LONG QT SYNDROME: IMPORTANCE OF GENETIC TESTING

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CURRENT STATUS

GENOTYPE:

- **17 genes, >600 mutations**
- **LQTS dominated by mutations in:**
  - **LQT1 ($\downarrow I_{Ks}$) ~ 45%**
  - **LQT2 ($\downarrow I_{Kr}$) ~ 45%**
  - **LQT3 ($\uparrow$Na+) ~ 5%**
  - **LQT4-11 ~5%**

PHENOTYPE:

- **QTc**
- **Events: syncope, aborted cardiac arrest, SCD**

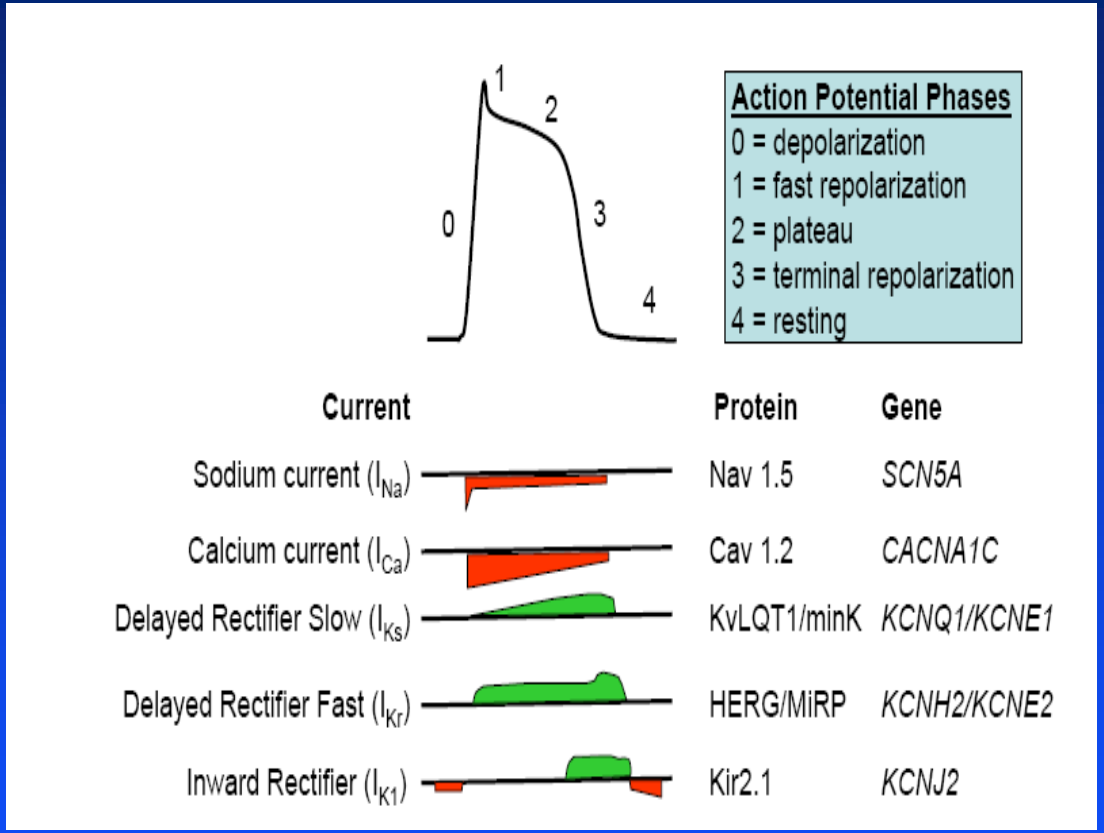
LQTS: CLINICAL RISK FACTORS for SYNCOPE, ACA, & SCD

(based on 35 years of studies from the LQTS Registry)

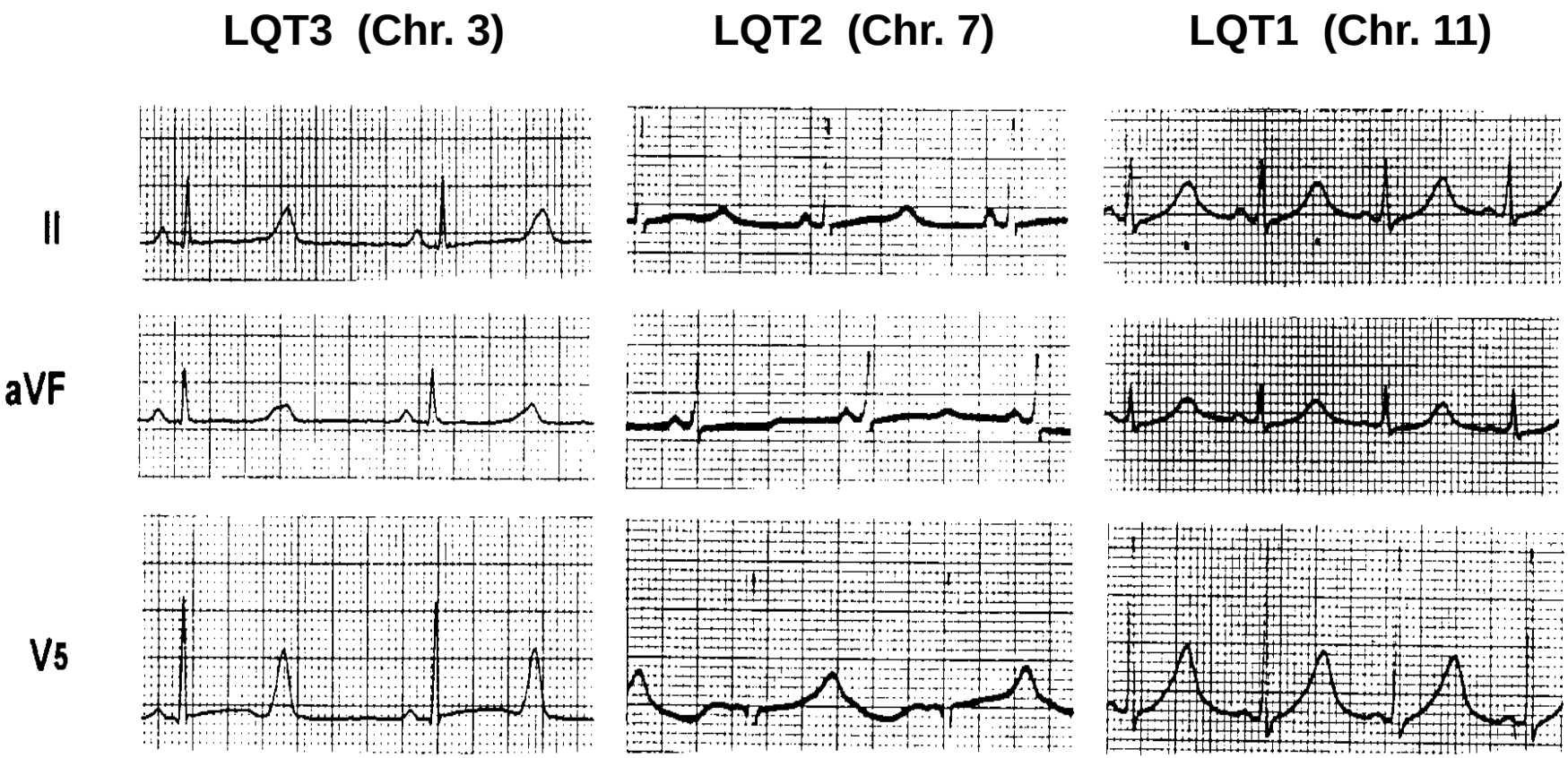
- **Gender**
  - **↑ risk for males age 1-12**
  - **↑ risk for females age 18- 75**
- **Length of the QTc interval (>0.50s)**
- **Hx of recent syncope (past 2 years)**

BACKGROUND: GENOTYPE-PHENOTYPE CORRELATIONS

- LQTS genes affect different ion-current mechanisms
- Phenotypic expression affected by type of ion channel mutation

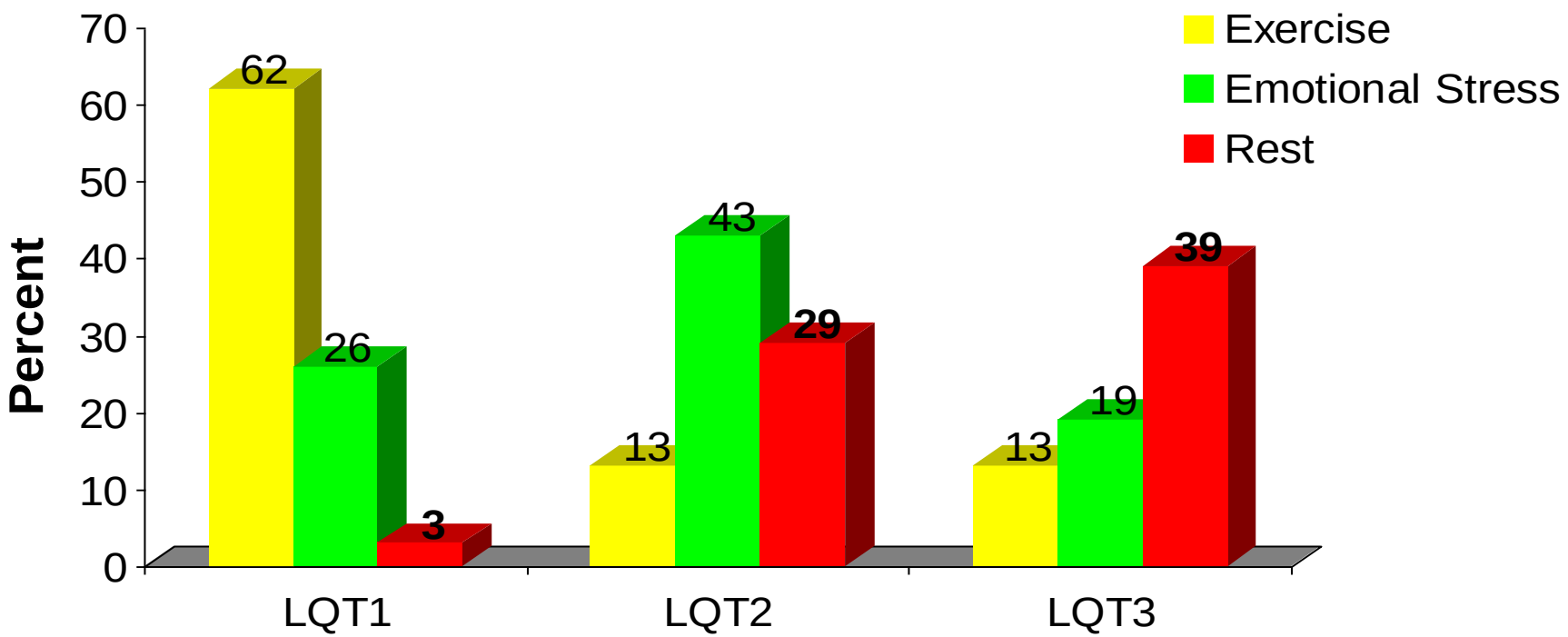


T-wave Morphology in LQTS by Genotype



Moss AJ, et al. Circulation 1995

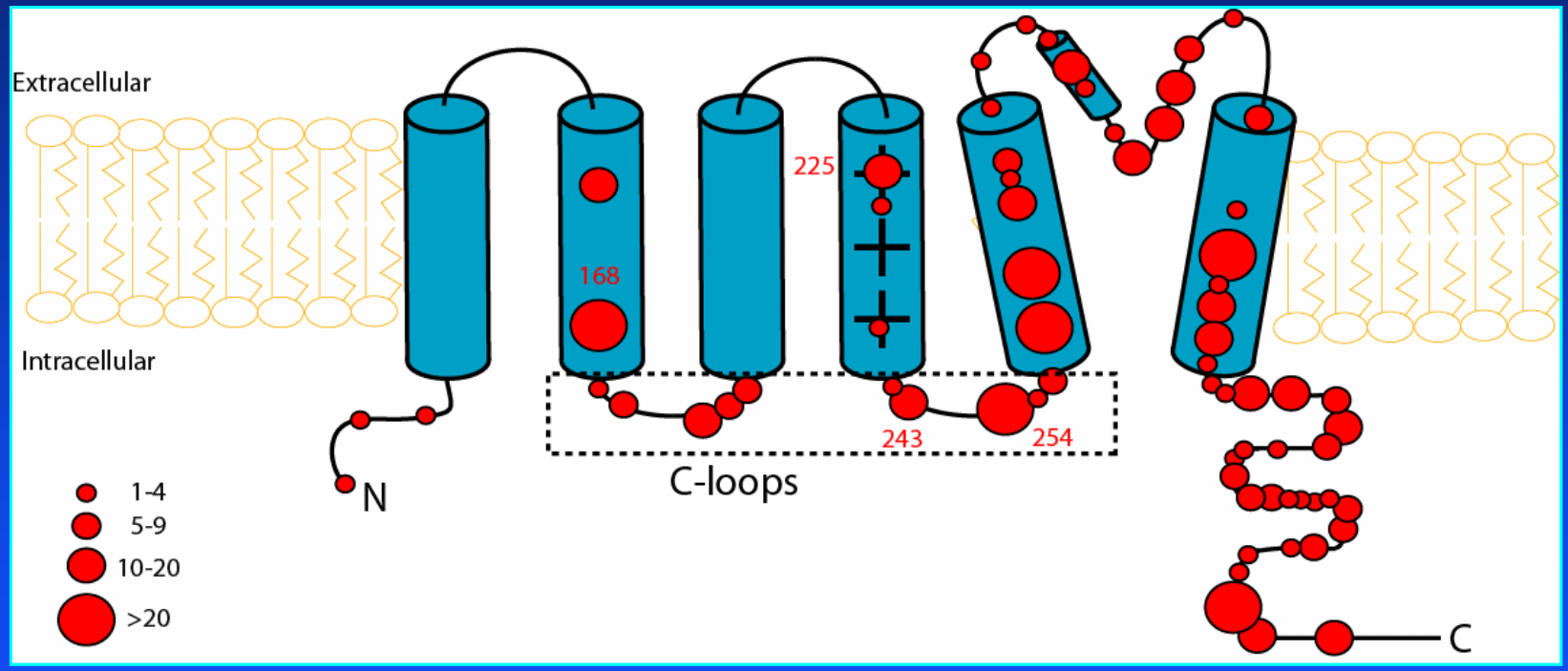
Triggers for Syncope by LQTS Genotype



Schwartz, Moss et al. Circulation 2001

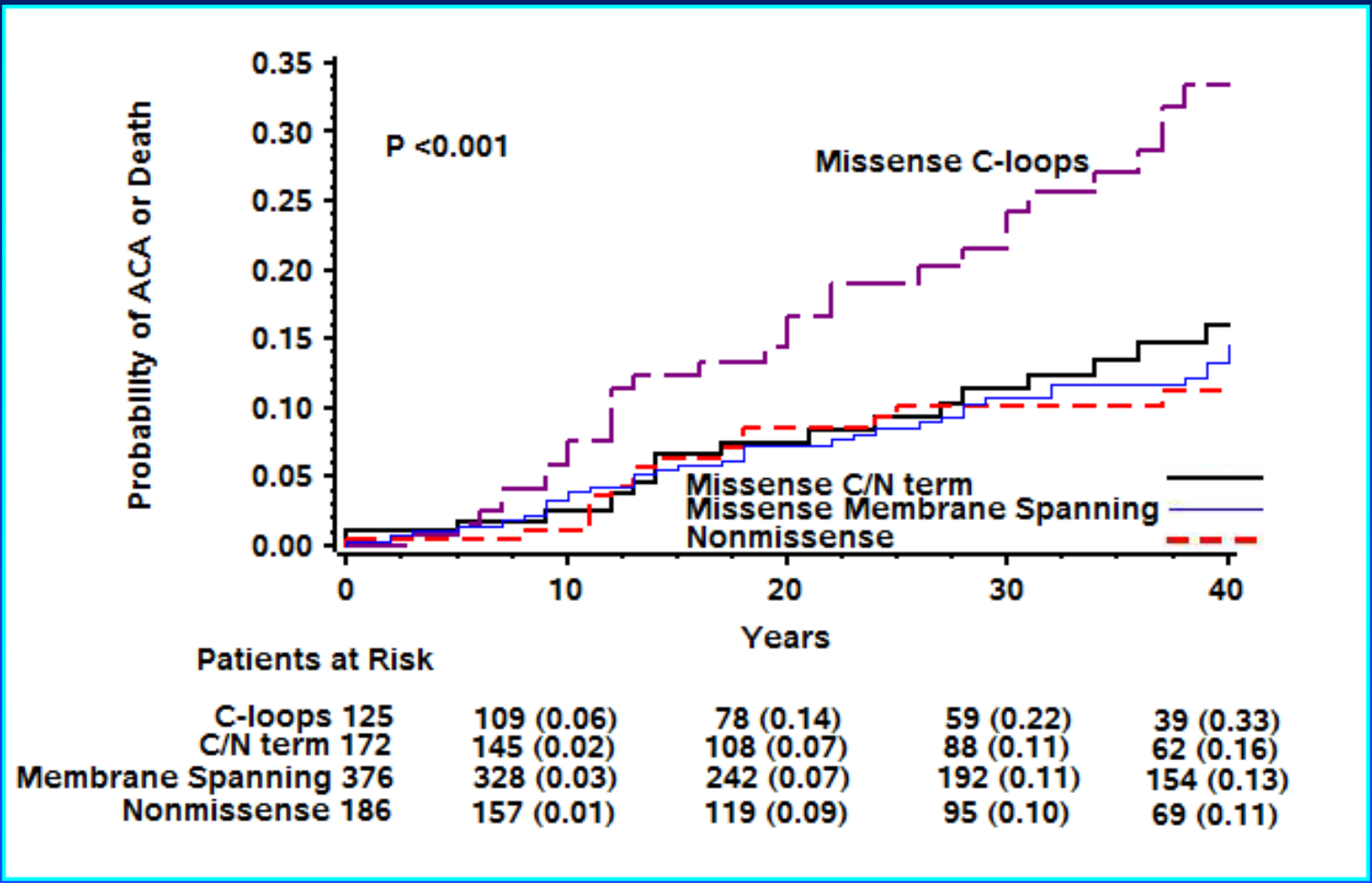
LQT1: KCNQ1 Potassium Channel

- Total 860 patients, 170 proband-identified families
- 100 different KCNQ1 mutations



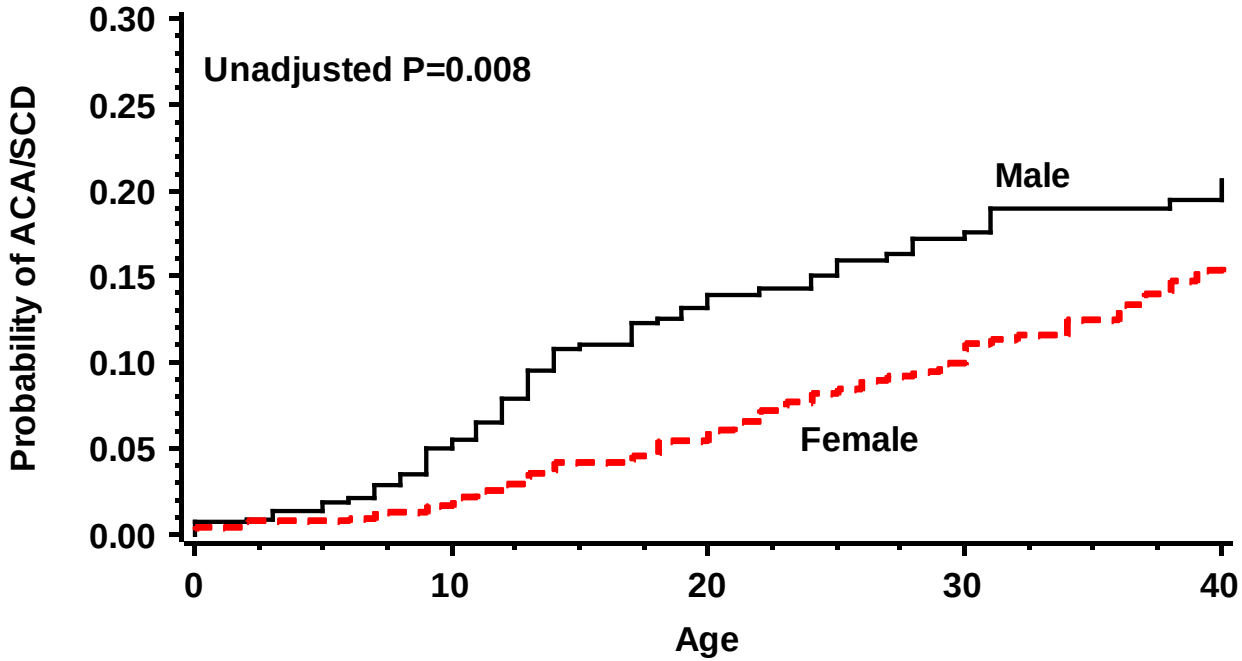
C-loops: modulate β-adrenergic stimulation of I_{ks} via direct protein kinase A (PKA)

Probability of life threatening cardiac event by mutation location and type



Barsheshet, Lopes, Goldenberg Circulation, 2012

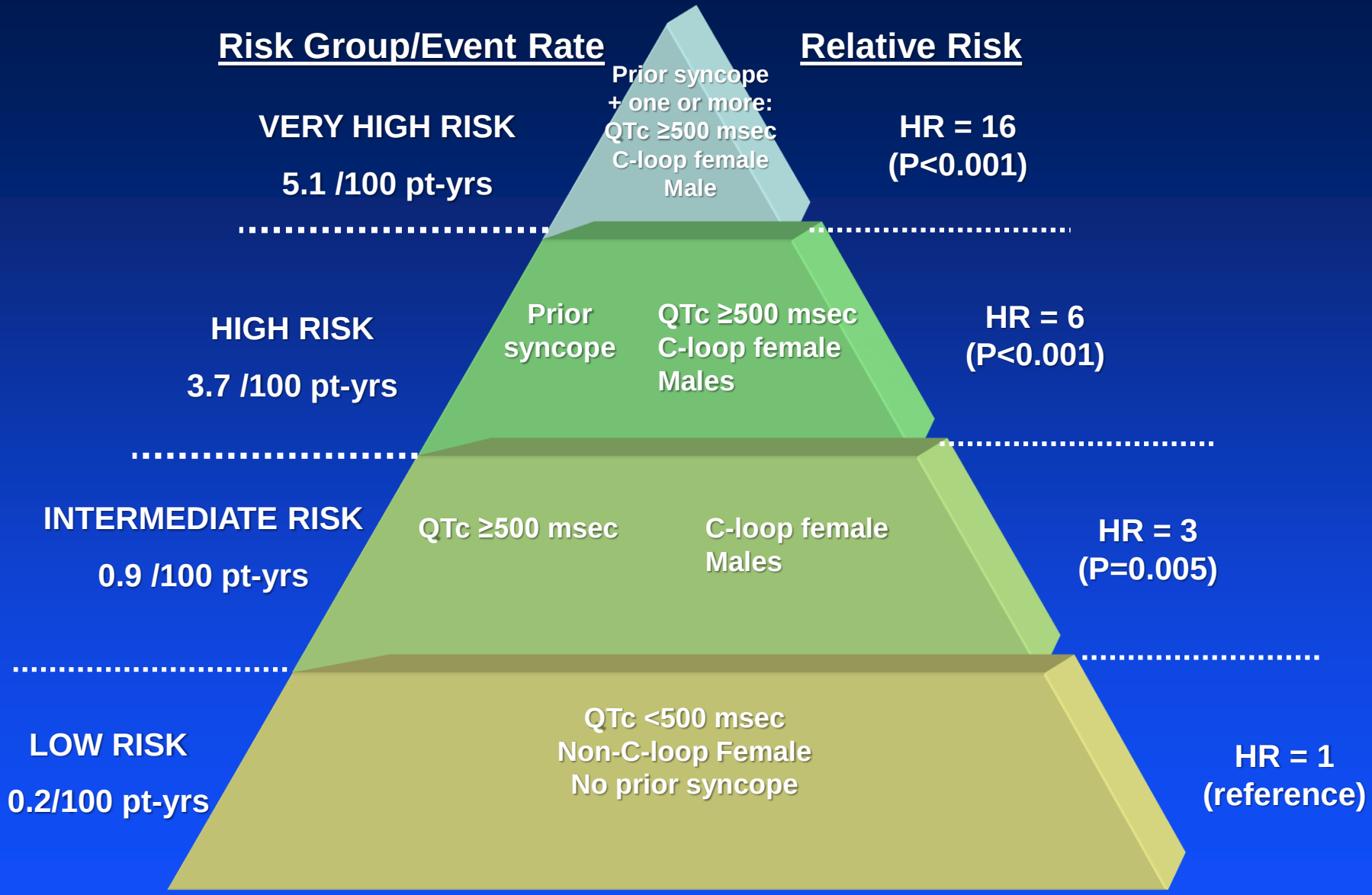
Probability of ACA/SCD in LQT1 Patients by Gender



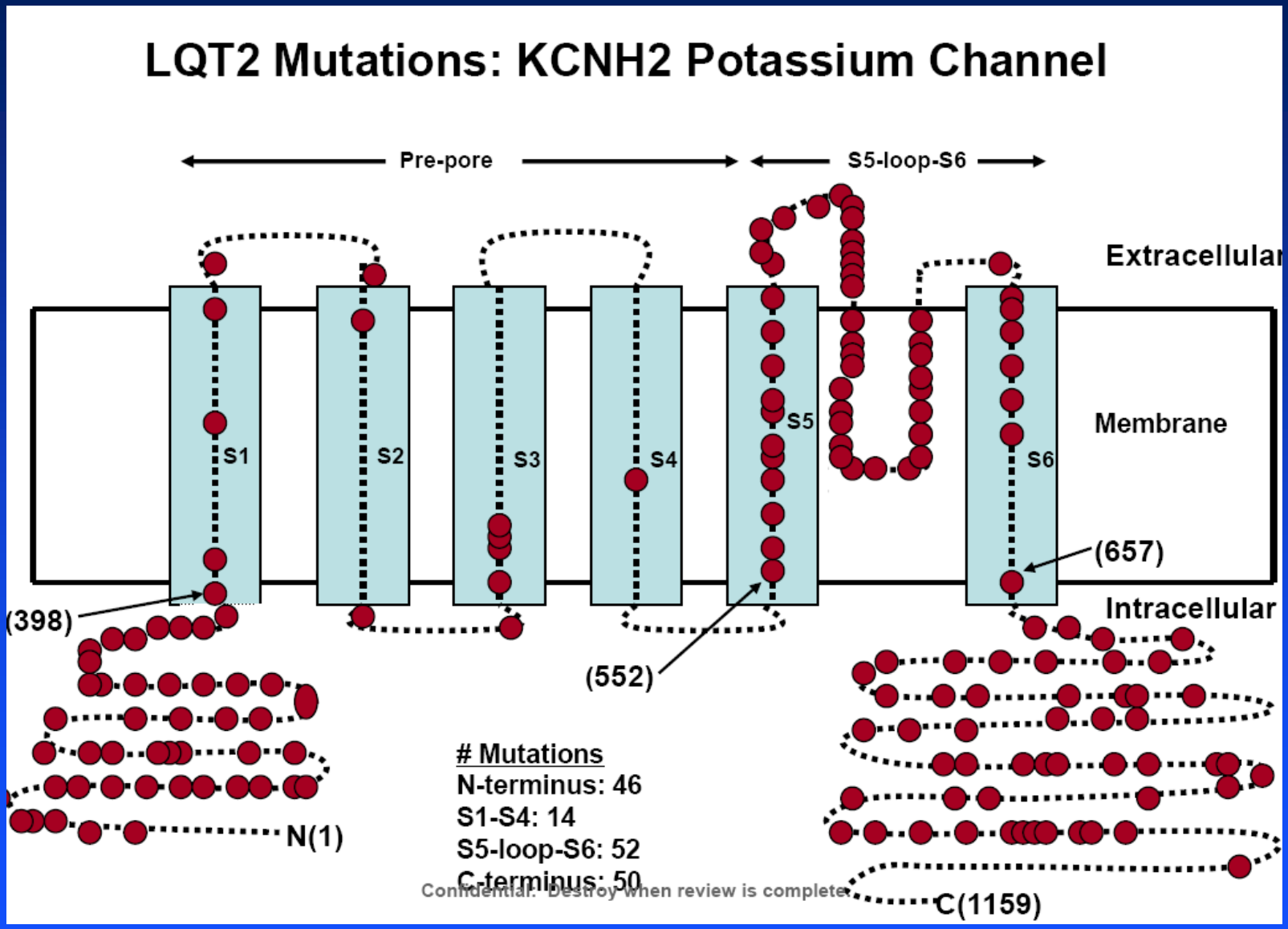
Patients at Risk					
Male	450	376 (0.05)	251 (0.13)	191 (0.17)	146 (0.19)
Female	601	536 (0.02)	420 (0.05)	335 (0.10)	244 (0.15)

Costa, Goldenberg, Heart Rhythm, 2012

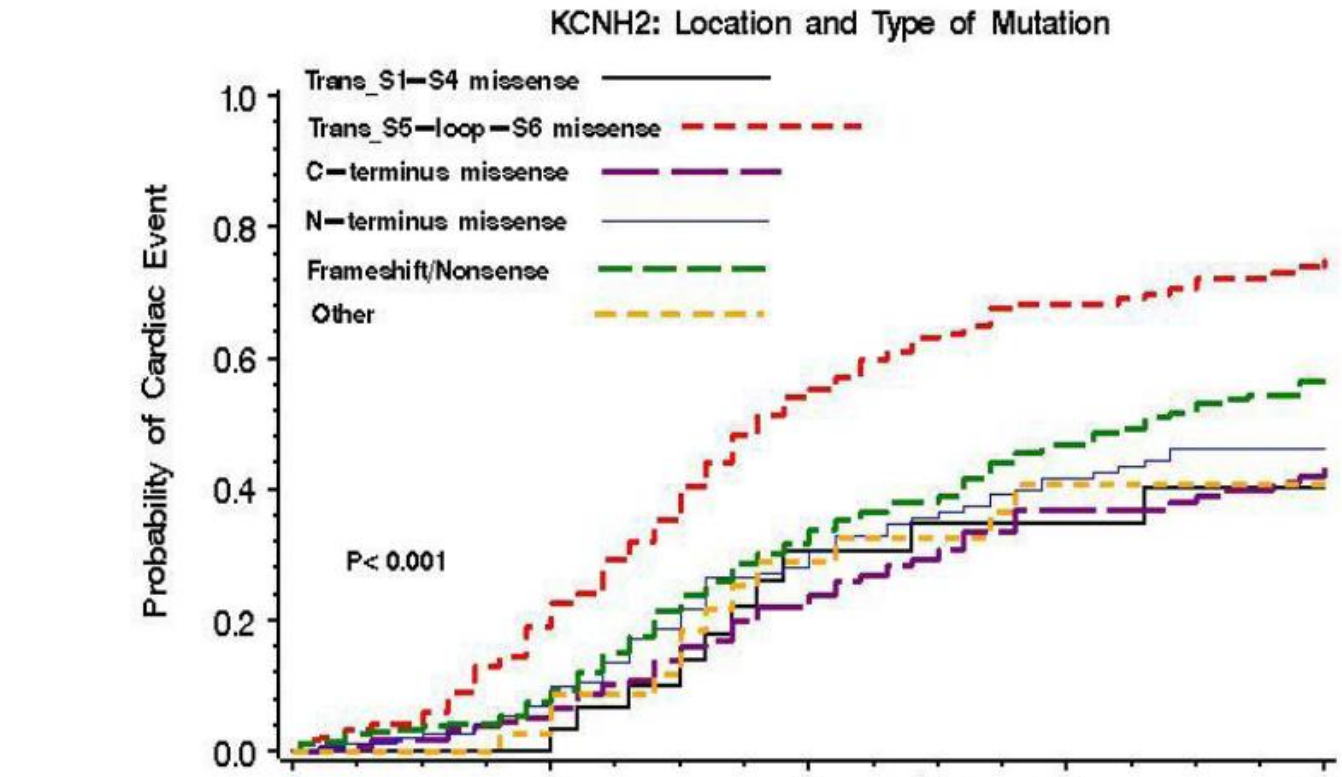
Proposed Risk Stratification Scheme for ACA or SCD in LQT1



Mutation-Specific Risk Factors: LQT2



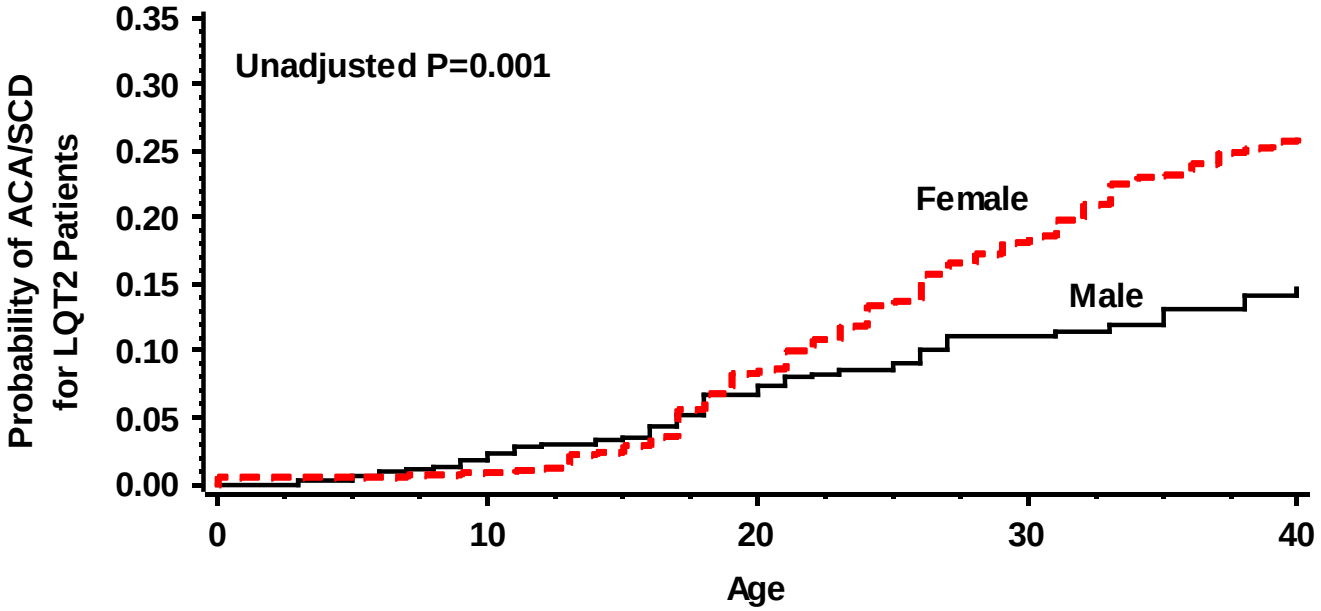
Mutation-Specific Risk Factors: LQT2



PATIENTS AT RISK					
Trans_S1–S4	33	29 (0.03)	16 (0.31)	12 (0.35)	11 (0.40)
Trans_S5–loop–S6	217	144 (0.23)	70 (0.55)	44 (0.68)	23 (0.75)
C_term	161	131 (0.07)	98 (0.24)	70 (0.37)	44 (0.43)
N_term	146	124 (0.10)	84 (0.31)	64 (0.42)	52 (0.46)
Frameshift/nonsense	261	207 (0.09)	127 (0.34)	88 (0.47)	56 (0.57)
Other	42	30 (0.09)	19 (0.29)	13 (0.41)	11 (0.41)

Shimizu et al. JACC 2009

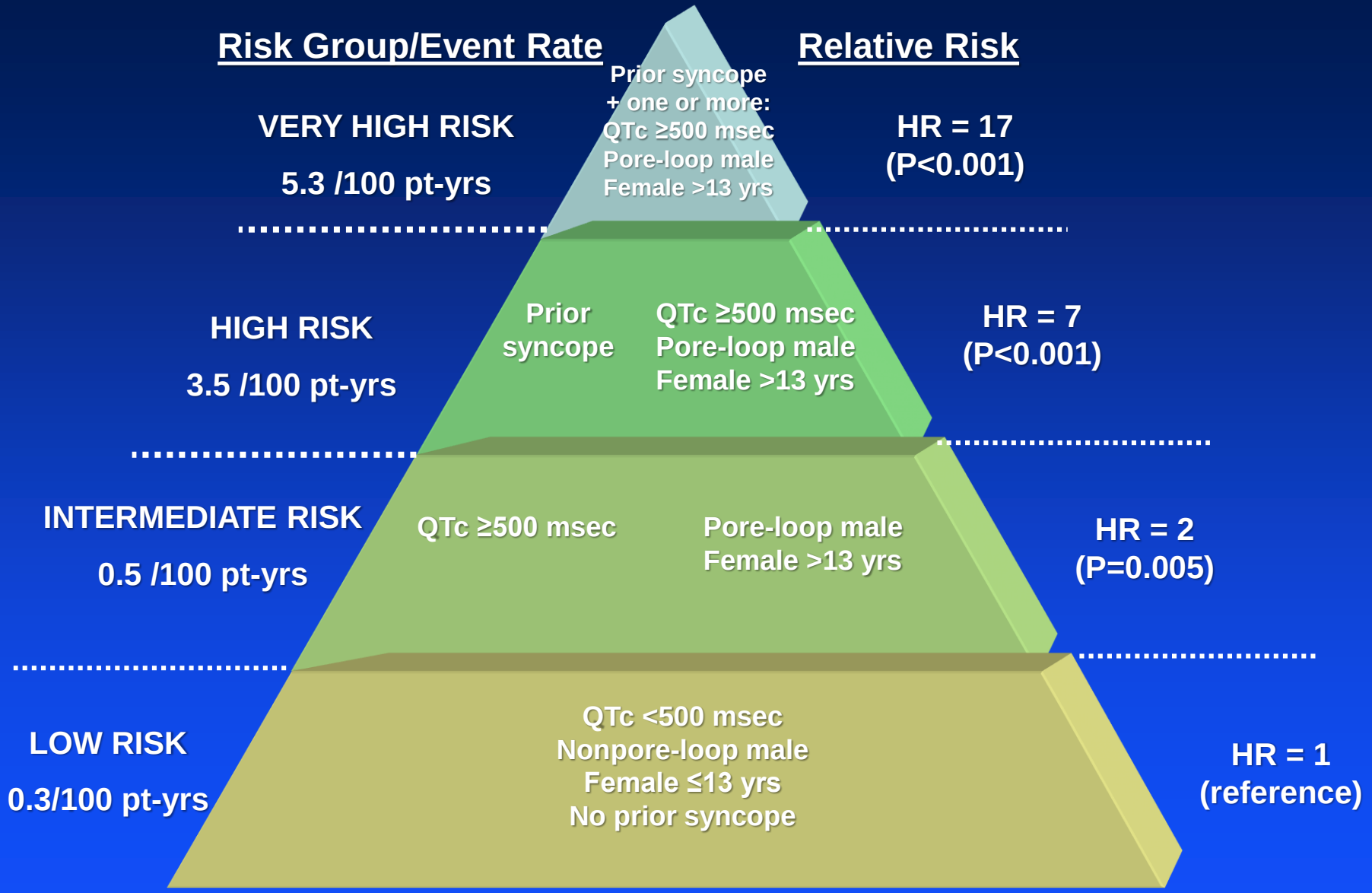
Cumulative Probability of a First ACA or SCD in LQT2 Patients by Gender



Patients at Risk				
Male 490	411 (0.02)	300 (0.07)	235 (0.11)	171 (0.14)
Female 676	613 (0.01)	488 (0.08)	366 (0.18)	245 (0.26)

Migdalovich and Goldenberg, Heart Rhythm, 2011

Proposed Risk Stratification Scheme for ACA or SCD in LQT2



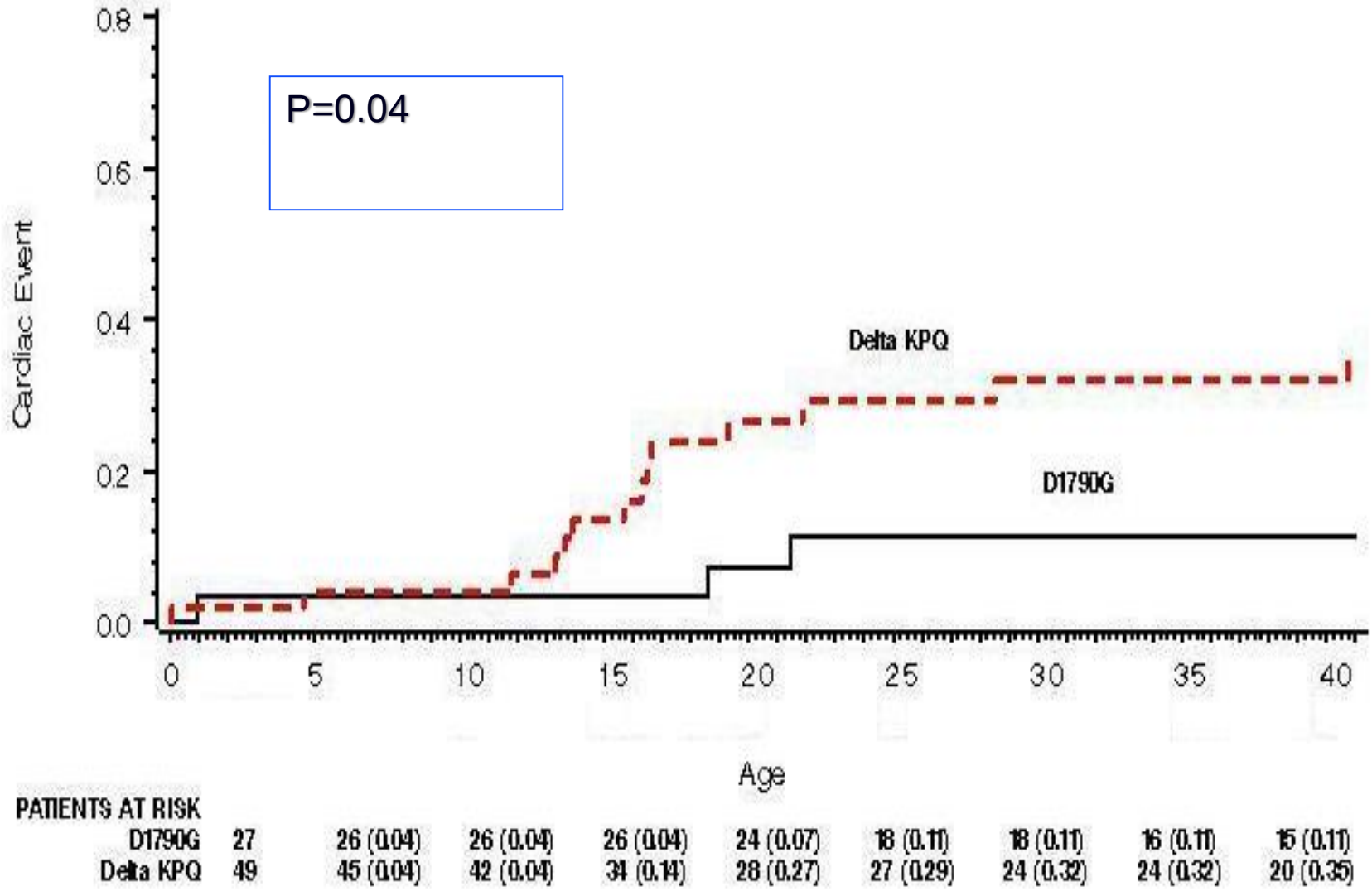
Migdalovich and Goldenberg, Heart Rhythm, 2011

Genotype-Phenotype Studies in LQT3 (SCN5A)

- ΔKPQ
- D1790G

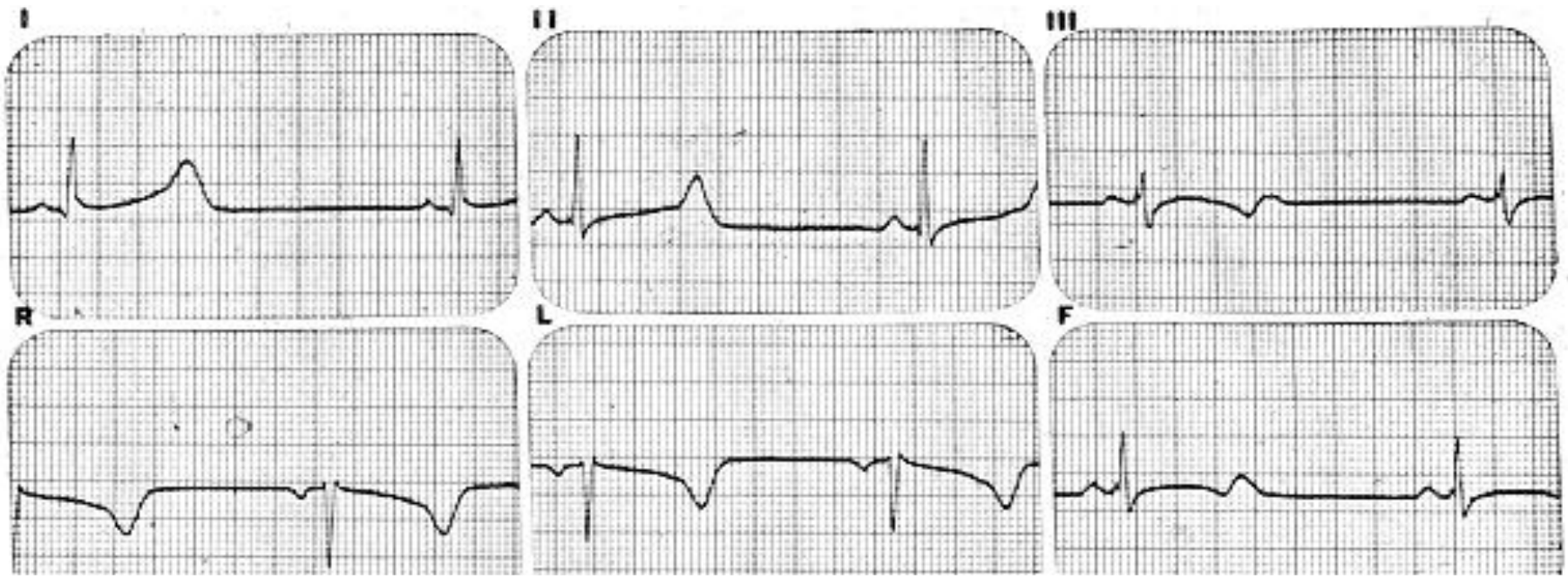
Liu J, Goldenberg, et al. (2010)

Cardiac Events in Two SCN5A Mutations



LQT3 Family from Iowa

with SCN5A Mutation (LQT3)

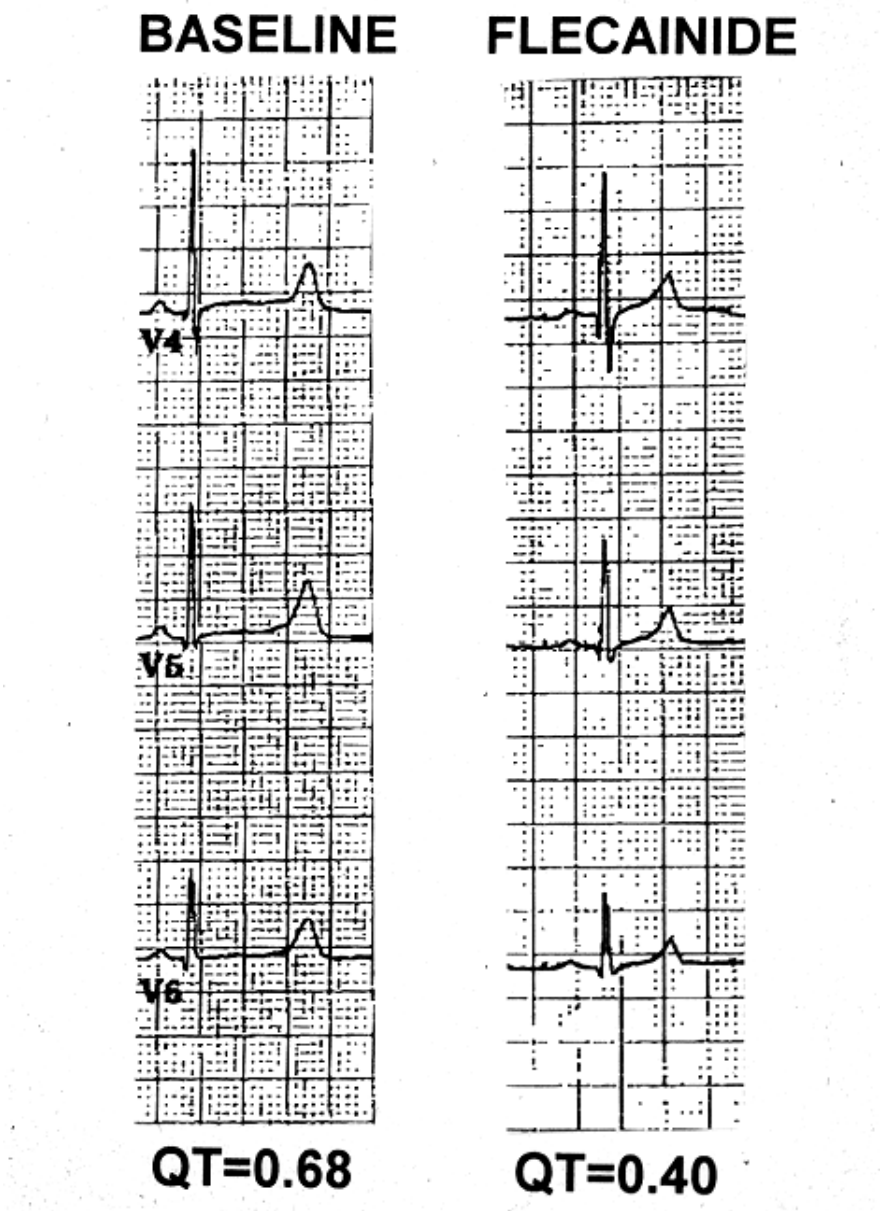


ECG (limb-leads) in an 18-y/o M with LQT3 form of LQTS.

The patient was not receiving beta-blockers or any medication.

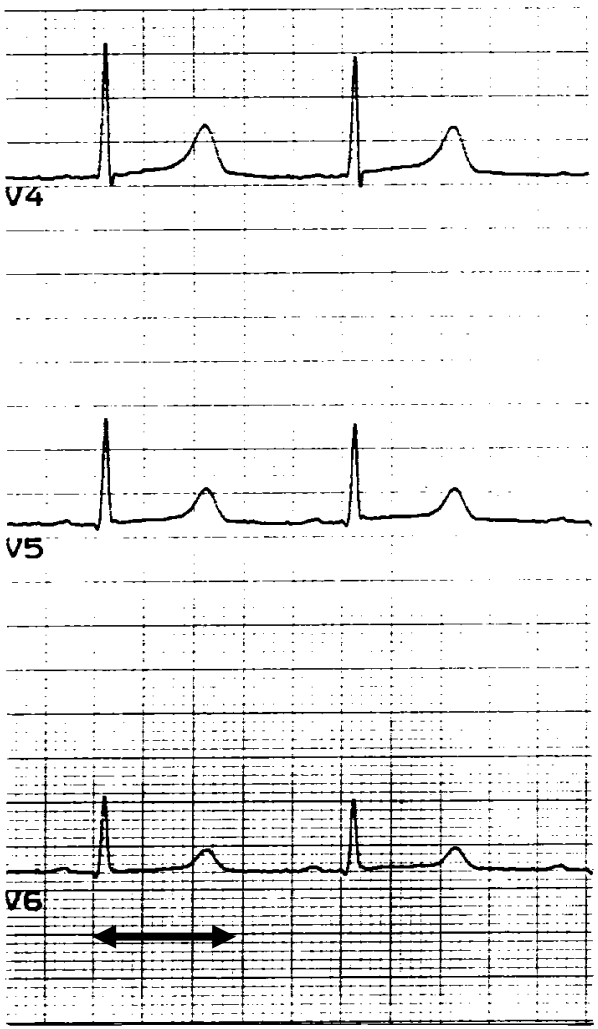
QTc = 0.58sec. 1 Year later he developed an episode of AF.

LQT3



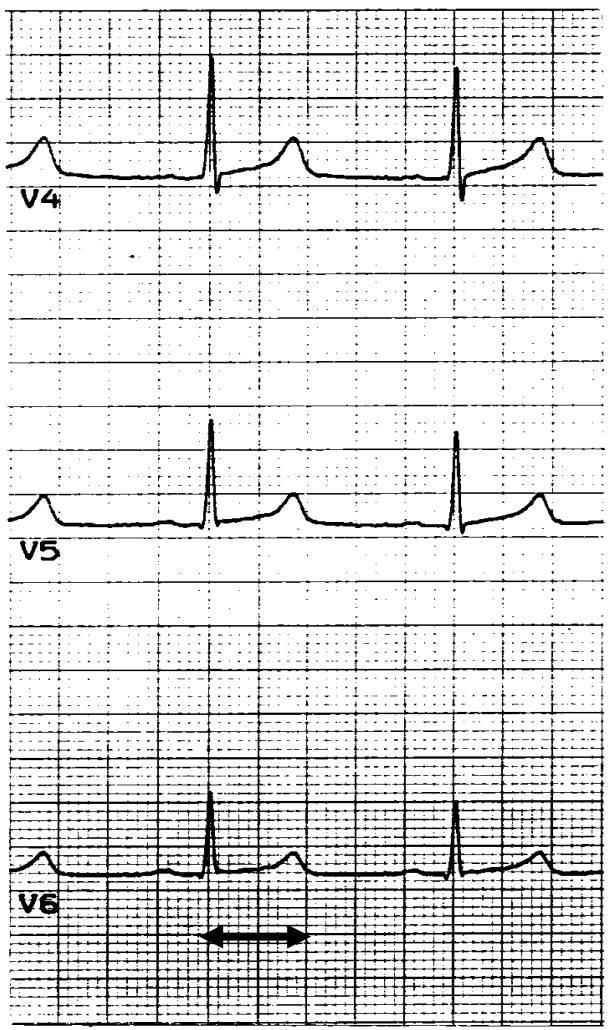
FLECAINIDE STUDY

Baseline



QTc=0.56s

Flecainide 100mg po bid



QTc=0.46s

Windle, Moss, et al. ANE 2001

Proposed Outline for Genotype-Specific Management of Young LQTS Patients

LQT1

Lifestyle Modifications:
Restriction from competitive sports and swimming

Primary Prevention: Low-Risk
Consider beta-blockers

Primary Prevention: High-Risk
(Symptomatic preadolescent males, recurrent syncope, symptoms on BB, DN mutations):
ICD and/or LCSD with beta-blockers

Secondary Prevention
(prior ACA or spontaneous TdP):
ICD with beta-blockers

LQT2

Lifestyle Modifications:
Avoidance of unexpected auditory stimuli in the bedroom, especially during rest or sleep

Primary Prevention: Low-Risk
Consider beta-blockers with careful F-U for residual symptoms

Primary Prevention: High-Risk
(Symptomatic adolescent females, recurrent syncope, symptoms on BBs, pore mutations)
ICD

Secondary Prevention
(prior ACA or spontaneous TdP)
ICD

LQT3

Lifestyle Modifications:
Intercom system in bedroom; avoidance of sleep alone in young patients

Primary Prevention: Low-Risk
Limited data: assess QTc response to sodium channel blockers, consider tx if QTc shortening is observed

Primary Prevention: High-Risk
(prolonged QTc, recurrent syncope, symptoms on medical therapy, non-D1790G mutations):
ICD

Secondary Prevention
(prior ACA or spontaneous TdP):
ICD

THANK YOU