Is there an Asymptomatic Patient with LQT You Would Not Treat?

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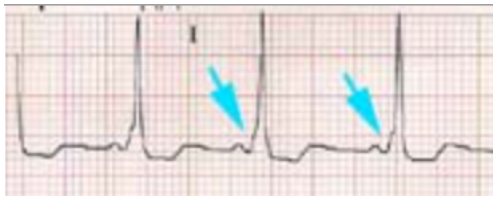
Natural History of WPW

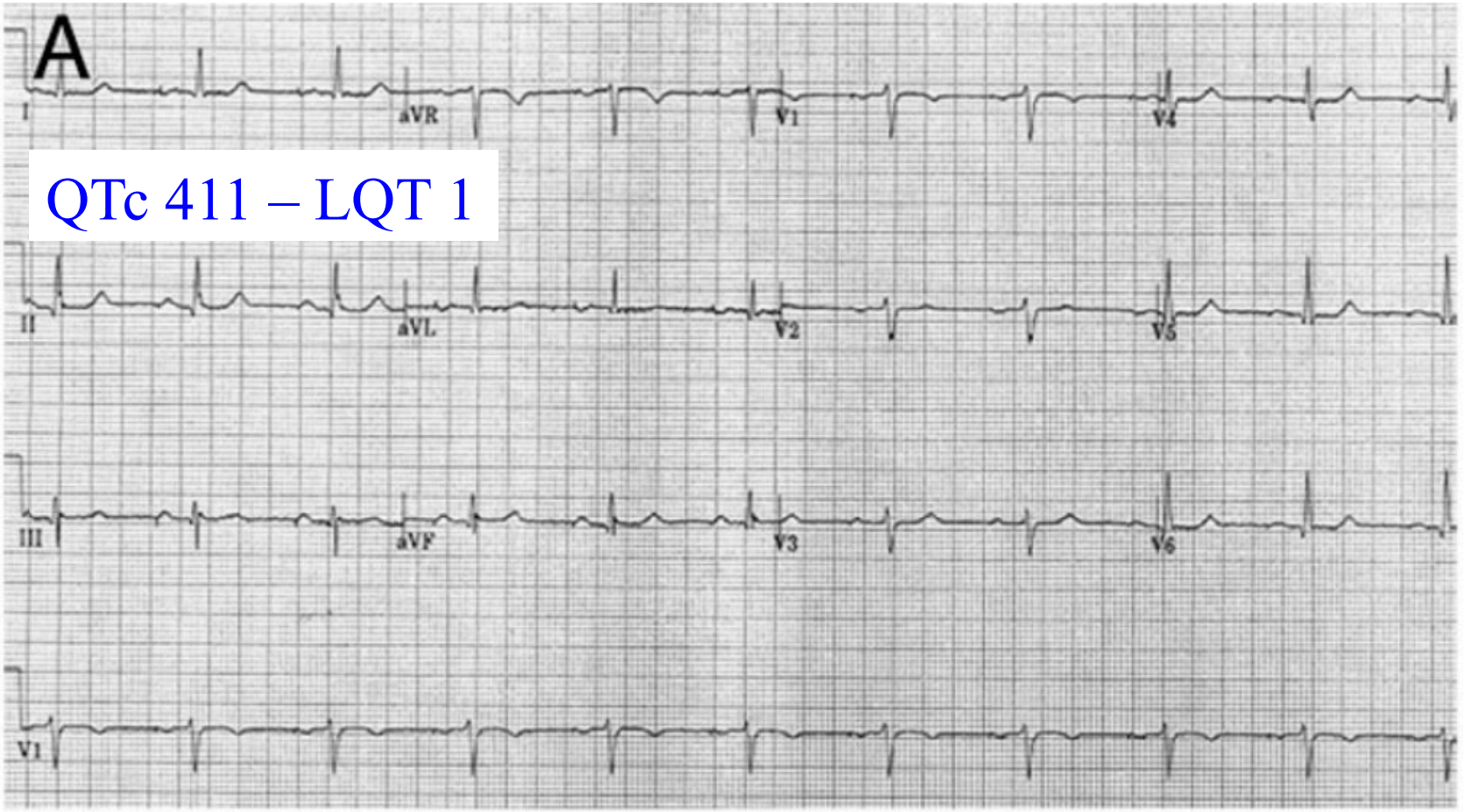


Incidence of sudden cardiac death in natural history studies involving children and young adults

Author	Patients	Years studied	Age	Follow-up (y)	Died	SCD per patient-year	Comments
Berkman (1968)[155]	128	1933–1968	21	20	3	0.0039	
Leitch (1990)[80]	75	1980–1988	34 ± 13	4.3	0	0.0000	
Klein (1989)[28]	27	1981–1989	45	4.5	0	0.0000	
Munger (1993)[17]	113*	1953–1989	33 ± 16	12	2	0.0015	Both SCD patients were symptomatic
Inoue (2000)[156]	57	1985–1993	10.2	8	0	0.0000	
Goudevenos (2000)[16]	157	1990–1997	20	4.6	0	0.0000	
Fitzsimmons (2001)[49]	238*	1955–1999	34.3	21.8	1	0.0002	SCD patient had SVT and atrial fibrillation
Sarubbi (2003)[30]	98	1985–2001	5.4	4	1	0.0019	
Pappone (2003)[38]	212	1993–1996	36 ± 21	3.2	1	0.0150	2 patients had VF and were resuscitated
Santinelli (2009)[29]	184	1995–2005	10	4.6	0	0.0000	3 patients had VF and were resuscitated
	1289				8		

the incidence of sudden cardiac death per patient year 0.0000-0.0150 (we ablate almost all of them)

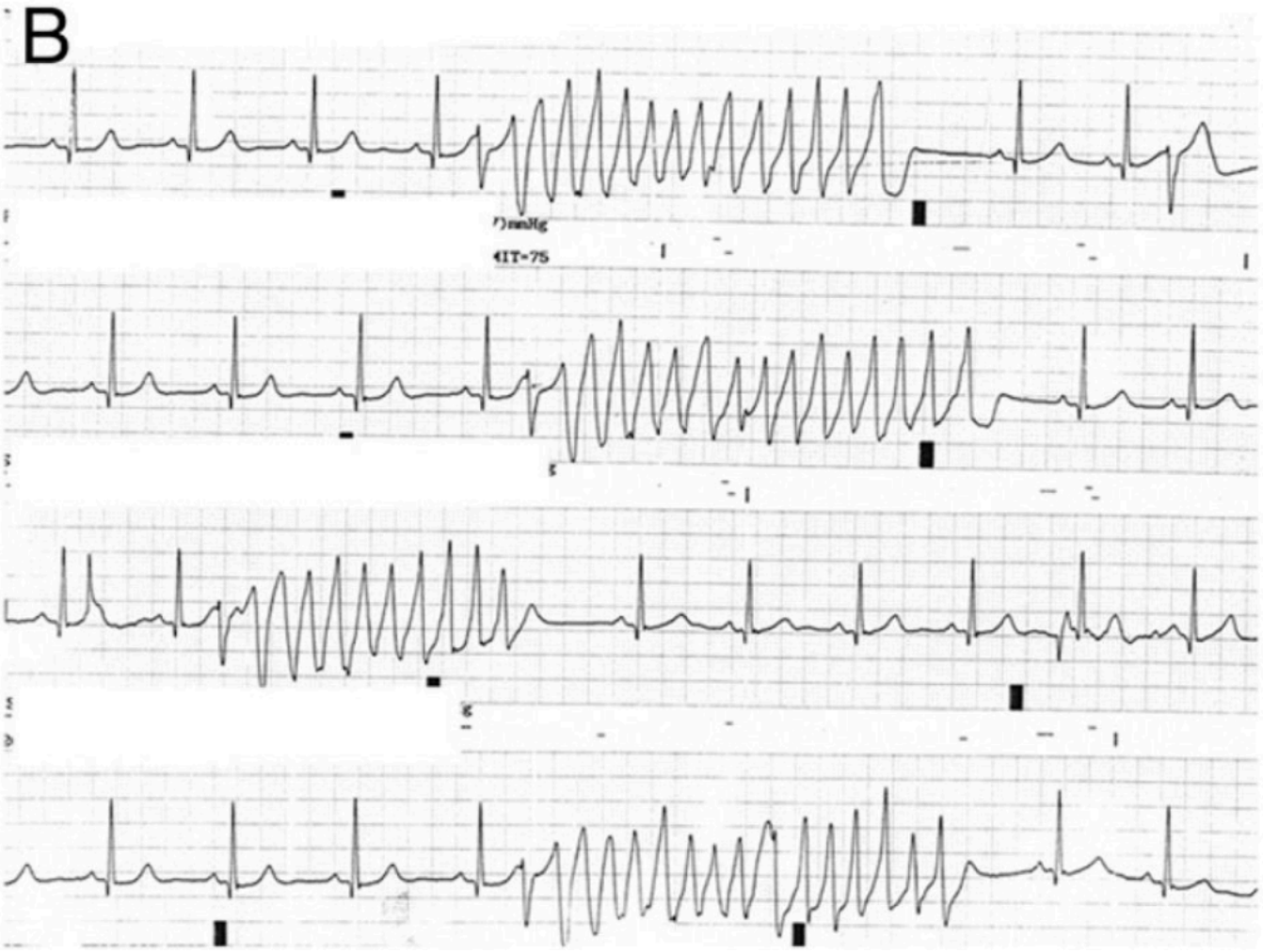
International LQT Registry



QTc 411 – LQT 1

J Am Coll Cardiol 2011;57(1)51-59

Then the Patient Does This

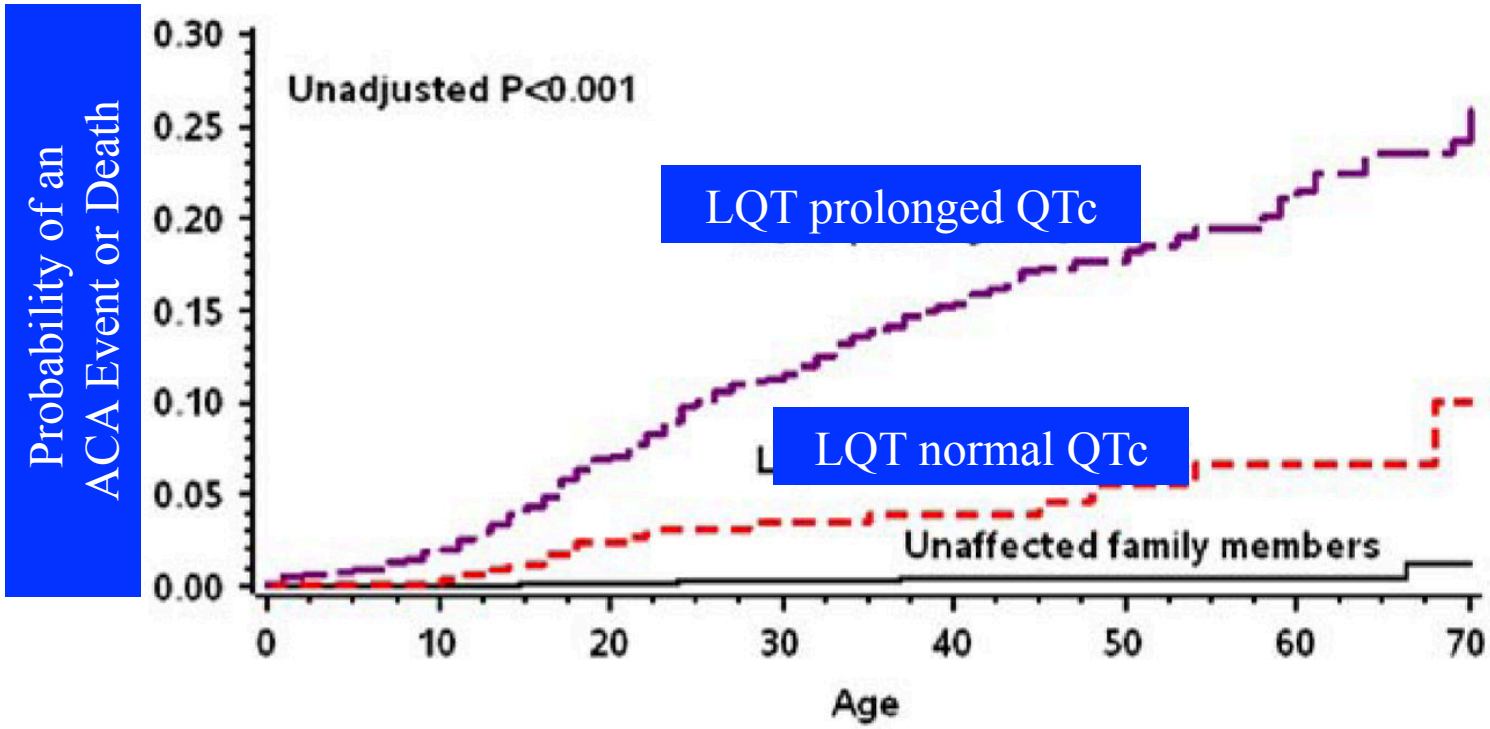


Of children with WPW who have had a cardiac arrest, 10-48% were previously asymptomatic

The first manifestation of LQTS ≈13% is sudden cardiac death

Klein G et al. NEJM 1979;301:1080-85
Russell MW et al. Circulation 1993:484 (A)
Deal B, et al. PACE 1995 18:815(A)
Bromberg BL, et al. JACC 1996:27:690-95
Priori SG, et al. NEJM 2003;348:1866-1874

Risk of a Cardiac Arrest or Sudden Cardiac Death Event is Low But Not Zero and Probably More than WPW

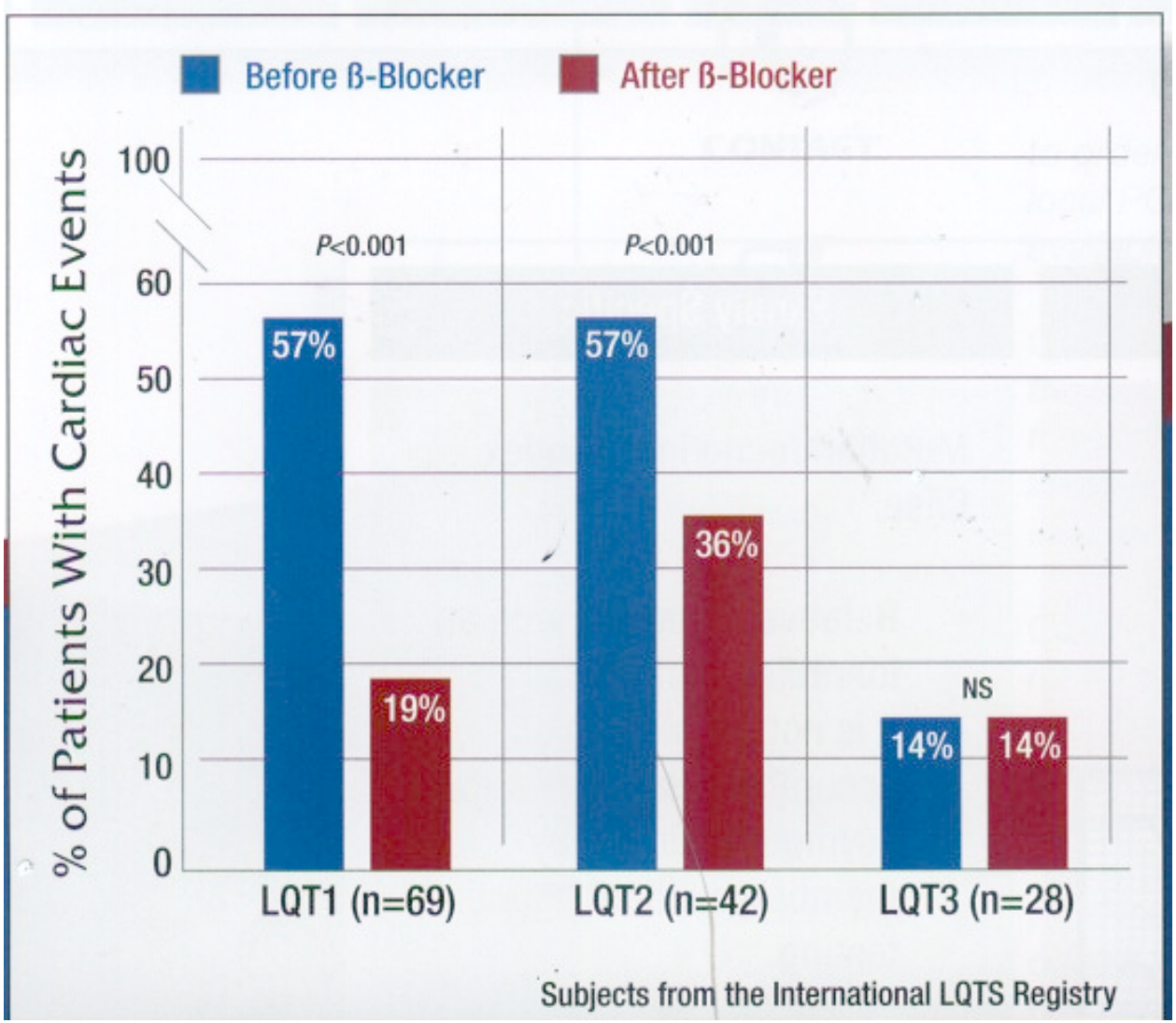


Patients at Risk				
Gen-/Phen-	1525	1377 (0)	728 (0)	348 (0)	92 (0.01)
Gen+/Phen-	469	406 (0)	236 (0.04)	97 (0.06)	20 (0.10)
Gen+/Phen+	1392	1235 (0.02)	729 (0.11)	334 (0.18)	94 (0.24)

So in LQT patients with a greater risk of sudden cardiac death than WPW, variable expressivity, increased heterogeneity, maybe more parental and familial anxiety regarding the condition- why would I not treat everyone?

The mainstay of therapy in LQTS is the prophylactic, regular, and uninterrupted use of beta-blockers

Observational Research – Reduced Risk of Cardiac Events in those Taking Beta-Blockers



Beta-Blockers are Not Entirely Benign

- Dyspnea
- Fatigue
- Nightmares
- Dizziness
- Low Blood Sugar
- Precipitation or worsening of asthma
- Depression
- Moodiness

Getting an Adolescent to Take Medication is a Challenge and a Constant Reminder of the Disease Itself

why is there confusion about starting beta-blockers or is there?

HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes

Silvia G. Priori, MD, PhD, (HRS Chairperson)[1], Arthur A. Wilde, MD, PhD, (EHRA Chairperson)[2], Minoru Horie, MD, PhD, (APHRS Chairperson)[3], Yongkeun Cho, MD, PhD, (APHRS Chairperson)[4], Elijah R. Behr, MA, MBBS, MD, FRCP[5], Charles Berul, MD, FHRS, CCDS[6], Nico Blom, MD, PhD[7,*], Josep Brugada, MD, PhD[8], Chern-En Chiang, MD, PhD[9], Heikki Huikuri, MD[10], Prince Kannankeril, MD[11,‡], Andrew Krahn, MD, FHRS[12], Antoine Leenhardt, MD[13], Arthur Moss, MD[14], Peter J. Schwartz, MD[15], Wataru Shimizu, MD, PhD[16], Gordon Tomaselli, MD, FHRS[17,†], Cynthia Tracy, MD[18,%]

From the [1]Maugeri Foundation IRCCS, Pavia, Italy, Department of Molecular Medicine, University of Pavia, Pavia, Italy and New York University, New York, New York, [2]Department of Cardiology, Academic Medical Centre, Amsterdam, Netherlands, Princess Al-Jawhara Al-Brahim Centre of Excellence in Research of Hereditary Disorders, Jeddah, Kingdom of Saudi Arabia, [3]Shiga University of Medical Sciences, Otsu, Japan, [4]Kyungpook National University Hospital, Daegu, South Korea, [5]St. Georges University of London, United Kingdom, [6]Children's National Medical Center, Washington, DC, United States, [7]Academical Medical Center, Amsterdam, Leiden University Medical Center, Leiden, Netherlands, [8]University of Barcelona, Barcelona, Spain, [9]Taipei Veteran's General Hospital, Taipei, Taiwan, [10]Oulu University Central Hospital, Oulu, Finland, [11]Vanderbilt Children's Hospital, Nashville, Tennessee, United States, [12]Sauder Family and Heart and Stroke Foundation University of British Columbia, British Columbia, Canada, [13]Bichat University Hospital, Paris, France, [14]University of Rochester Medical Center, Rochester, New York, United States, [15]Department of Molecular Medicine, University of Pavia, Pavia, Italy, [16]Nippon Medical School, Tokyo, Japan, [17]Johns Hopkins University, Baltimore, Maryland, United States, and [18]George Washington University Medical Center, Washington, DC, United States.

Document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013

Beta-blockers are clinically indicated in LQTS, including those with a genetic diagnosis and normal QTc, unless there is a contraindication such as active asthma.

Beta-blockers are recommended for patients with a diagnosis of LQTS who are asymptomatic with a QTc $\geq$ 470 msec.

Beta-blockers can be useful in patients with a diagnosis of LQTS who are asymptomatic with a QTc $\leq$ 470 msec.

are the terms "can be useful" and "clinically indicated" the same?

asymptomatic (ā′sĭmp-tə-măt′ĭk)

adj.

Neither causing nor exhibiting symptoms of disease.

Syncope Increases the Risk of a Sudden Cardiac Event

(27X girls, 6X boys future cardiac event)

When You Have Syncope You are No Longer Asymptomatic

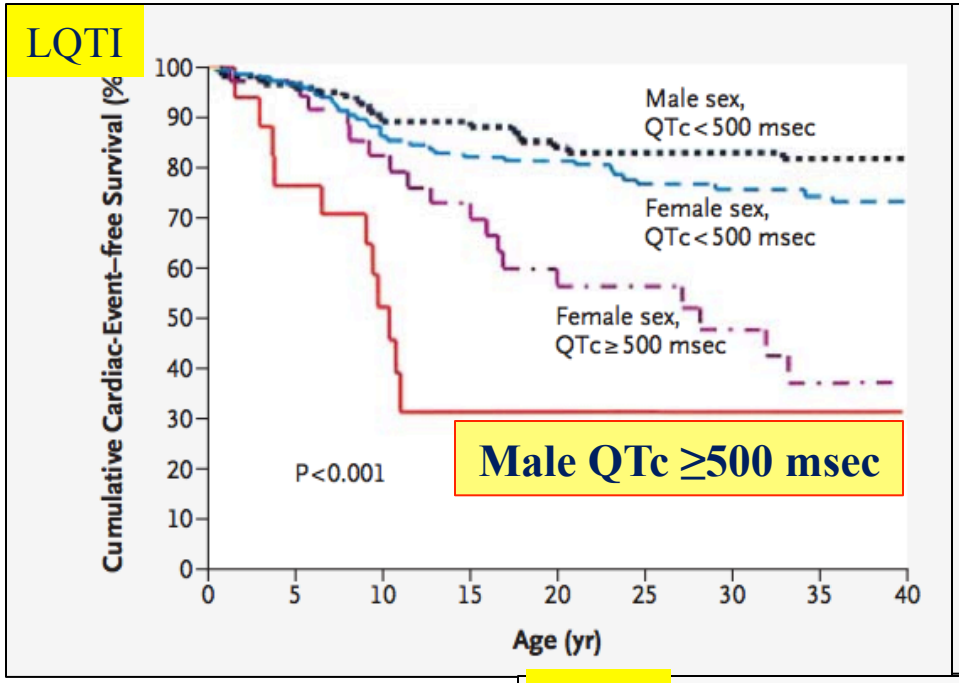
Goldenberg I et al Circulation 2008

First Steps

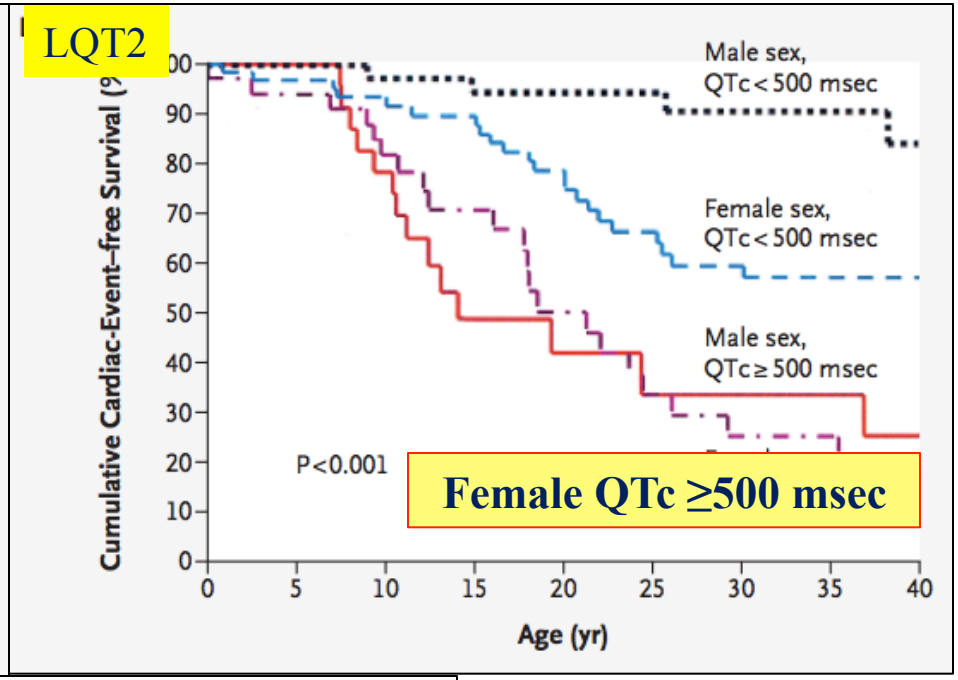
- Any decision regarding to treat or not to treat in the asymptomatic LQT patient should be taken seriously and should be a shared decision based on the best evidence between the physician, patient, and family.
- A decision not to treat is not a forever decision (time changes, puberty occurs, interests in activities change)
- A decision NOT to treat can only be made if you know the genetic abnormality
- A decision not to treat is not the same thing as doing nothing
  - Ongoing surveillance
  - Ongoing shared risk decision
  - Constant reinforcement of medications to avoid

Understanding the RISK can only be done if you know the genotype

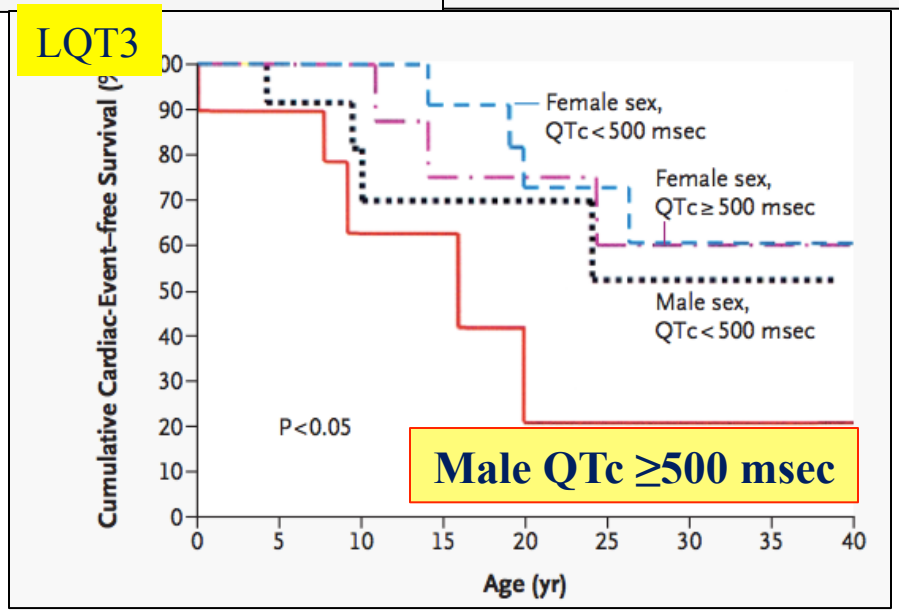
LQTI



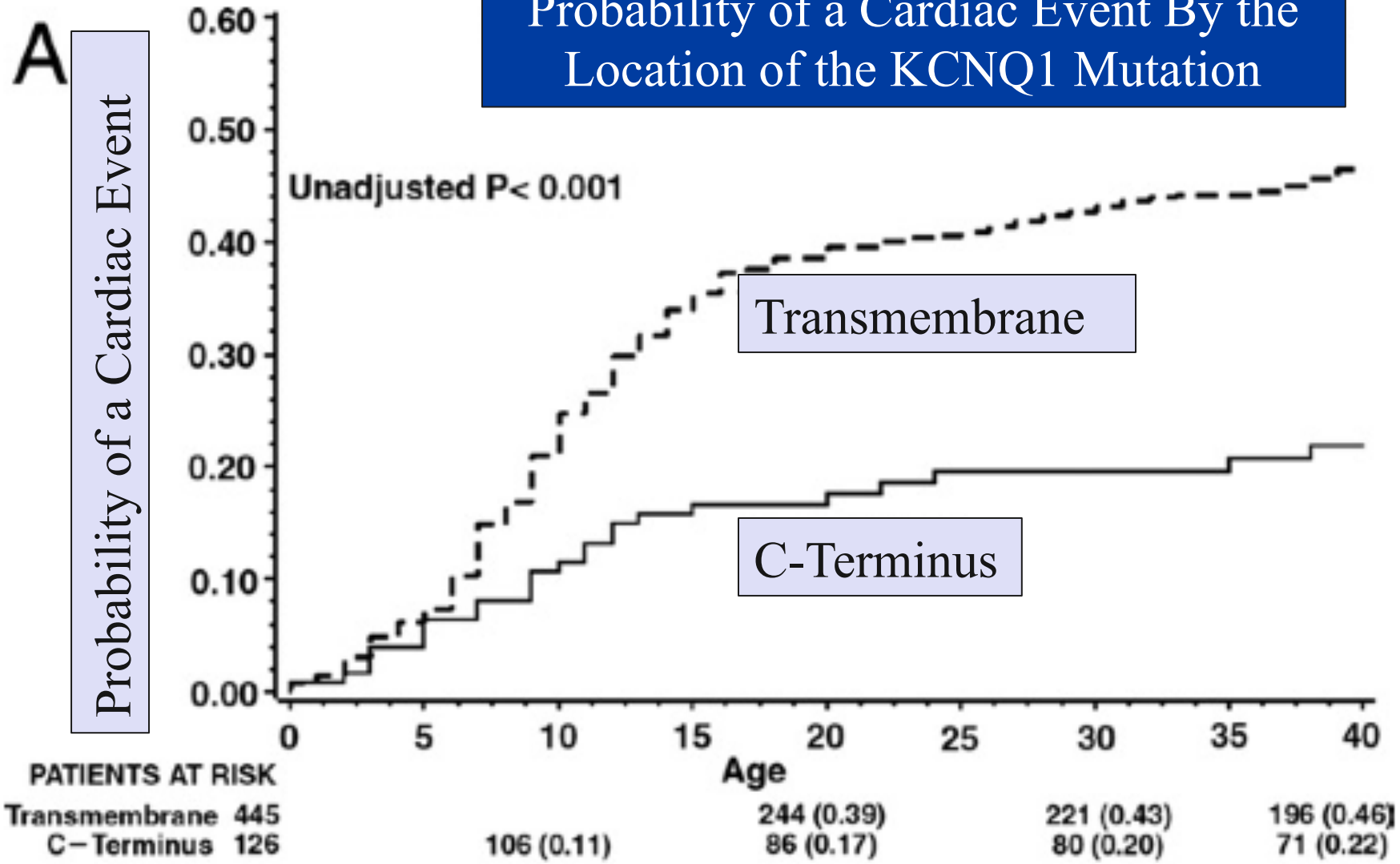
LQT2



LQT3



Probability of a Cardiac Event By the Location of the KCNQ1 Mutation



Mutations in Cytoplasmic Loops of the KCNQ1 Channel and the Risk of Life-Threatening Events

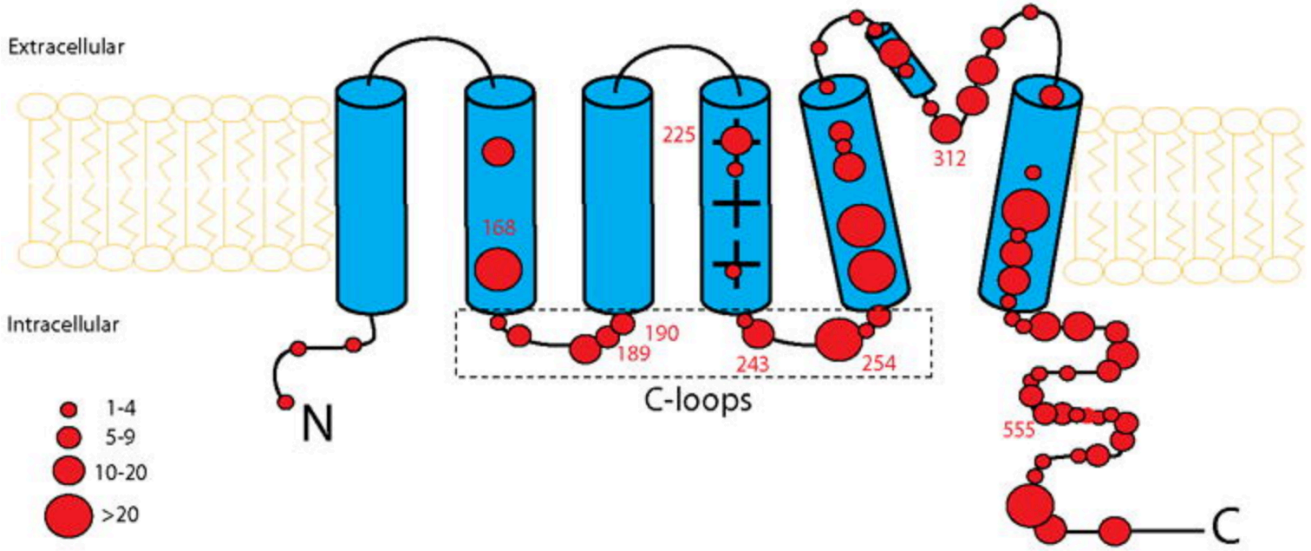
Implications for Mutation-Specific Response to β-Blocker Therapy in Type 1 Long-QT Syndrome

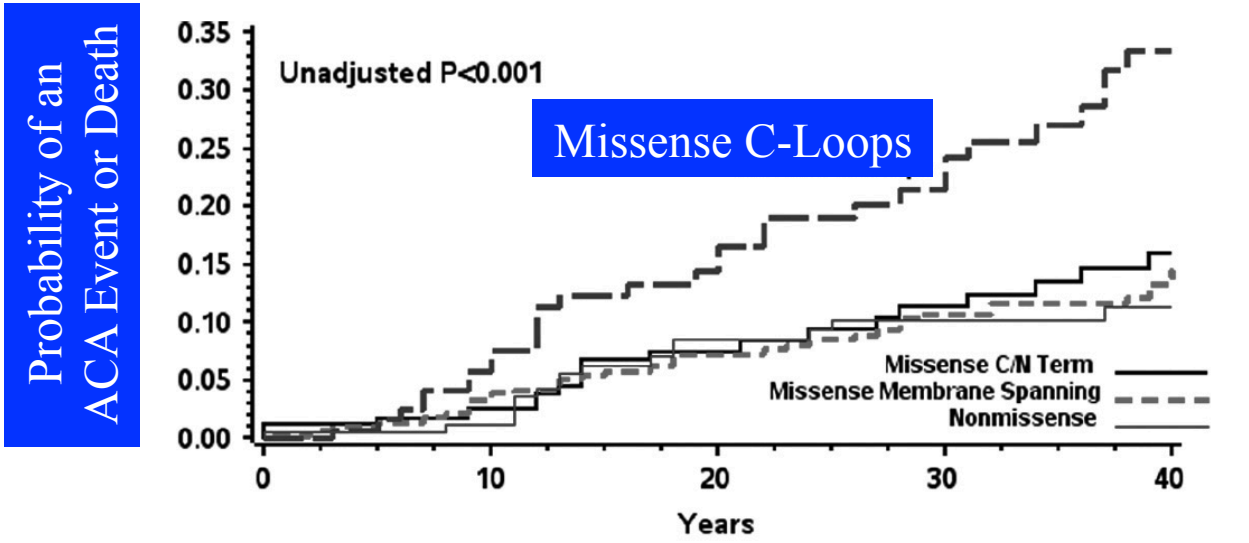
Alon Barsheshet, MD*; Ilan Goldenberg, MD*; Jin O-Uchi, MD, PhD*; Arthur J. Moss, MD; Christian Jons, MD; Wataru Shimizu, MD; Arthur A. Wilde, MD, PhD; Scott McNitt, MS; Derick R. Peterson, PhD; Wojciech Zareba, MD, PhD; Jennifer L. Robinson, MS; Michael J. Ackerman, MD; Michael Cypress, BS; Daniel A. Gray, MD, PhD; Nynke Hofman, MS; Jorgen K. Kanters, MD; Elizabeth S. Kaufman, MD; Pyotr G. Platonov, MD, PhD; Ming Qi, PhD; Jeffrey A. Towbin, MD; G. Michael Vincent, MD; Coeli M. Lopes, PhD

Background—β-Adrenergic stimulation is the main trigger for cardiac events in type 1 long-QT syndrome (LQT1). We evaluated a possible association between ion channel response to β-adrenergic stimulation and clinical response to β-blocker therapy according to mutation location.

Methods and Results—The study sample comprised 860 patients with genetically confirmed mutations in the *KCNQ1* channel. Patients were categorized into carriers of missense mutations located in the cytoplasmic loops (C loops), membrane-spanning domain, C/N terminus, and nonmissense mutations. There were 27 aborted cardiac arrest and 78 sudden cardiac death events from birth through 40 years of age. After multivariable adjustment for clinical factors, the presence of C-loop mutations was associated with the highest risk for aborted cardiac arrest or sudden cardiac death (hazard ratio versus nonmissense mutations=2.75; 95% confidence interval, 1.29–5.86; $P=0.009$). β-Blocker therapy was associated with a significantly greater reduction in the risk of aborted cardiac arrest or sudden cardiac death among patients with C-loop mutations than among all other patients (hazard ratio=0.12; 95% confidence interval, 0.02–0.73; $P=0.02$; and hazard ratio=0.82; 95% confidence interval, 0.31–2.13; $P=0.68$, respectively; P for interaction=0.04). Cellular expression studies showed that membrane spanning and C-loop mutations produced a similar decrease in current, but only C-loop mutations showed a pronounced reduction in channel activation in response to β-adrenergic stimulation.

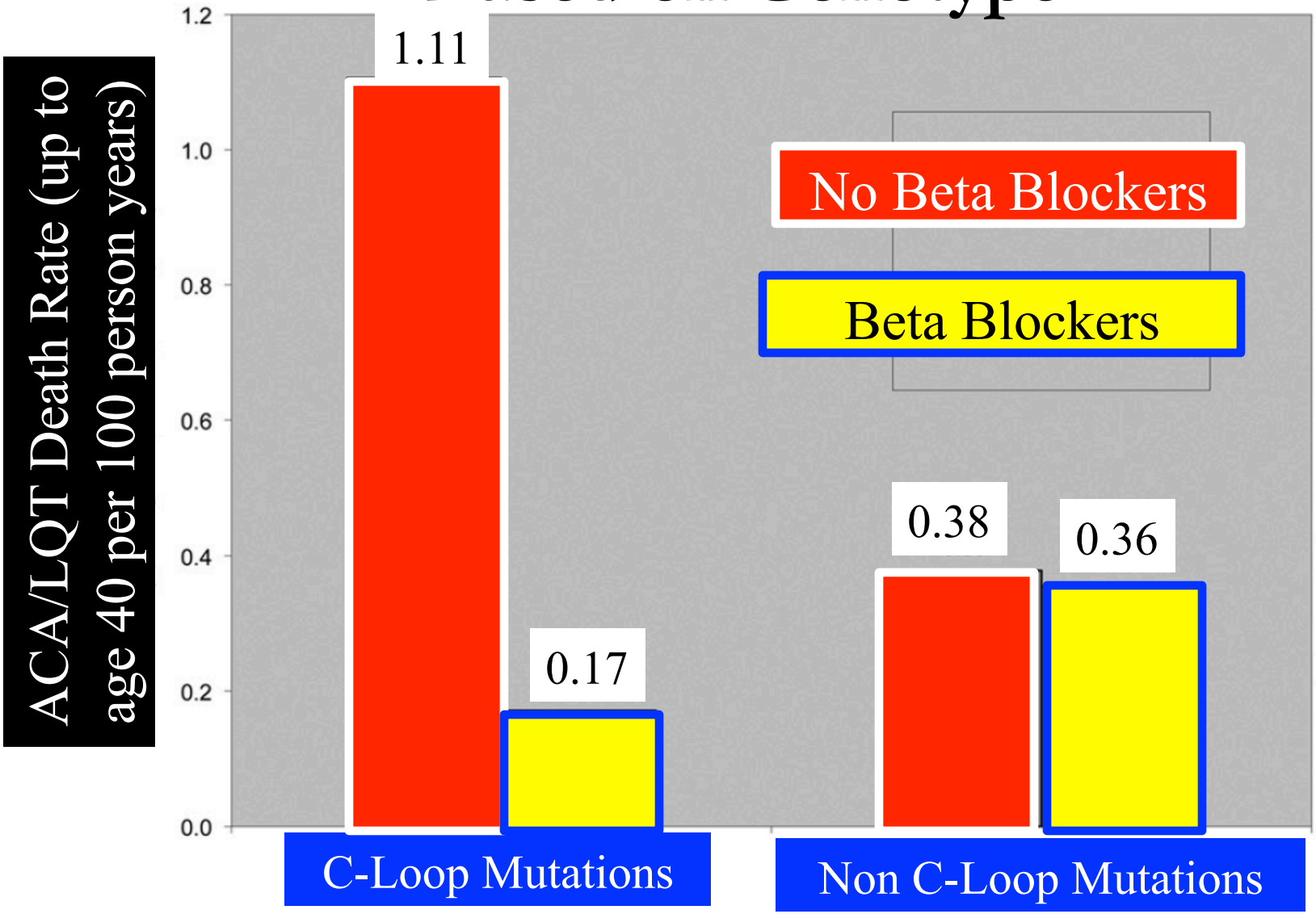
Conclusions—Patients with C-loop missense mutations in the *KCNQ1* channel exhibit a high risk for life-threatening events and derive a pronounced benefit from treatment with β-blockers. Reduced channel activation after sympathetic activation can explain the increased clinical risk and response to therapy in patients with C-loop mutations. **(*Circulation*. 2012;125:1988-1996.)**

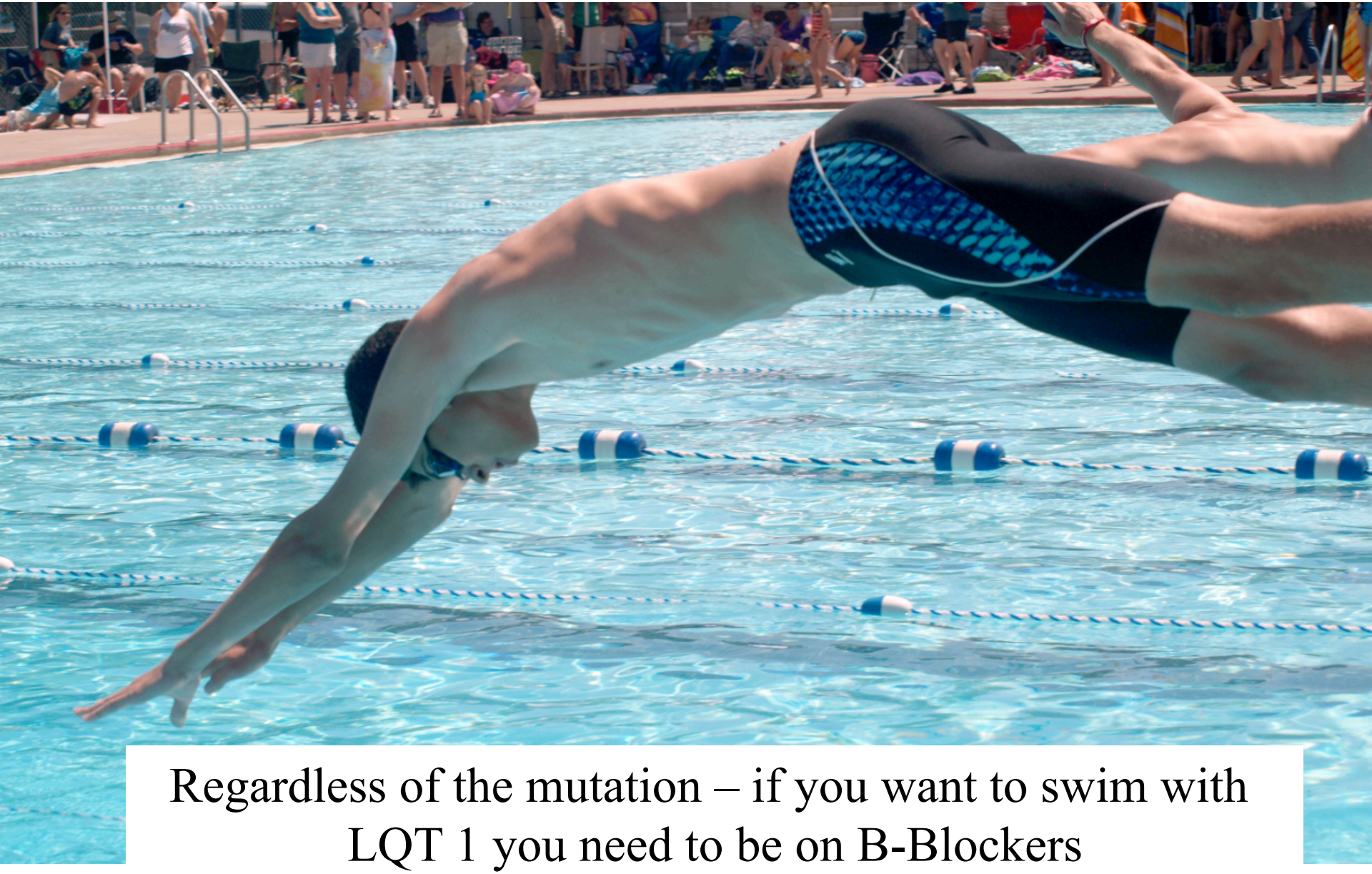




Patients at Risk					
C/N Term	172	145 (0.02)	108 (0.07)	88 (0.11)	62 (0.16)
Membr Spanning	376	328 (0.03)	242 (0.07)	192 (0.11)	154 (0.13)
C-loops	125	109 (0.06)	78 (0.14)	59 (0.22)	39 (0.33)
Nonmissense	186	157 (0.01)	119 (0.09)	95 (0.10)	69 (0.11)

Beta-Blocker Effectiveness in LQT 1 Based on Genotype





Regardless of the mutation – if you want to swim with LQT 1 you need to be on B-Blockers

Aerial View of Arizona – Can You Find a Home without a Pool? – Good Luck

Maybe A LQT 1 Shared Risk Decision Making Recommendation?

- Asymptomatic
- QTc < 460 msec (repeatedly observed over years)
- Normal T wave morphologies (repeatedly observed over years)
- Age >30 years
- Normal Exercise Stress Test & Epinephrine
- Avoiding Swimming (beyond getting feet wet)
- Avoiding all QT prolonging medications
- I would be OK discontinuing B-Blockers

Long QT Syndrome in Women

An Information Booklet for Patients and their Families

Long QT 2 females (post puberty) carries the highest risk and likely relates to increased estrogen levels post-puberty. So no matter what girls with LQT2 are treated (regardless of the QT, genotype location).

Sauer AJ, Moss AJ, McNitt S, Peterson DR, Zareba W, Robinson JL, Qi M, Goldenberg I, Hobbs JB, Ackerman MJ, Benhorin J, Hall WJ, Kaufman ES, Locati EH, Napolitano C, Priori SG, Schwartz PJ, Towbin JA, Vincent GM, Zhang L (2007) Long QT syndrome in adults. J Am Coll Cardiol 49:329–337

. Zareba W, Moss AJ, Locati EH, Lehmann MH, Peterson DR, Hall WJ, Schwartz PJ, Vincent GM, Priori SG, Benhorin J, Towbin JA, Robinson JL, Andrews ML, Napolitano C, Timothy K, Zhang L, Medina A, International Long QT Syndrome Registry (2003) Modulating effects of age and gender on the clinical course of long QT syndrome by genotype. J Am Coll Cardiol 42:103–109

Mutation and gender-specific risk in type 2 long QT syndrome: Implications for risk stratification for life-threatening cardiac events in patients with long QT syndrome

Dimitry Migdalovich, BS,* Arthur J. Moss, MD,* Coeli M. Lopes, PhD,† Jason Costa, MA,* Gregory Ouellet, MA,* Alon Barsheshet, MD,* Scott McNitt, MS,* Slava Polonsky, MS,* Jennifer L. Robinson, MS,* Wojciech Zareba, MD, PhD,* Michael J. Ackerman, MD, PhD,‡ Jesaia Benhorin, MD,§ Elizabeth S. Kaufman, MD,□ Pyotr G. Platonov, MD,¶ Wataru Shimizu, MD, PhD,# Jeffrey A. Towbin, MD,** G. Michael Vincent, MD,†† Arthur A.M. Wilde, MD, PhD,‡‡ Ilan Goldenberg, MD*

*From the *Cardiology Division, University of Rochester Medical Center, Rochester, New York; †Cardiovascular Research Institut... ‡Divisio... §Medica... ‖Univer... ¶Depart... #of Cin... **Cardio...*

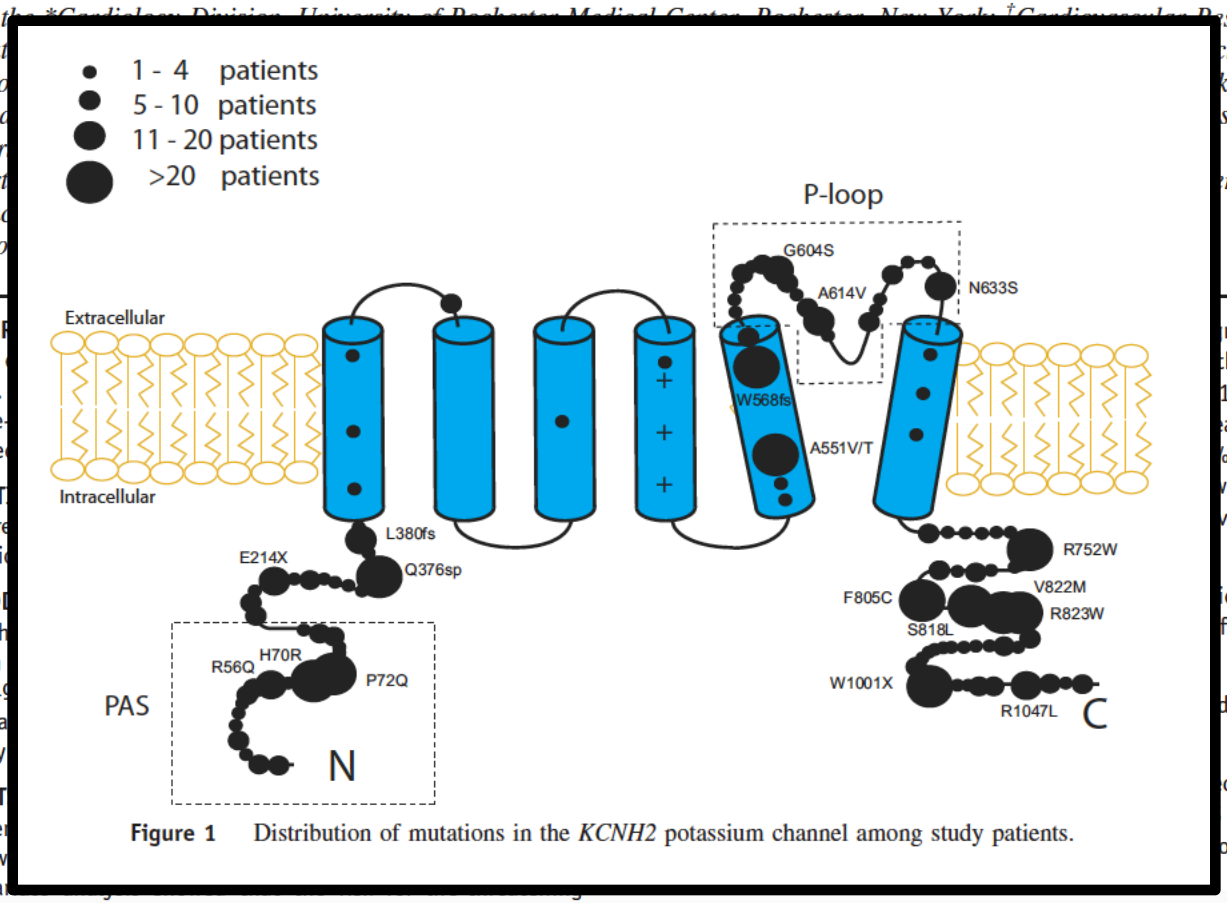


Figure 1 Distribution of mutations in the *KCNH2* potassium channel among study patients.

BACKGR... (LQT2) ... events. ... disease-... der-spe...

OBJECT... life-thre... formati...

METHOD... through... sudden ... (n = 49... LQTS-ca... primary...

RESULT... threate... LQT2 w... Multiva...

cardiac events was not significantly different between women with and without pore-loop mutations (hazard ratio 1.20; P =.33). In

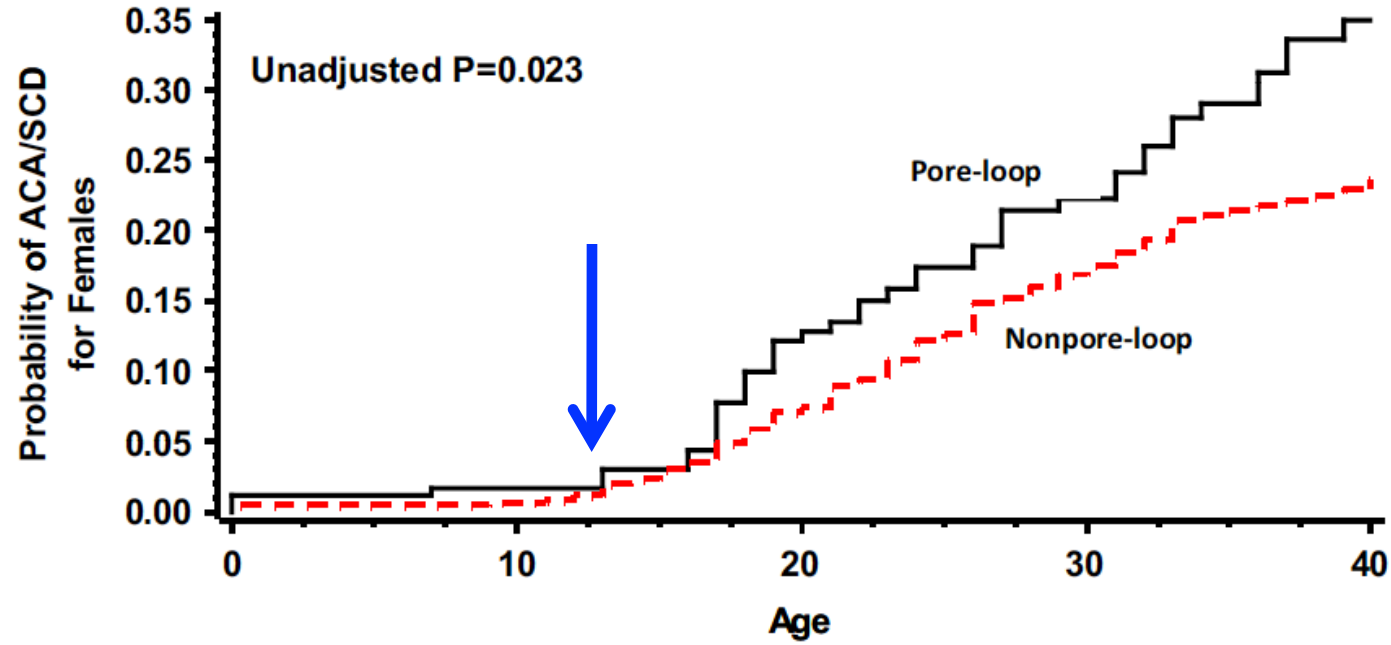
...nificant ...th those ...1). Con- ...atening ...%, non– ...vas high ...vely low

...ion-spe- ...for life- ...den car-

...ctrocar- ... = long ...orrected

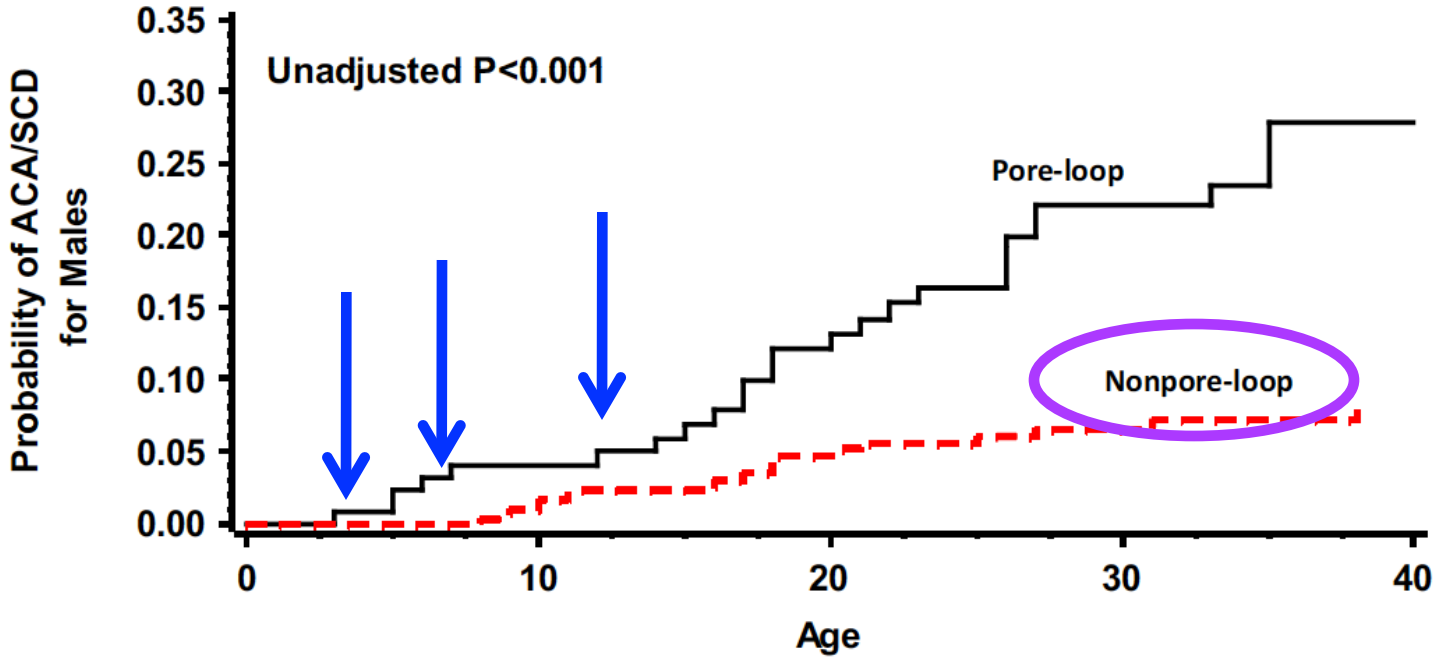
(Heart Rhythm 2011;8:1537–1543)

Probability of an ACA/SCD for LQT2 Females

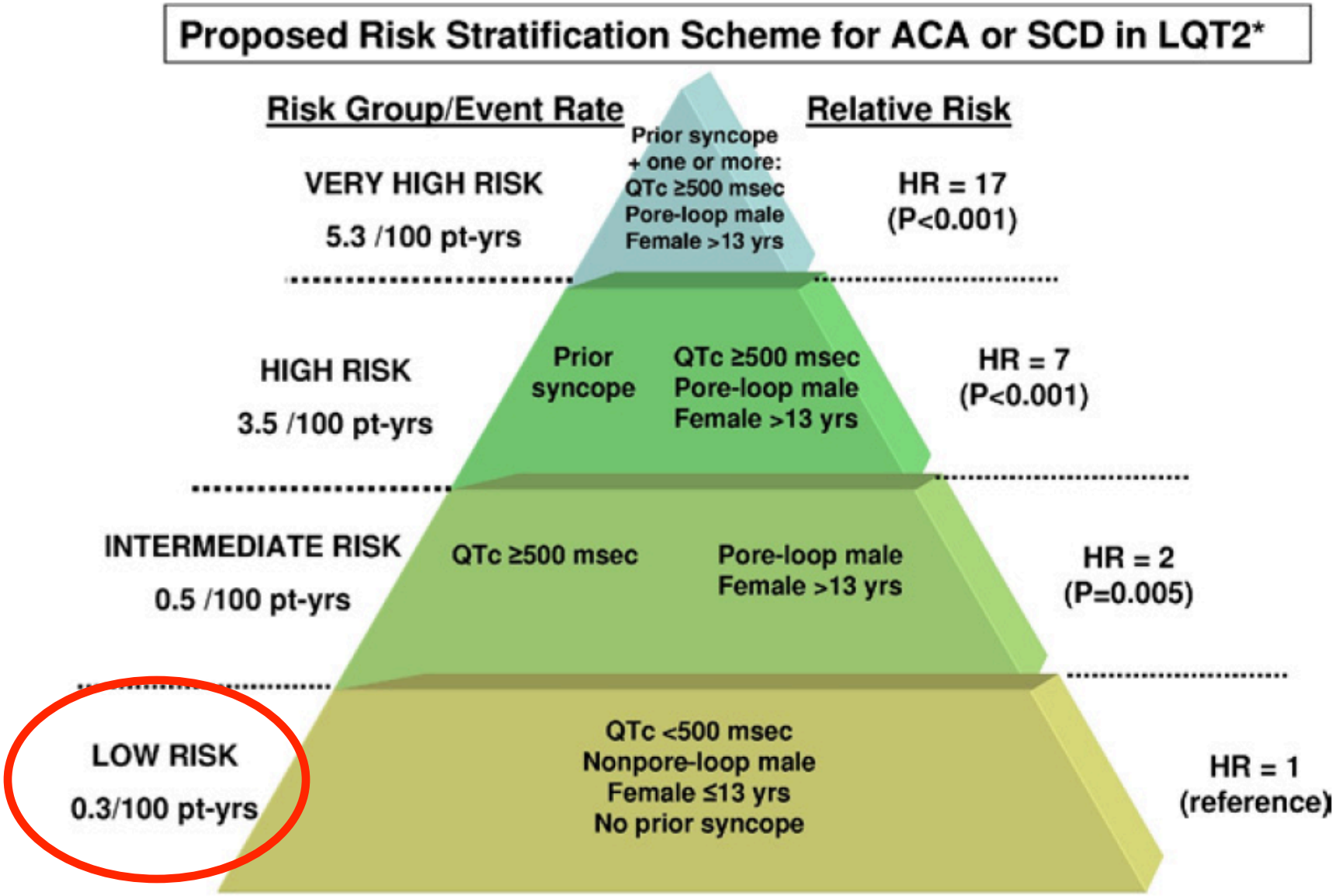


Probability of an ACA/SCD for LQT2 Males

Where is your comfort level for risk????



Patients at Risk				
Pore 136	109 (0.04)	84 (0.12)	63 (0.22)	41 (0.28)
Non-pore 354	302 (0.01)	216 (0.05)	172 (0.07)	130 (0.08)



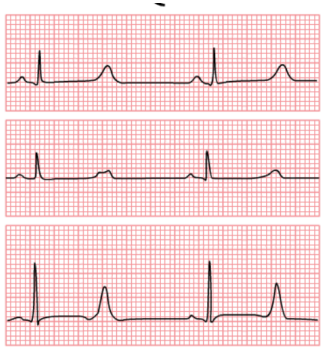
LOW RISK IS NOT ZERO RISK

Maybe A LQT 2 Shared Risk Decision Making Recommendation?

- **Asymptomatic Females**
- Only prior to puberty (maybe)
- But will have to start BB once puberty begins

- **Asymptomatic Males**
- QTc < 440 msec (repeatedly observed over years)
- Normal T wave morphologies (repeatedly observed)
- Normal Exercise Stress Test
- Nonpore Mutation
- Avoiding all QT prolonging medications
- I might be OK watching off B-Blockers but probably not my preference

Long QT3



- Major events occur more frequently despite B-blocker therapy (10-15%)
- Incorrect to think that B-blocker are of limited or no value and could potentially be pro-arrhythmic
- Most studies of LQT3 patients are pooled registry data
- Cardiac events in 1st year of life in LQT3 poor prognosis

Circulation. 2016 Sep 20;134(12):872-82. doi: 10.1161/CIRCULATIONAHA.116.021823. Epub 2016 Aug 26.

Clinical Aspects of Type 3 Long-QT Syndrome: An International Multicenter Study.

Wilde AA[1], Moss AJ[2], Kaufman ES[2], Shimizu W[2], Peterson DR[2], Benhorin J[2], Lopes C[2], Towbin JA[2], Spazzolini C[2], Crotti L[2], Zareba W[2], Goldenberg I[2], Kanters JK[2], Robinson JL[2], Qi M[2], Hofman N[2], Tester DJ[2], Bezzina CR[2], Alders M[2], Aiba T[2], Kamakura S[2], Miyamoto Y[2], Andrews ML[2], McNitt S[2], Polonsky B[2], Schwartz PJ[2], Ackerman MJ[2].

Author information

Abstract

BACKGROUND: Risk stratification in patients with type 3 long-QT syndrome (LQT3) by clinical and genetic characteristics and effectiveness of β-blocker therapy has not been studied previously in a large LQT3 population.

METHODS: The study population included 406 LQT3 patients with 51 sodium channel mutations; 391 patients were known to be event free during the first year of life and were the focus of our study. Clinical, electrocardiographic, and genetic para is was used to evaluate t of time-dependent c

RESULTS: O cope, aborted card lated aborted cardiac arres Cox regression a n in CEs in females (P= ction (P=0.04). Each 10-ms increase in QTc duration up to 500 ms was associated with a 19% increase in CEs. Prior syncope doubled the risk for life-threatening events (P<0.02).

CONCLUSIONS: Prolonged QTc and syncope predispose patients with LQT3 to life-threatening CEs. However, β-blocker therapy reduces this risk in females; efficacy in males could not be determined conclusively because of the low number of events.

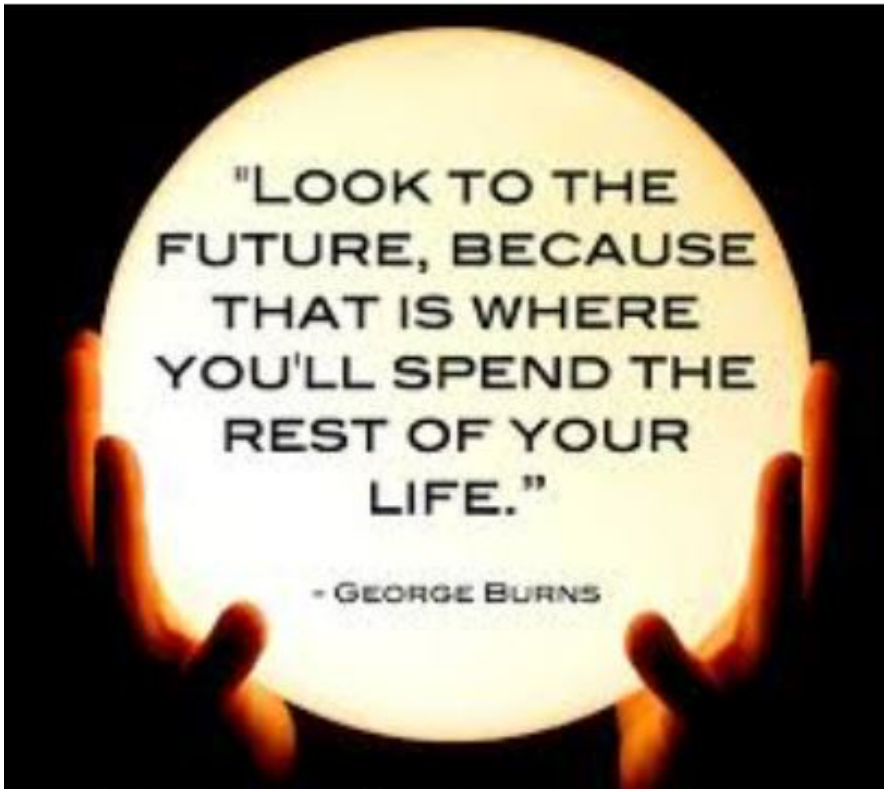
B-Blocker therapy 83% reduction in cardiac events in females with LQT 3 but not in males where the incidence of cardiac events is significantly less

Maybe A LQT 3 Shared Risk Decision Making Recommendation?

- Asymptomatic Men (age >25-30)
- QTc < 460 msec (repeatedly observed over years)
- Normal T wave morphologies (repeatedly observed over years)
- Normal Exercise Stress Test
- No evidence of concerning pauses on Holter
- Avoiding all QT prolonging medications
- I would be OK discontinuing B-Blockers

Family History
May Change

Personalized Medicine
Better Understanding of
Genetic Abnormalities



Functional Genetic Testing
on an Individualized Basis

No Treatment Does Not
Mean No Follow-up

Thank You