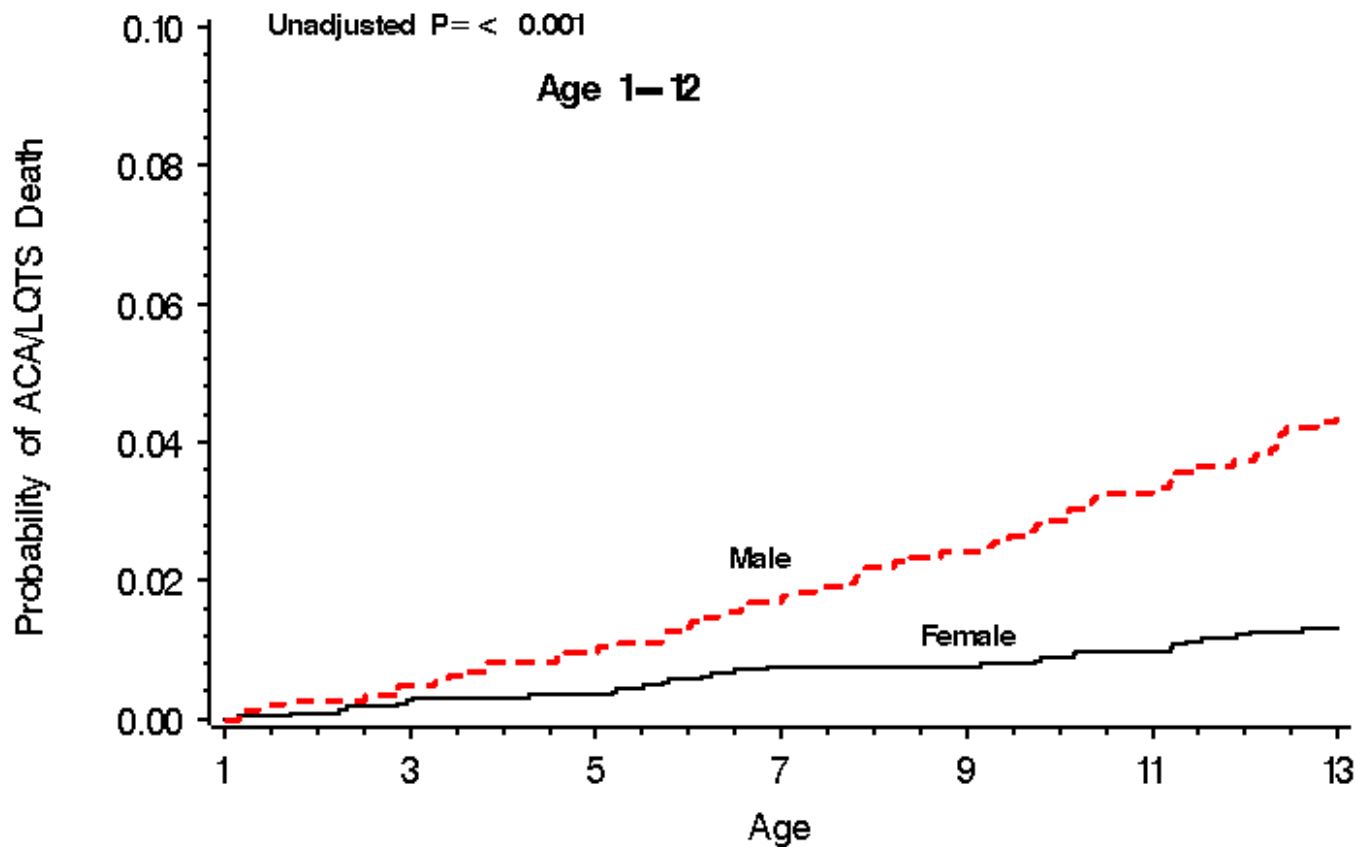
Current	Protein	Gene
Sodium current (I_{Na})	Nav 1.5	SCN5A
Calcium current (I_{Ca})	Cav 1.2	CACNA1C
Delayed Rectifier Slow (I_{Ks})	KvLQT1/minK	KCNQ1/KCNJ2
Delayed Rectifier Fast (I_{Kr})	HERG/MiRP	KCNH2/KCNJ2
Inward Rectifier (I_{K1})	Kir2.1	KCNJ2



Risk factors: Age and Sex



Risk of Sudden Death by Sex during Childhood

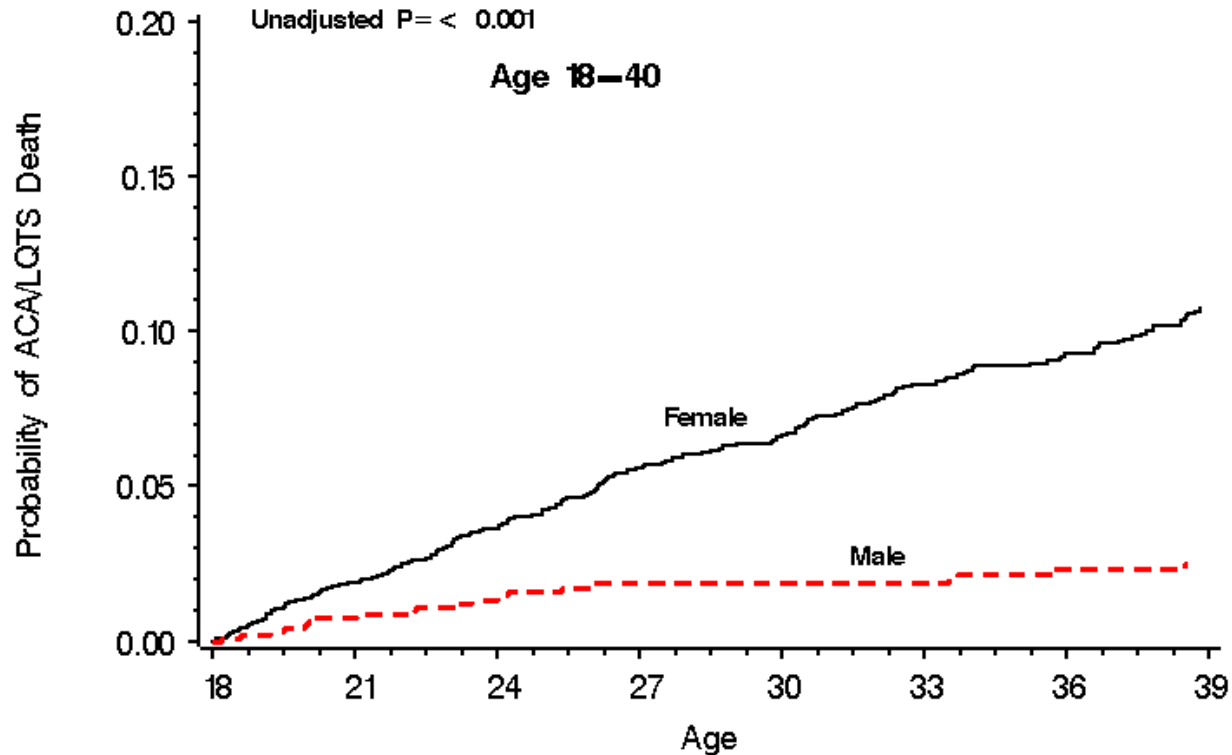


PATIENTS AT RISK

Female	2319	2286 (0)	2252 (0)	2207 (0.01)	2171 (0.01)	2120 (0.01)
Male	1450	1420 (0)	1393 (0.01)	1356 (0.02)	1303 (0.02)	1235 (0.03)



Risk of Sudden Death by Sex during Adulthood

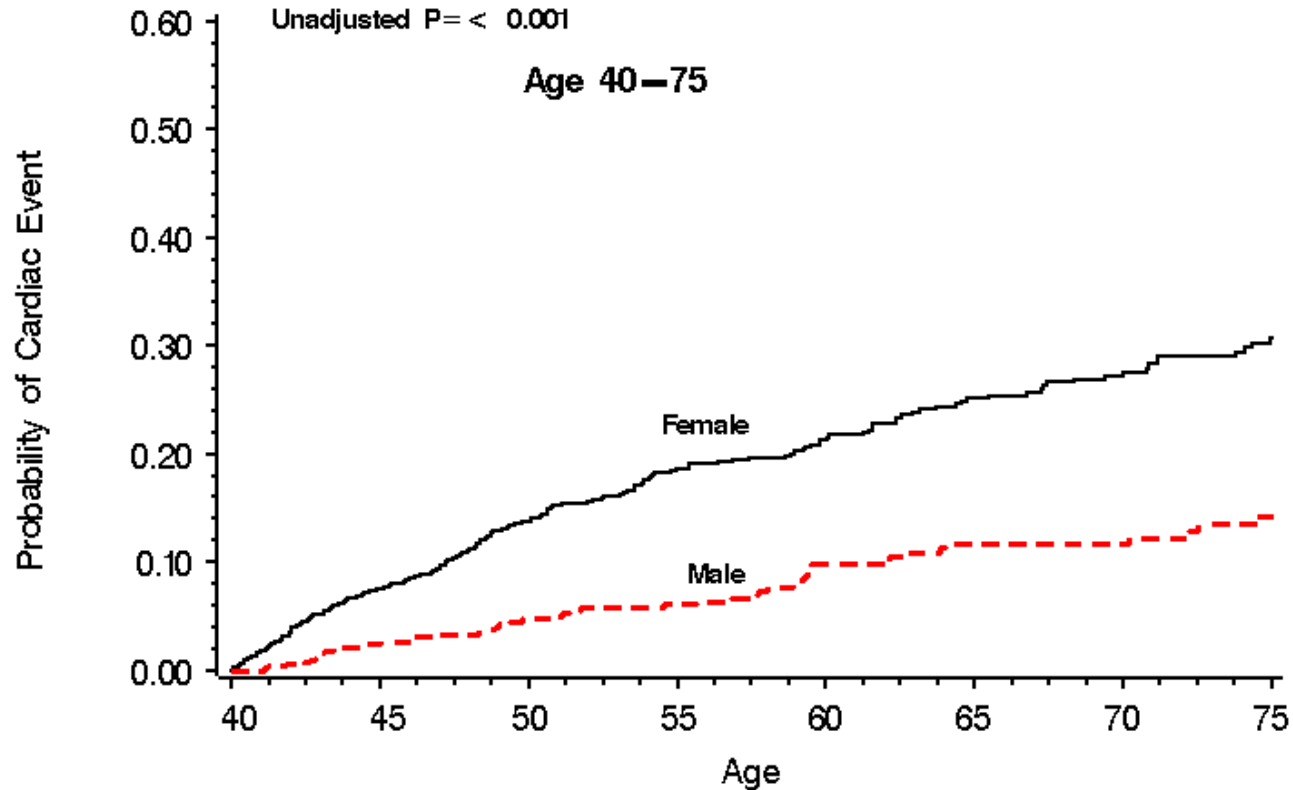


PATIENTS AT RISK

Female	1897	1748 (0.02)	1583 (0.04)	1449 (0.06)	1325 (0.07)	1223 (0.09)	1139 (0.09)	1042 (0.11)
Male	995	865 (0.01)	774 (0.01)	708 (0.02)	666 (0.02)	624 (0.02)	584 (0.02)	542 (0.03)



Risk of Cardiac Events by Sex after age 40 years



PATIENTS AT RISK

Female	1045	817 (0.07)	620 (0.14)	458 (0.19)	363 (0.21)	281 (0.25)	215 (0.27)	153 (0.31)
Male	527	456 (0.02)	376 (0.05)	309 (0.06)	252 (0.10)	202 (0.12)	170 (0.12)	118 (0.14)

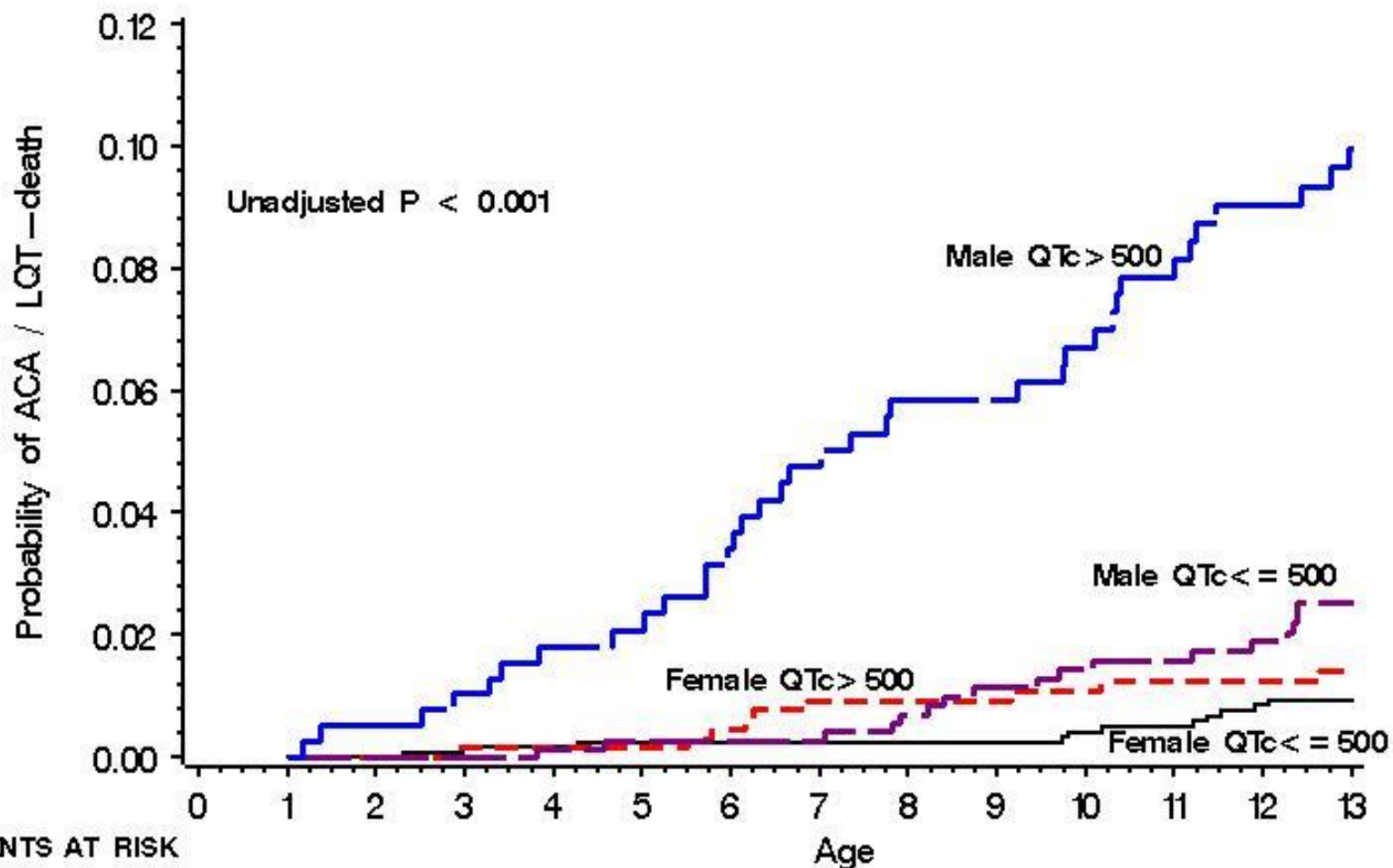


Risk factors: ECG: QTc Duration



Fig. 8A

QTc and the Risk of Sudden Death during Childhood



PATIENTS AT RISK		Age												
		1	2	3	4	5	6	7	8	9	10	11	12	13
Male QTc > 500	387	378 (0.01)	361 (0.034)	333 (0.059)	289 (0.10)									
Male QTc <= 500	735	726 (0)	707 (0.003)	676 (0.011)	608 (0.025)									
Female QTc > 500	654	647 (0.002)	636 (0.005)	620 (0.009)	598 (0.014)									
Female QTc <= 500	1239	1226 (0.002)	1200 (0.002)	1176 (0.002)	1116 (0.009)									

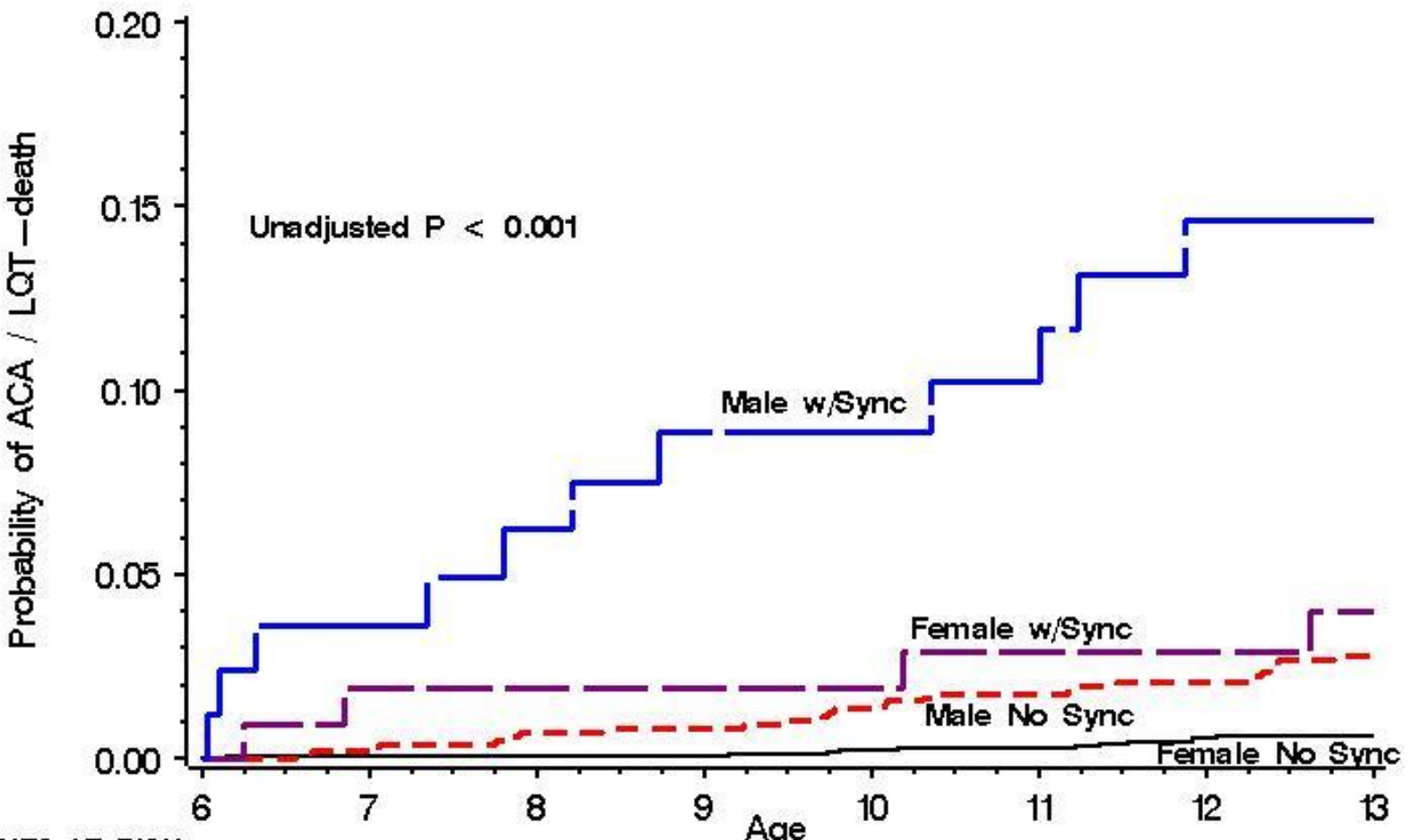


Risk factors: History of Syncope



Fig. 9A

Syncope and the Rate of Sudden Death during Childhood



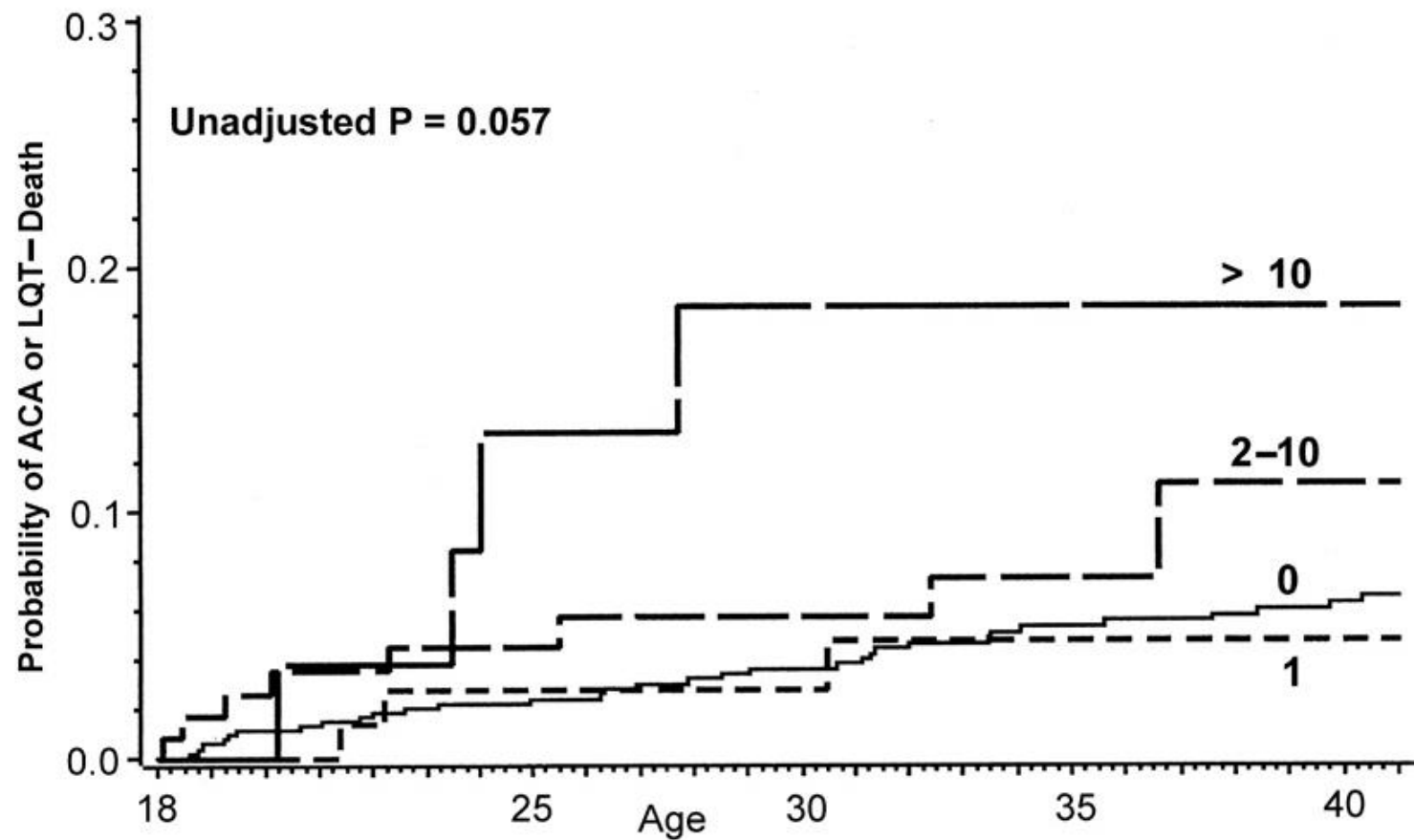
PATIENTS AT RISK		6	7	8	9	10	11	12	13
Male w/Sync	83		72 (0.062)		67 (0.089)		58 (0.146)		55 (0.146)
Female w/Sync	106		99 (0.019)		95 (0.019)		90 (0.029)		86 (0.04)
Male No Sync	985		956 (0.007)		919 (0.014)		876 (0.021)		842 (0.029)
Female No Sync	1730		1706 (0.001)		1684 (0.002)		1651 (0.005)		1628 (0.006)



Fig. 9B

Number of Prior Syncopal Events and the Rate of Sudden Death during adulthood

B



PATIENTS AT RISK

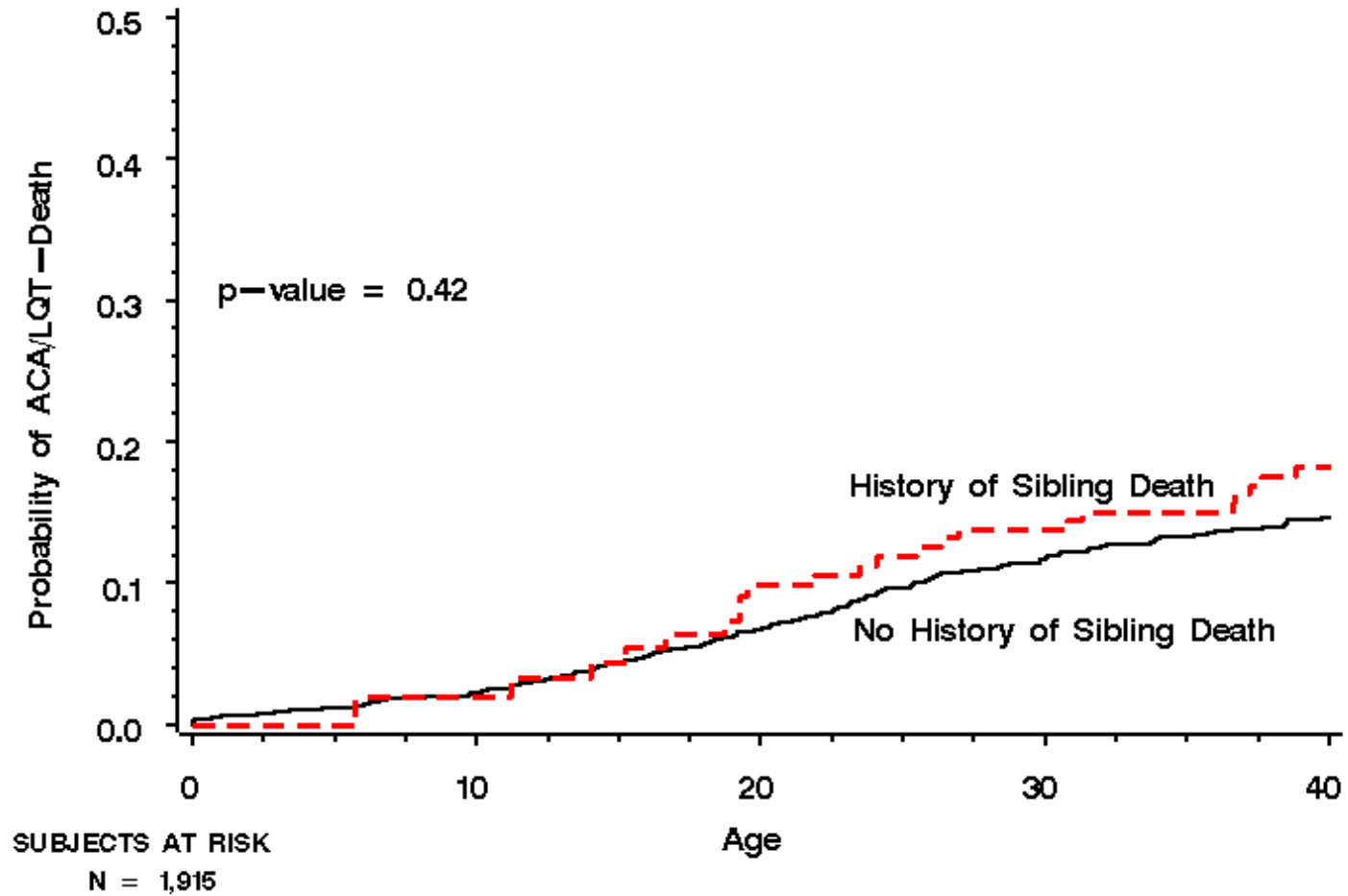
> 10	28	18 (0.13)	15 (0.18)	14 (0.18)	11 (0.18)
2-10	116	82 (0.05)	63 (0.06)	54 (0.07)	41 (0.11)
1	83	54 (0.03)	49 (0.03)	41 (0.05)	34 (0.05)
0	570	512 (0.02)	463 (0.04)	414 (0.05)	366 (0.06)



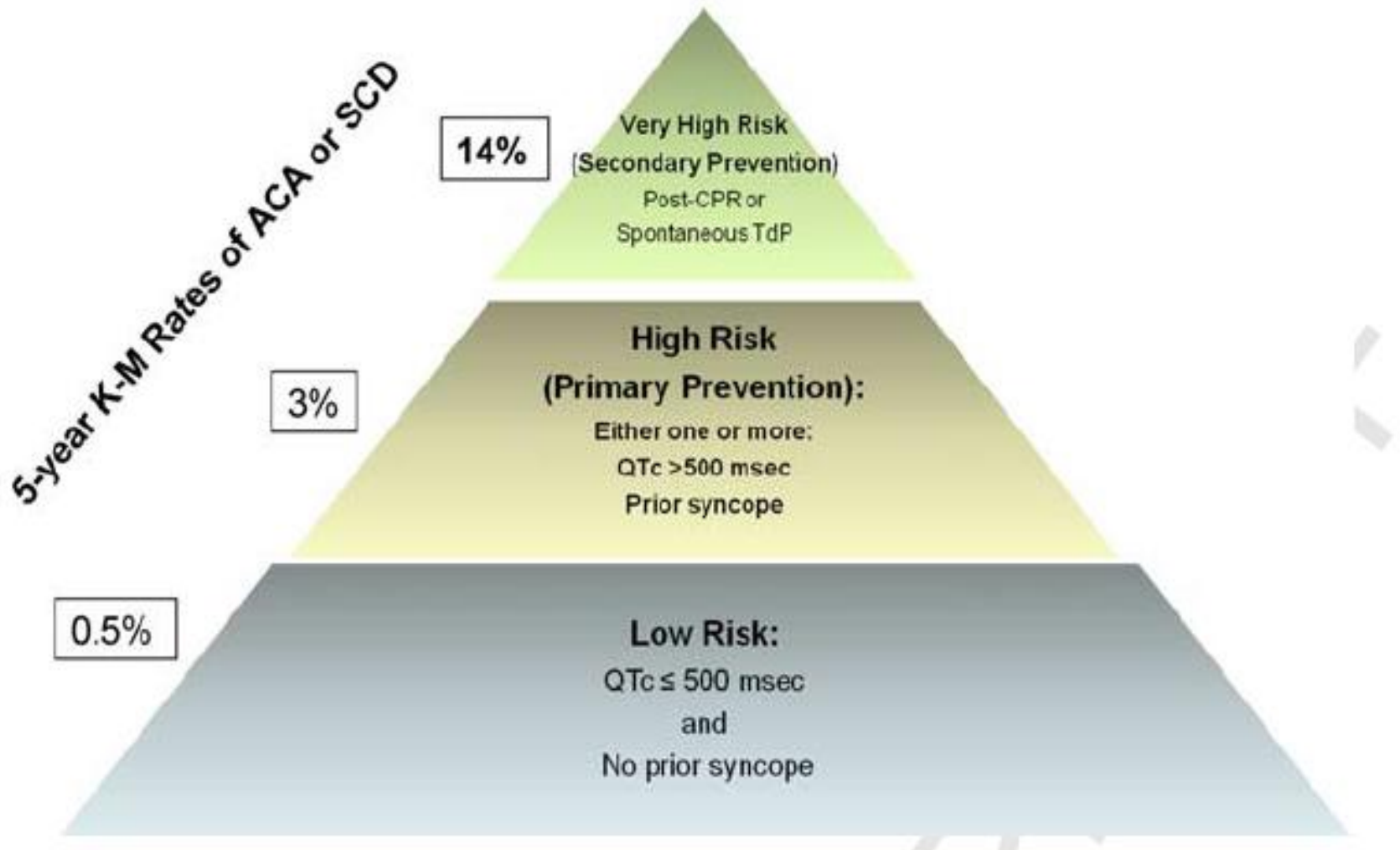
Risk factors: Family history



Sibling Death and the Risk of Subsequent Sudden Death



Risk Stratification for ACA or SCD in LQTS Patients

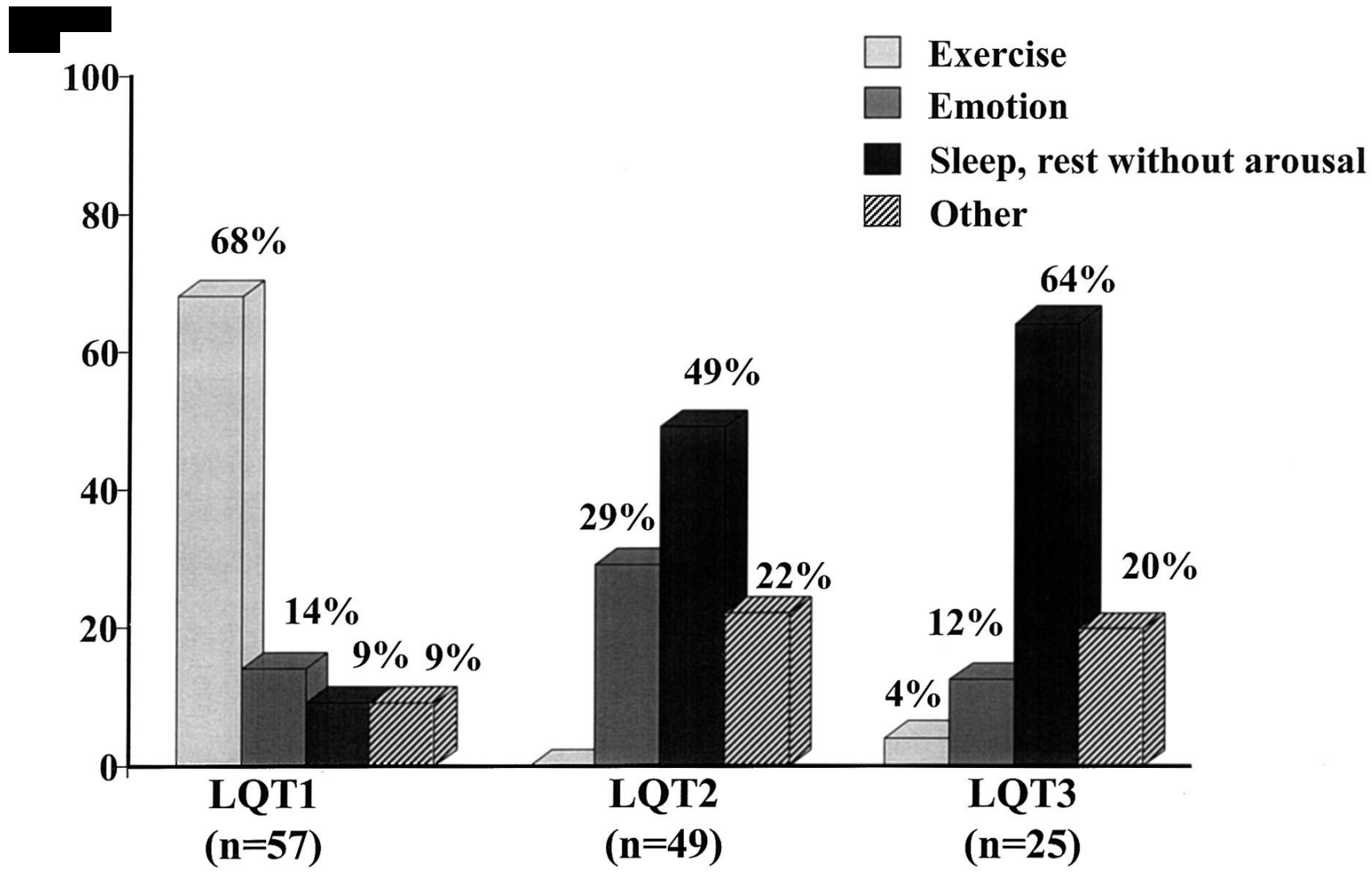


Risk factors: Genotype

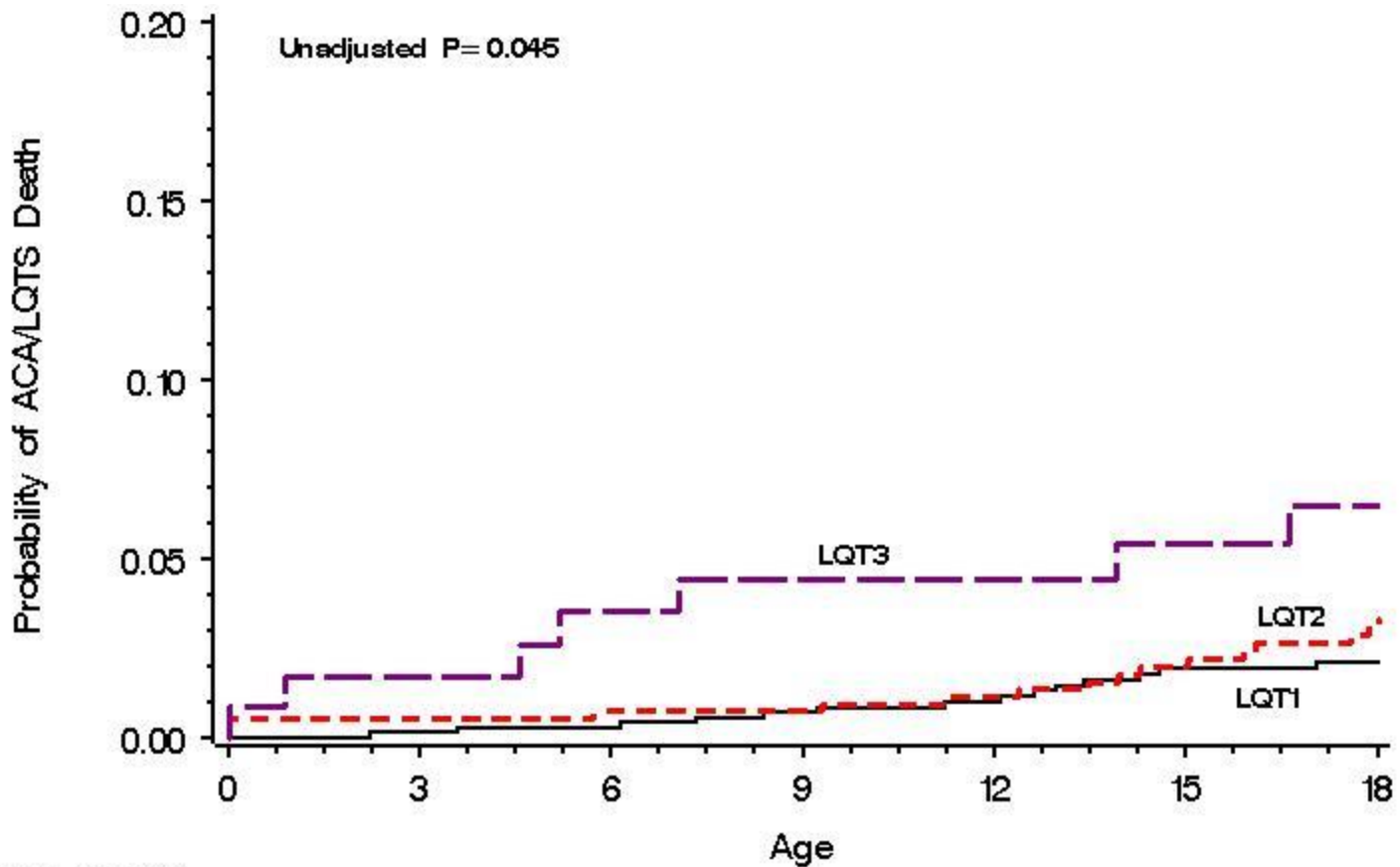


Fig. 11

Triggers for lethal Events in the 3 main LQTS Genotypes



Probability of ACA or SCD by the 3 Main LQTS genotypes (Age-Group: 1-18 years)

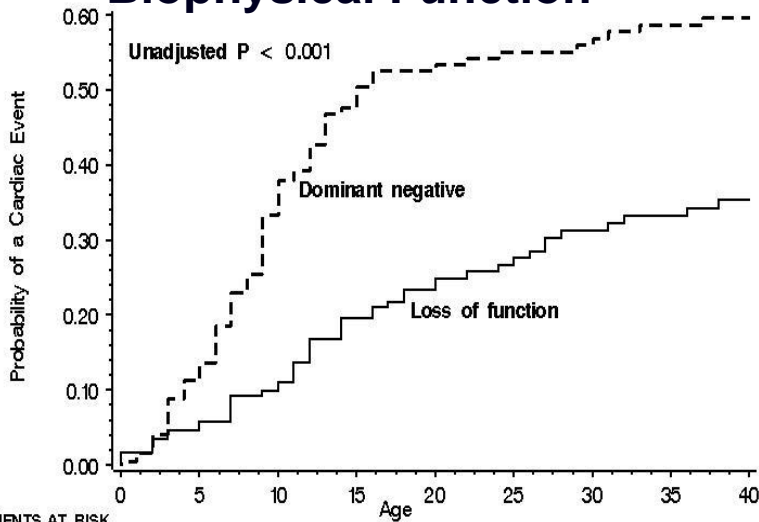


PATIENTS AT RISK

LQT1	744	732 (0)	711 (0)	680 (0.01)	650 (0.01)	600 (0.02)	564 (0.02)
LQT2	545	524 (0.01)	511 (0.01)	499 (0.01)	473 (0.01)	449 (0.02)	424 (0.03)
LQT3	115	111 (0.02)	107 (0.04)	102 (0.04)	98 (0.04)	93 (0.05)	87 (0.07)

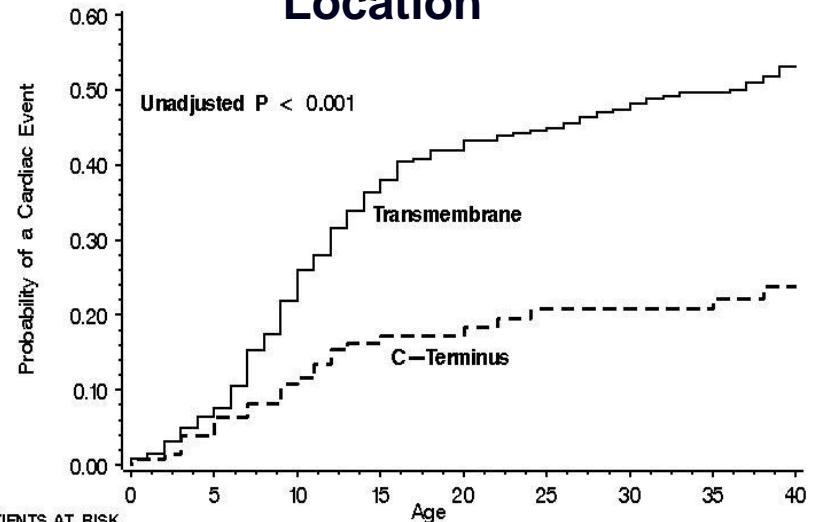
Mutation-Specific Risk Factors: LQT1

Biophysical Function



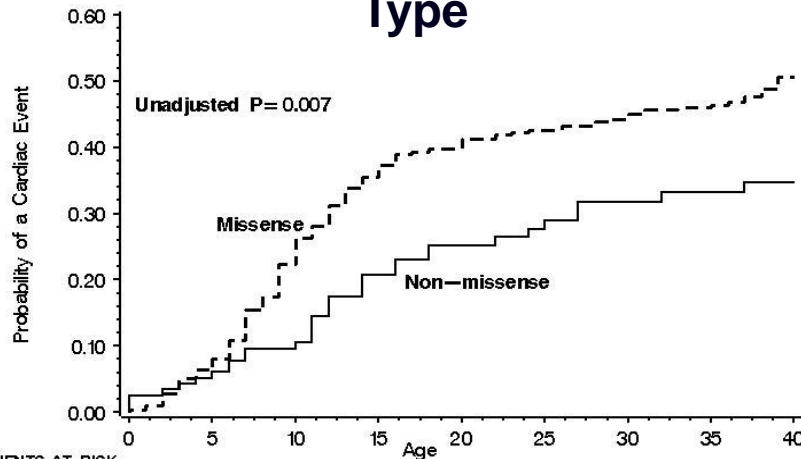
PATIENTS AT RISK		0	5	10	15	20	25	30	35	40
Dominant negative	172	101 (0.33)	61 (0.53)	49 (0.56)	39 (0.60)					
Loss of function	176	145 (0.10)	95 (0.23)	73 (0.31)	52 (0.36)					

Location



PATIENTS AT RISK		0	5	10	15	20	25	30	35	40
Transmembrane	447	315 (0.22)	181 (0.42)	143 (0.47)	103 (0.53)					
C-Terminus	128	99 (0.11)	76 (0.17)	62 (0.21)	44 (0.24)					

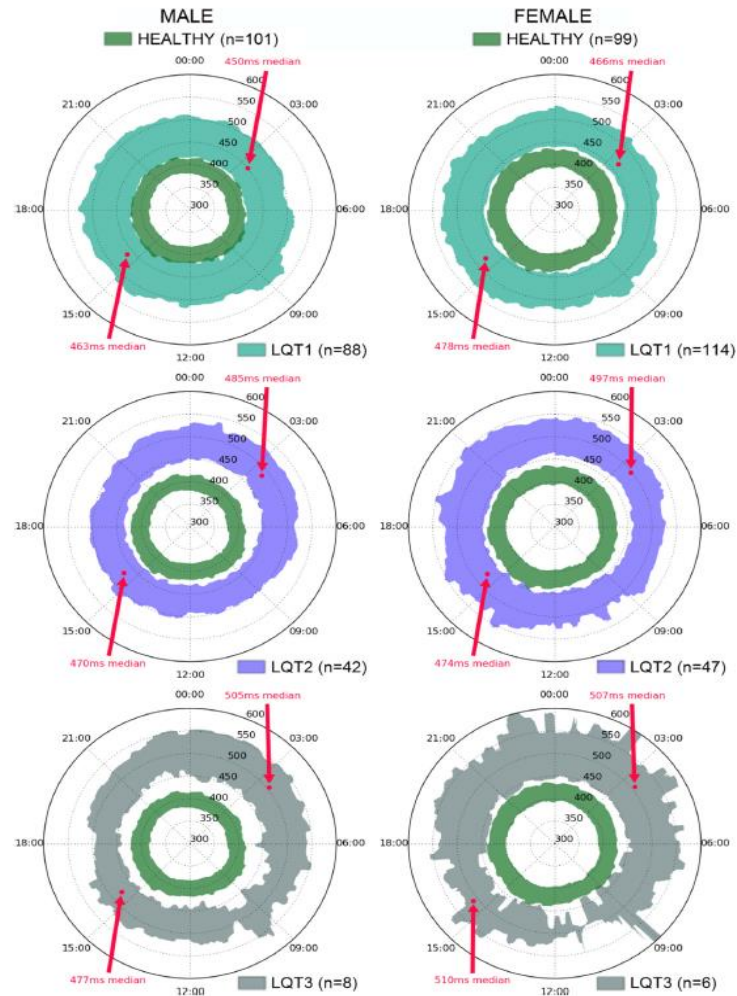
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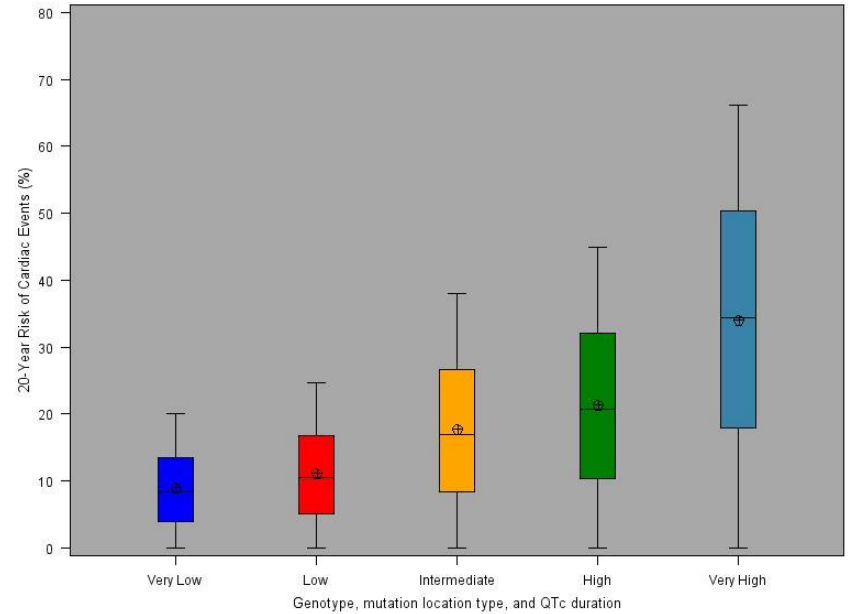
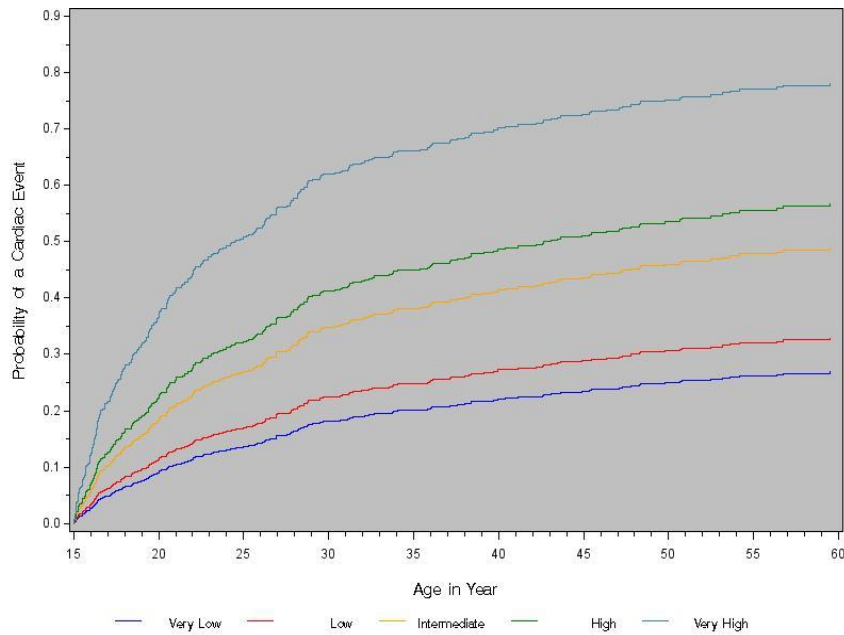
PATIENTS AT RISK		0	5	10	15	20	25	30	35	40
Missense	475	330 (0.22)	199 (0.40)	162 (0.44)	112 (0.51)					
Non-missense	117	94 (0.10)	64 (0.25)	49 (0.32)	38 (0.35)					

Moss et al.
Circulation 2007

QT CLOCK FOR PREDICTION OF SUDDEN CARDIAC DEATH RISK



PERSONALIZED PREDICTED RISK



PriorSync and baseline BB correspond to the sample means by 5 LQT and QTc groups

Risk group	Genotype	Mutation location	QTc duration (ms)
Very Low (n=173; 23%)	LQT1	<ul style="list-style-type: none"> ▪ C-loop ▪ Non-C-loop 	<ul style="list-style-type: none"> ▪ ≤450 ▪ <480
Low (n=86; 11%)	LQT2	<ul style="list-style-type: none"> ▪ Non-pore loop 	<ul style="list-style-type: none"> ▪ ≤450
Intermediate (n=231; 30%)	LQT1	<ul style="list-style-type: none"> ▪ Non-C-loop ▪ C-loop 	<ul style="list-style-type: none"> ▪ ≥480 ▪ >450
High (n=152; 20%)	LQT2	<ul style="list-style-type: none"> ▪ Pore-loop ▪ Non-pore-loop 	<ul style="list-style-type: none"> ▪ ≤460 ▪ 451-500
Very High (n=125; 16%)	LQT2	<ul style="list-style-type: none"> ▪ Pore-loop ▪ Non-pore-loop 	<ul style="list-style-type: none"> ▪ >460 ▪ >500

LQTS

**When is an ICD indicated?
(in high-risk pts)**

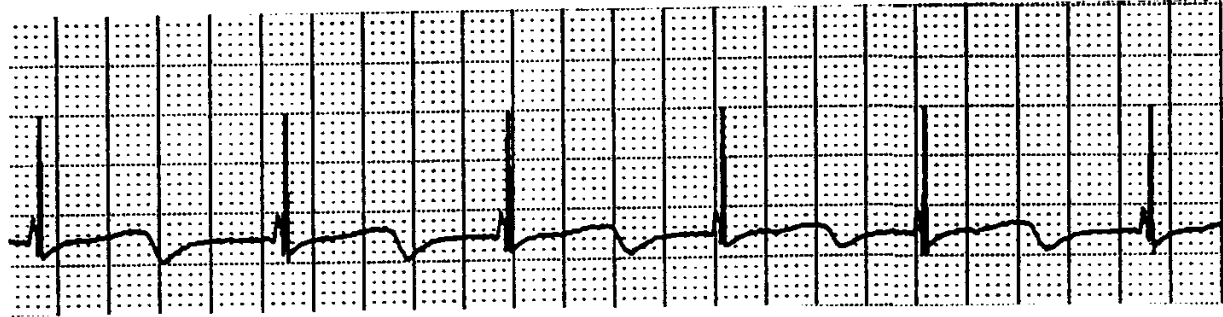
- **ACA**
- **Syncope on BB**
- **? pts. with high-risk genetic mutations**

LQTS: CASE REPORT

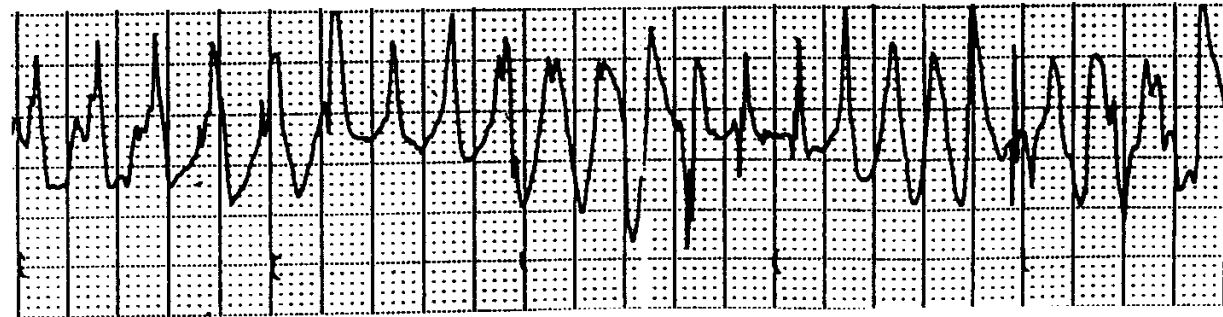
- **12 y/oM with known LQTS**
- **Hx recurrent syncope – Rx effectively with beta-blockers for several years**
- **Aborted cardiac arrest – June 1998**
- **ICD implanted after ACA**
- **Episode on first day of school Sept. 1998**

LQTS: ICD

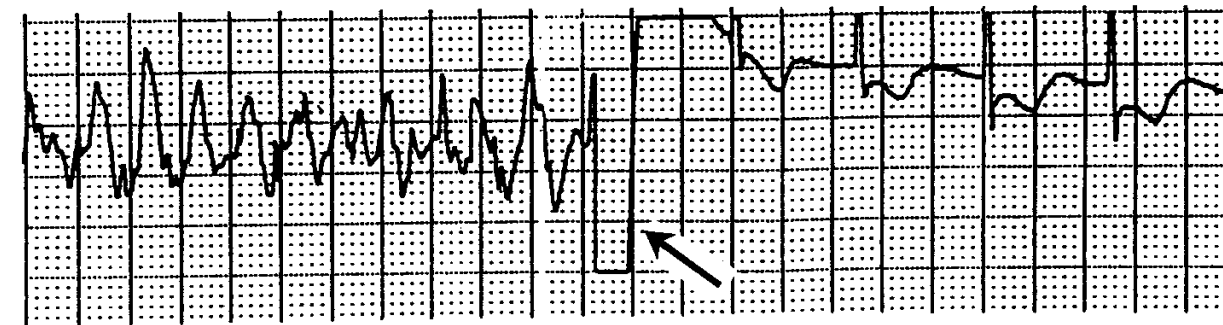
NSR



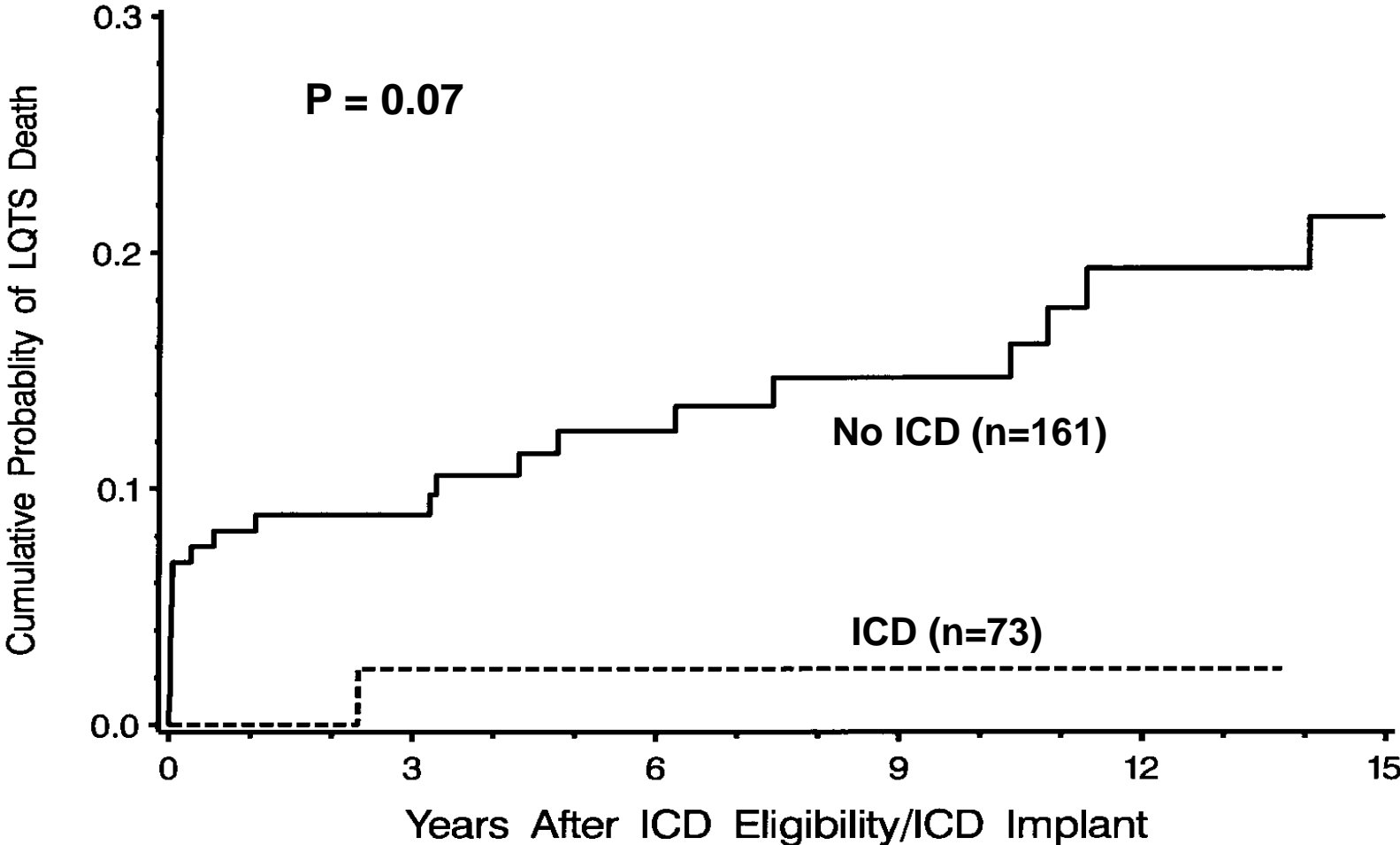
TdP



VF-CD-NSR



LQTS



SUMMARY

- **Throughout the years, based on the largest inherited arrhythmia Registry available we have expanded knowledge in the field of inherited arrhythmias and sudden cardiac death**
- **From:**
 - **Simple clinical risk factors**
- **To:**
 - **Genotype and personalized risk stratification and treatment**



THANK YOU

