VENICE 2015 ARRHYTHMIAS

Long QT syndrome

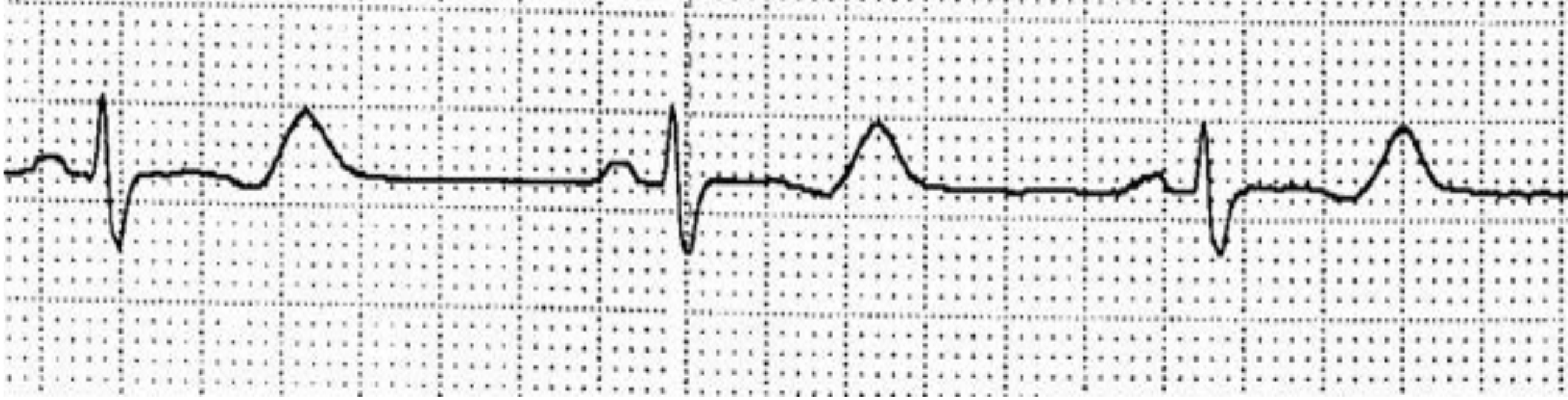
Should we treat all asymptomatic patients?

Venice Arrhythmia 2015

Arthur A.M. Wilde

October 16 - 18
14th EDITION 2015

NO CONFLICT OF INTEREST TO DECLARE



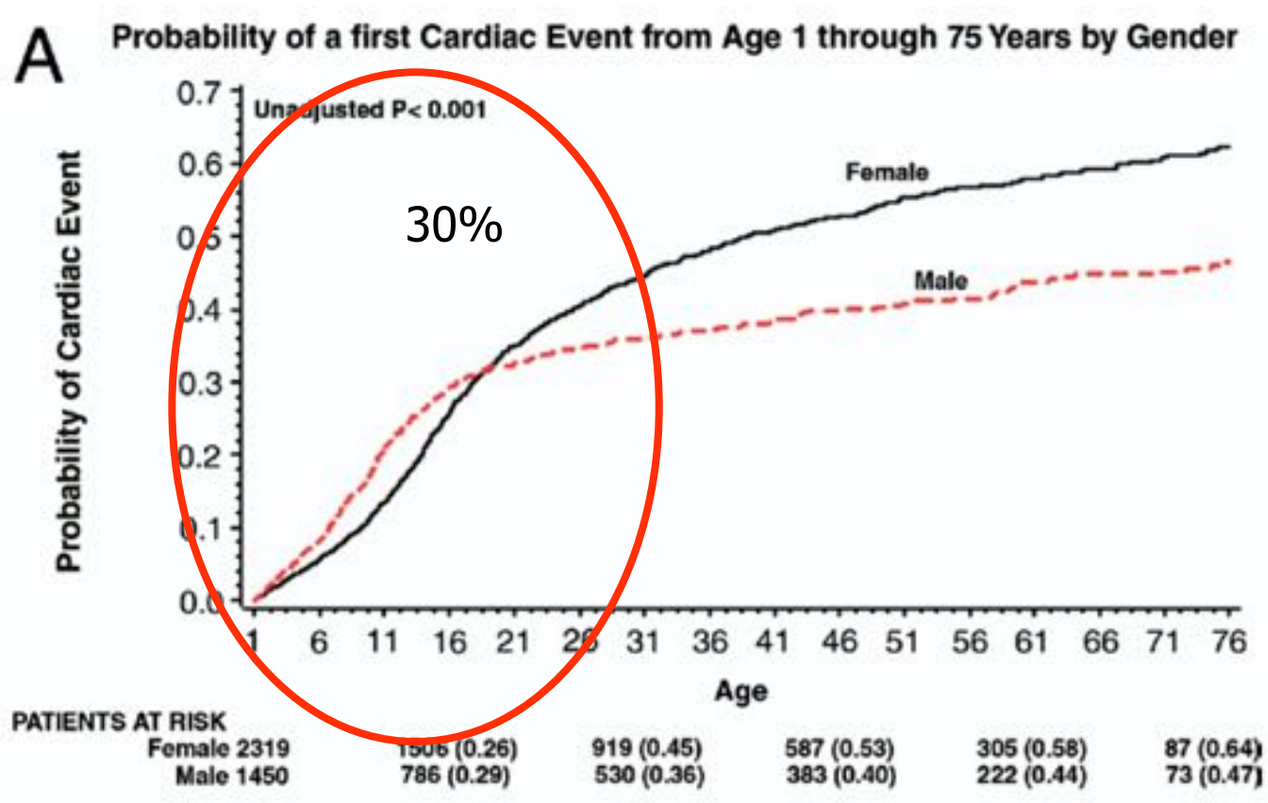
Long QT Syndrome(s)

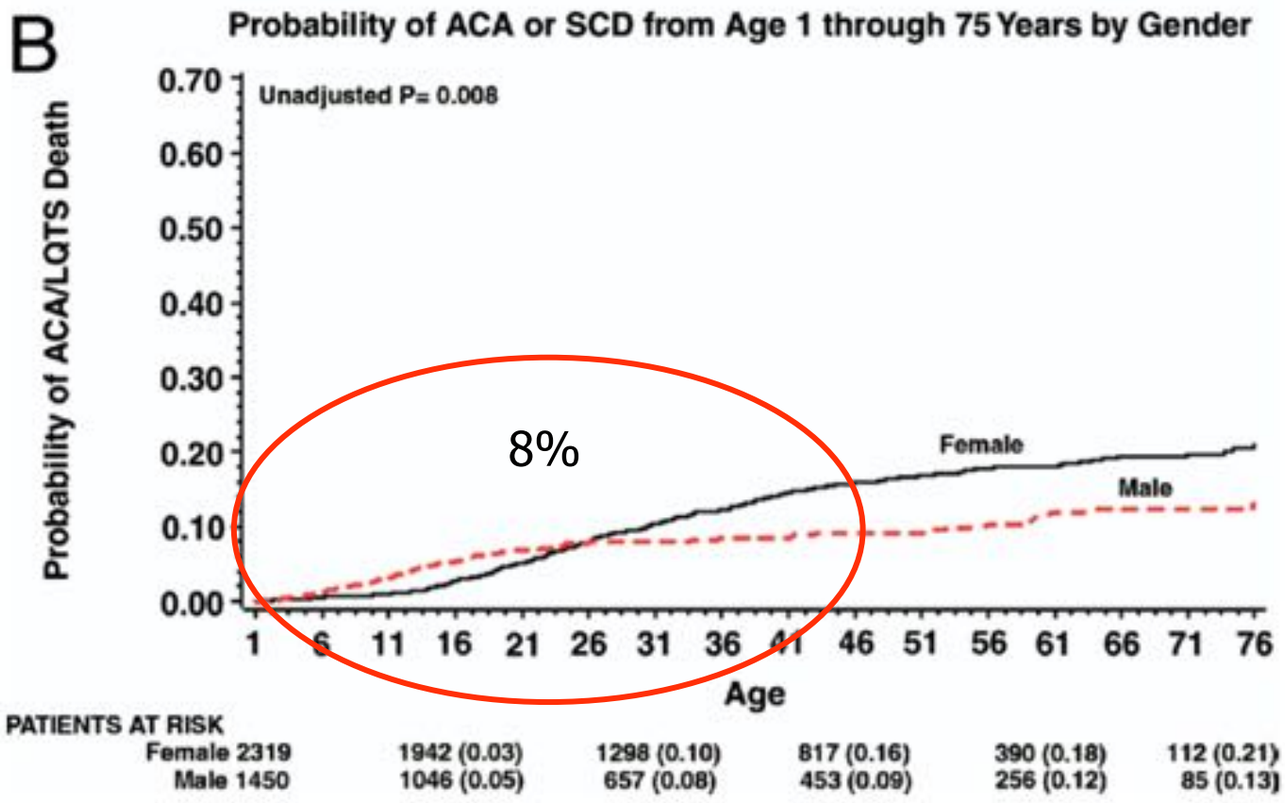
- ♥ Autosomal dominant/autosomal rec.
- ♥ genetically heterogeneous
- ♥ 16 genes ($LQTS_{1-16}$)
- ♥ ≥ 60% genotyped (≥ 90% in families)
- ♥ gene-specific features

Risk of syncope/ACA/SCD in LQTS population:

(age 1 through 75 yrs)

Moss and Goldenberg JACC 2008





Before puberty LQT1 (males), after puberty LQT2 (females)?

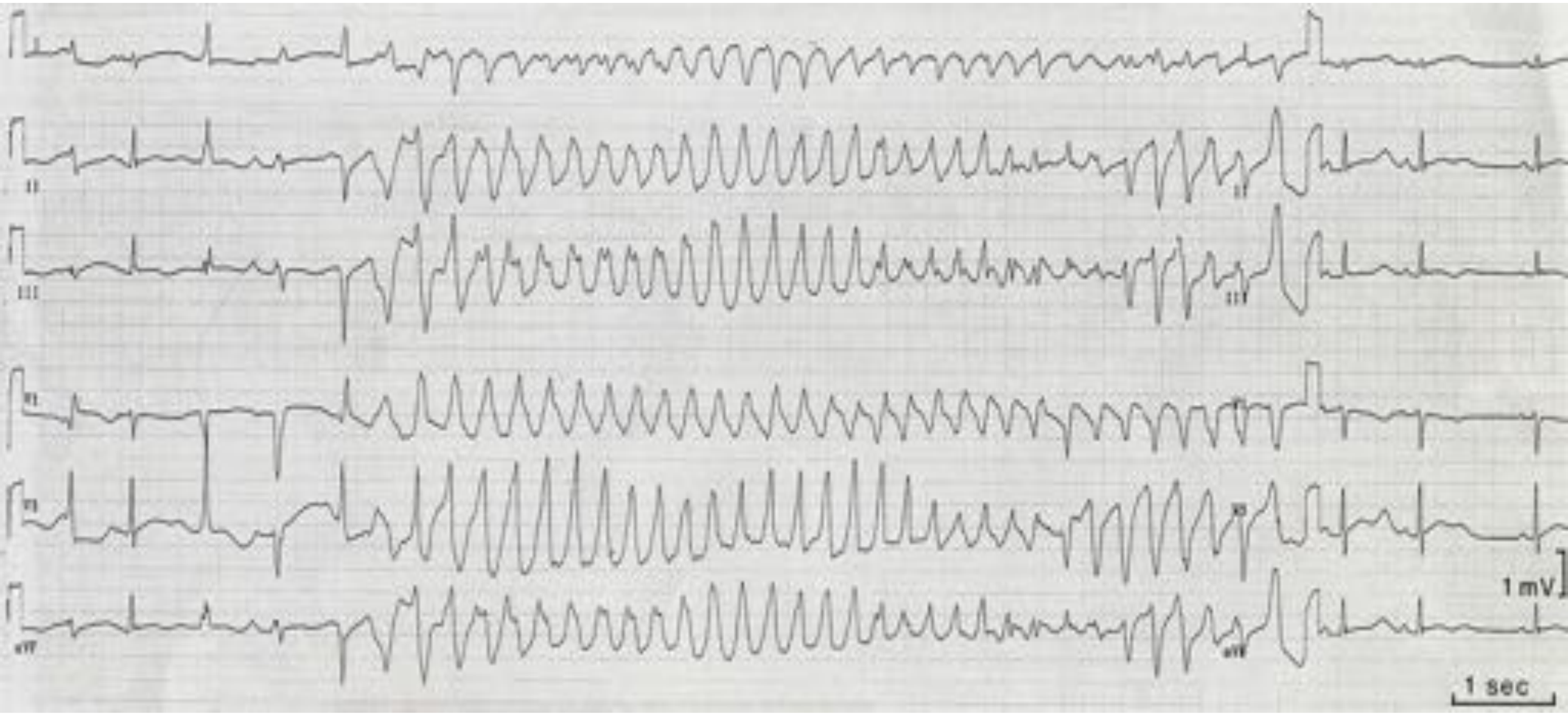
Long QT syndrome, risk stratification

Established risk factors

- ♥ Aborted sudden death
- ♥ Syncope
- ♥ congenital deafness (JLN)
- ♥ Torsades de Pointes, T-wave alternans
- ♥ Prolonged QT (> 500ms)
- ♥ Family history of (a)SCD not

Congenital LQTS

Symptomatology



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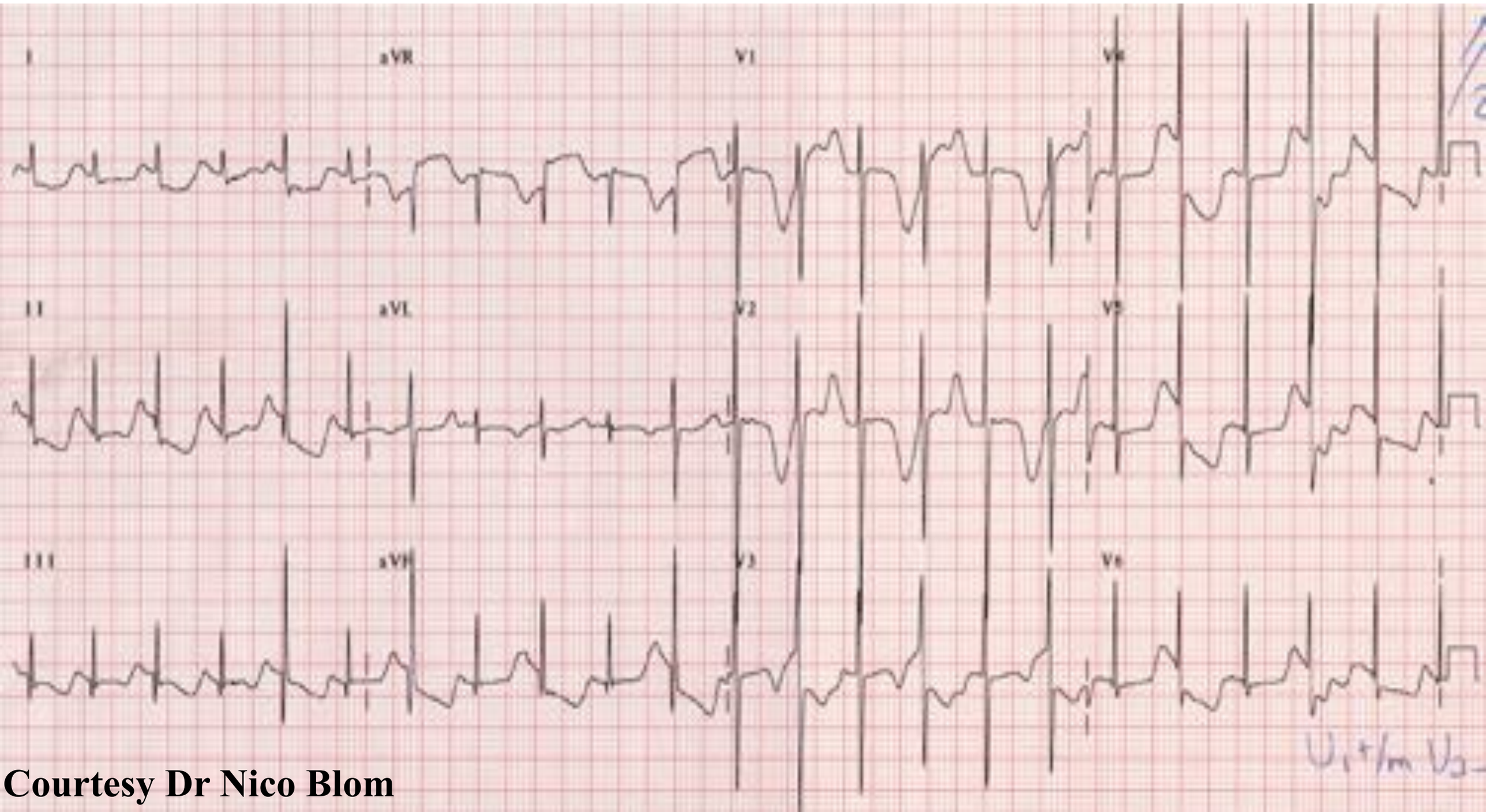
Long QT syndrome, risk stratification

Established risk factors, Asymptomatic pts

- ♥ Aborted sudden death
- ♥ Syncope
- ♥ congenital deafness (JLN)
- ♥ Torsades de Pointes, T-wave alternans
- ♥ Prolonged QT (> 500ms)
- ♥ Family history of (a)SCD not

A patient at risk

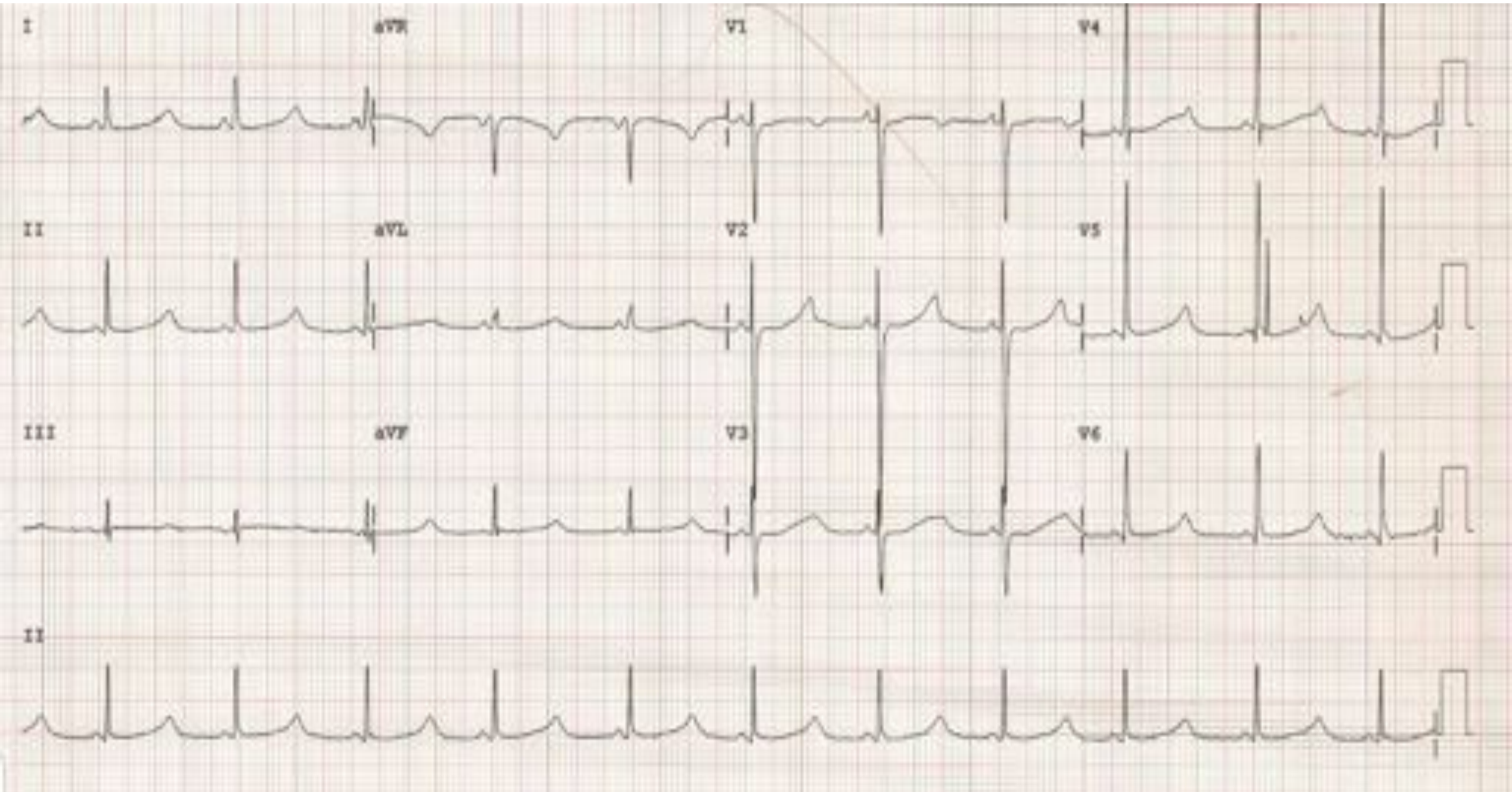
Neonate, prenatal bradycardia, hydrops, syndactyly.



Courtesy Dr Nico Blom

Jervell Lange-Nielsen Syndrome

Female 6y old, syncopal attacks, sensorinal bilateral deafness



Long QT syndrome, risk stratification

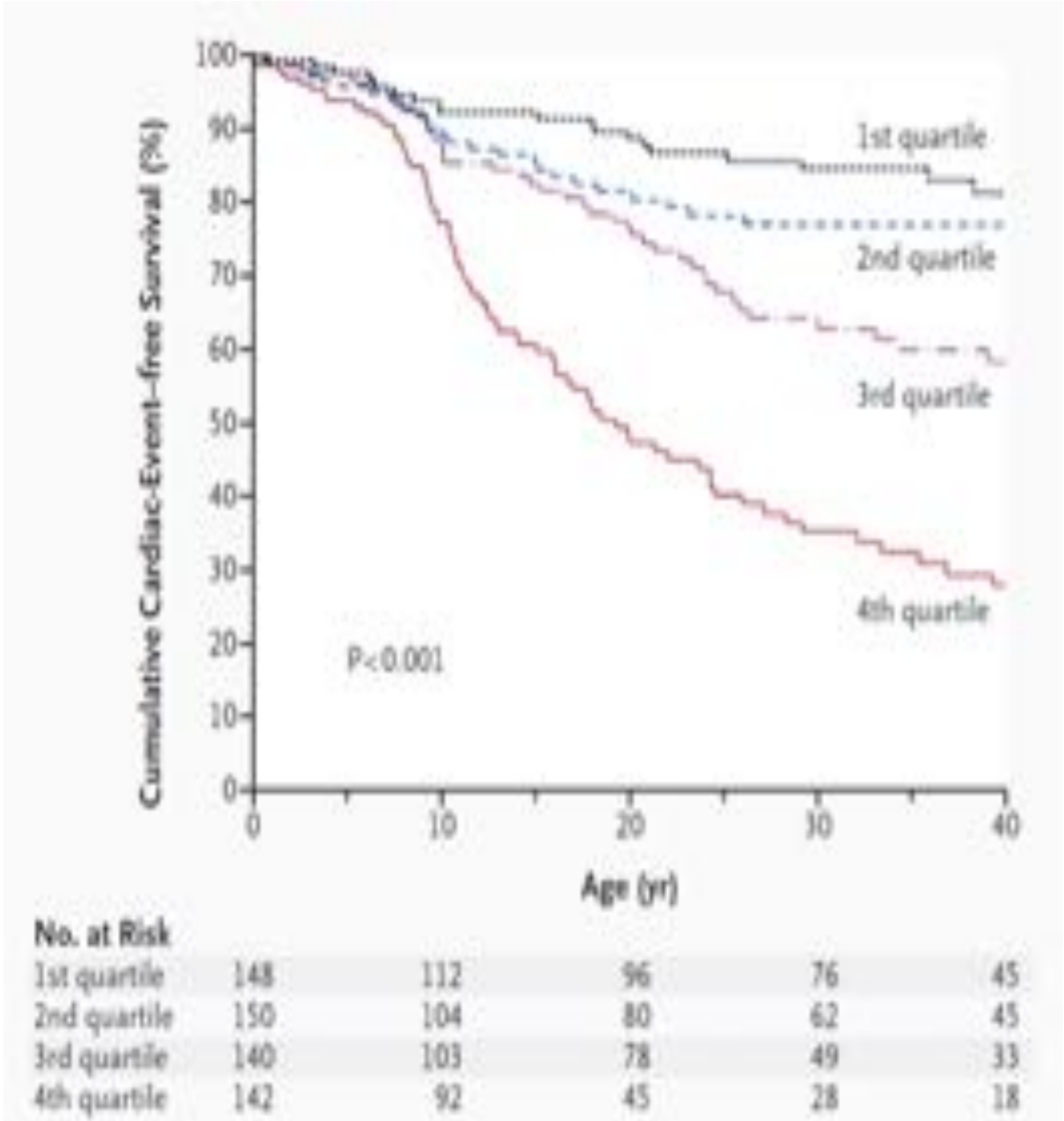
QT_C Quartiles:

1: ≤ 446 ms

2: 447 - 468 ms

3: 469 - 498 ms

4: ≥ 499 ms



NEJM 2003;348:1866-74

Long QT syndrome, role of genetics

Genetic ‘real estate’:

- Transmembrane LQTS2 mutations
- Missense LQTS1 mutations
- Specific LQTS1 mutations (e.g. A341V)
- Large variation in LQT3

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Risk for Life-Threatening Cardiac Events in Patients With Genotype-Confirmed Long-QT Syndrome and Normal-Range Corrected QT Intervals

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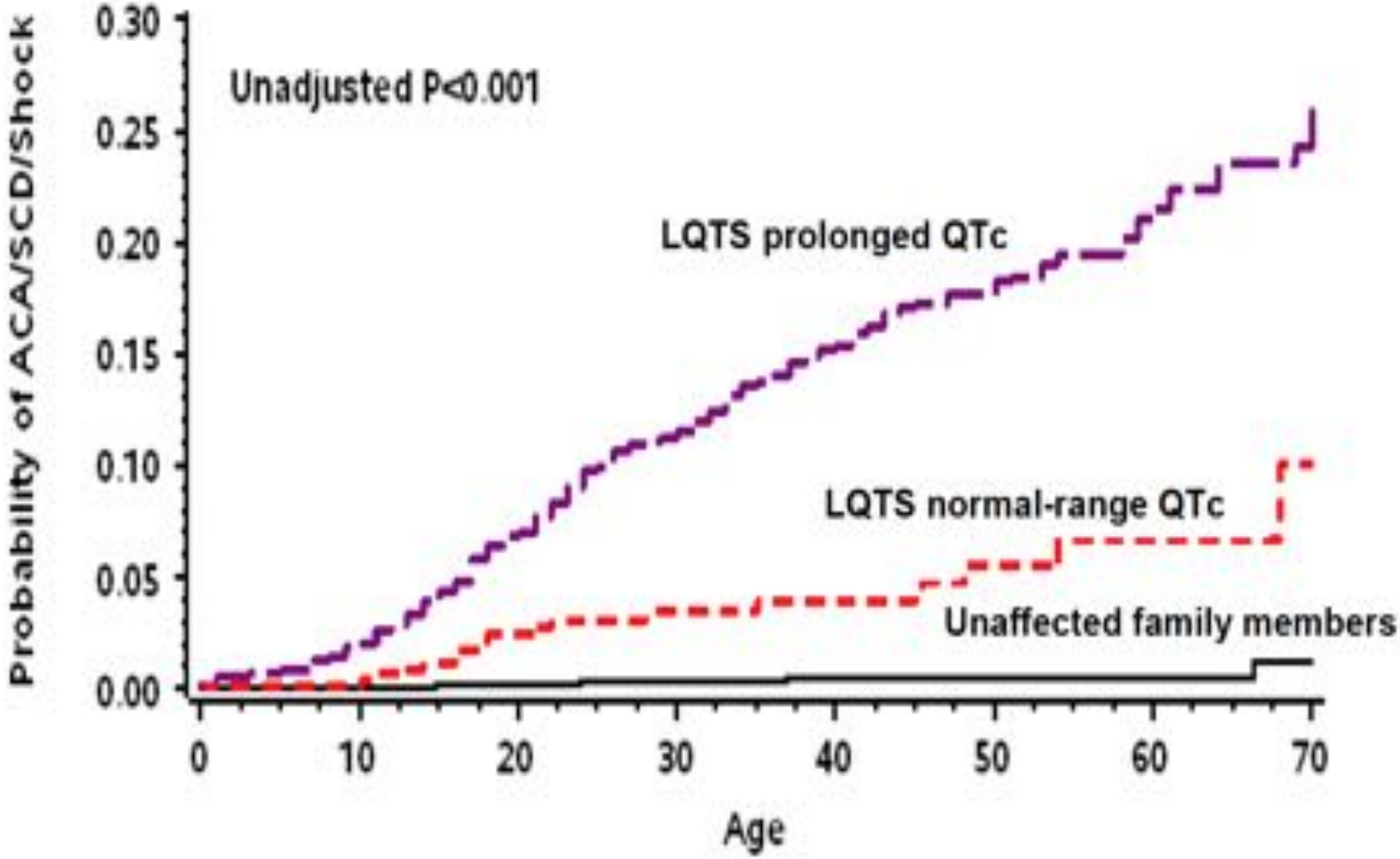
Rochester and New York, New York; Milan and Pavia, Italy; Tel Aviv, Israel; Rochester, Minnesota; Cleveland, Ohio; Lund, Sweden; Suita, Japan; Houston, Texas; Amsterdam, the Netherlands; and Salt Lake City, Utah

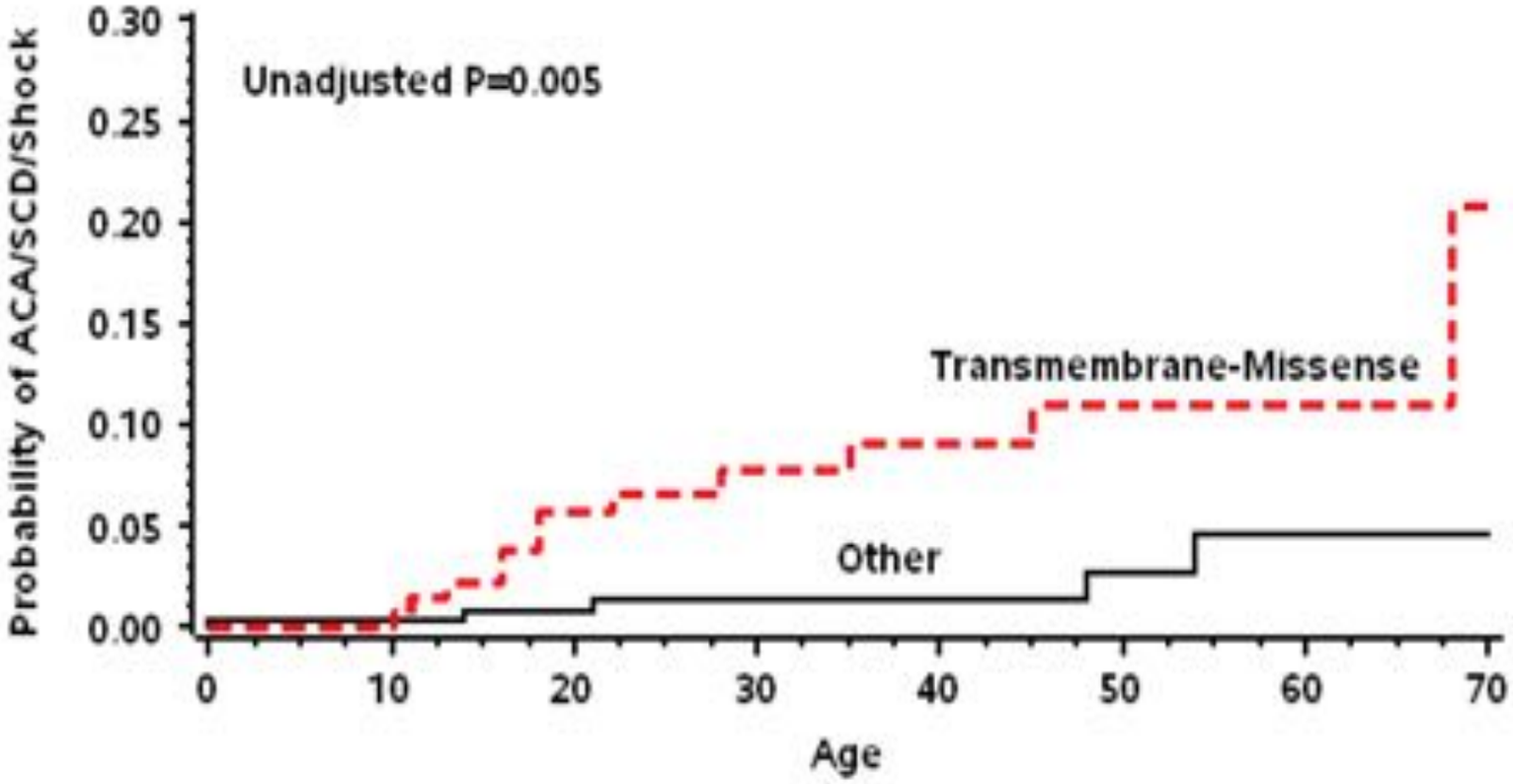
Table 1. Baseline and follow-up characteristics of the study population by genotype-phenotype

LQTS1&2

Characteristics	Unaffected Family Members (n=1525)	LQTS with Normal-Range QTc (n=469)	LQTS with Prolonged QTc (n=1392)
Female	52%	48%	61%*†
Family history of SCD	8%	12%	19%*†
QTc (msec)			
Mean ± SD	412 ± 22	419 ±20	501 ± 48
Median (IQ range)	420 (400-430)	420 (410-440)	490 (470-520)
Proband	8%	8%	29%*†
RR (msec)			
Mean ±SD	793 ±221	888 ±236	848 ±214 *†
Median (IQ range)	800 (640-930)	900 (740-1040)	840 (700-1000) *†
Genotype			
LQT1	NA	40%	39%
LQT2	NA	45%	47%
LQT3	NA	16%	14%
Mutation: TM-MS			
Overall	NA	35%	43%
LQT1	NA	45%	61%
LQT2	NA	16%	29%†
LQT3	NA	64%	31%†
Therapies			
beta-blockers	6.2%	38%	54%*†
Pacemaker	0.3%	0.6%	5%*†
LCSD	0.1%	0.2%	1.4%*†
ICD	0.6%	6%	14 %*†

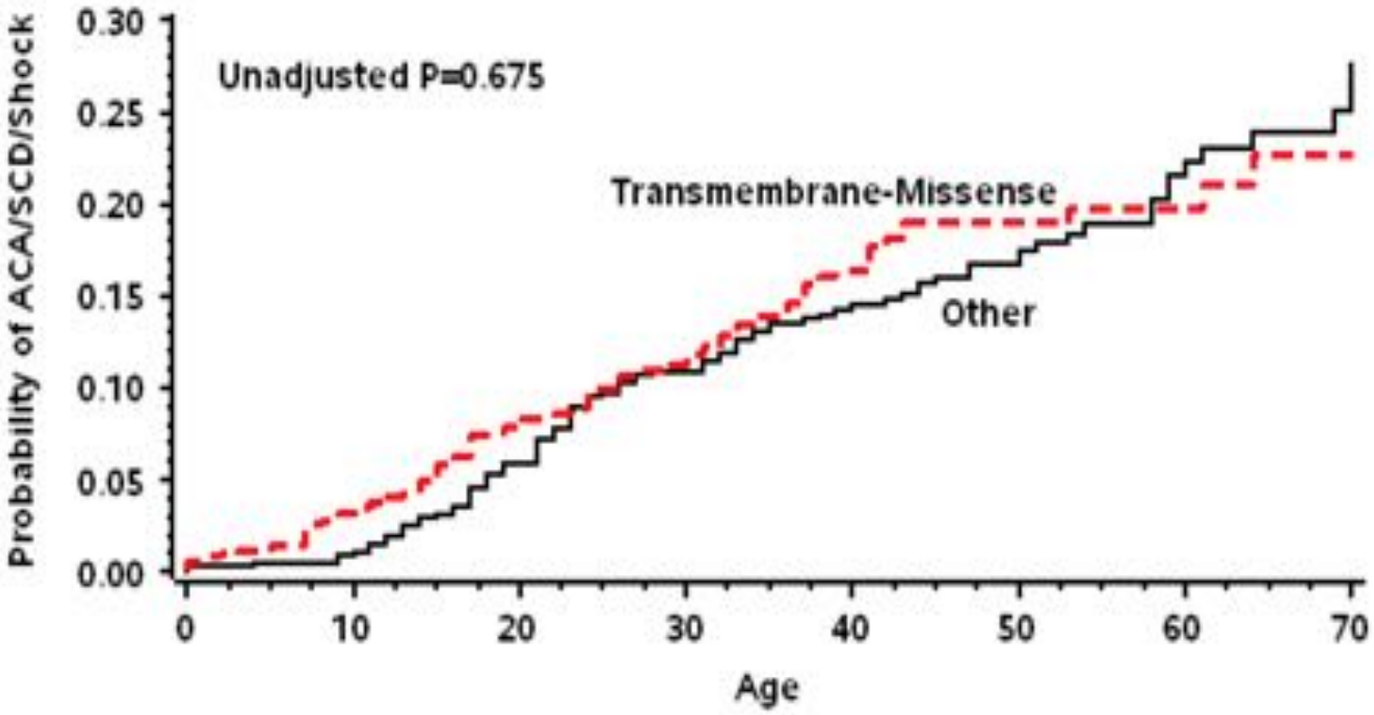


Patients at Risk				
Gen-/Phen- 1525	1377 (0)	728 (0)	348 (0)	92 (0.01)
Gen+/Phen- 469	406 (0)	236 (0.04)	97 (0.06)	20 (0.10)
Gen+/Phen+ 1392	1235 (0.02)	729 (0.11)	334 (0.18)	94 (0.24)



QTc ≤ 440ms

Patients at Risk				
Other 297	258 (0)	153 (0.01)	60 (0.03)	15 (0.05)
TMM 163	141 (0)	78 (0.08)	35 (0.11)	5 (0.21)



QTc > 441ms

Patients at Risk				
Other 794	713 (0.01)	430 (0.11)	208 (0.17)	60 (0.25)
TMM 586	511 (0.03)	294 (0.11)	123 (0.19)	34 (0.23)

Class	ICD Recommendations
Class I	ICD implantation **is recommended** for patients with a diagnosis of LQTS who are survivors of a cardiac arrest
Class IIa	IICD implantation **can be useful** in patients with a diagnosis of LQTS who experience recurrent syncopal events while on beta-blocker therapy.
Class III	Except under special circumstances, ICD implantation **is <u>not</u> indicated** in asymptomatic LQTS patients who have not been tried on beta-blocker therapy

Family history is NOT a risk factor

Long QT syndrome, asymptomatic pt

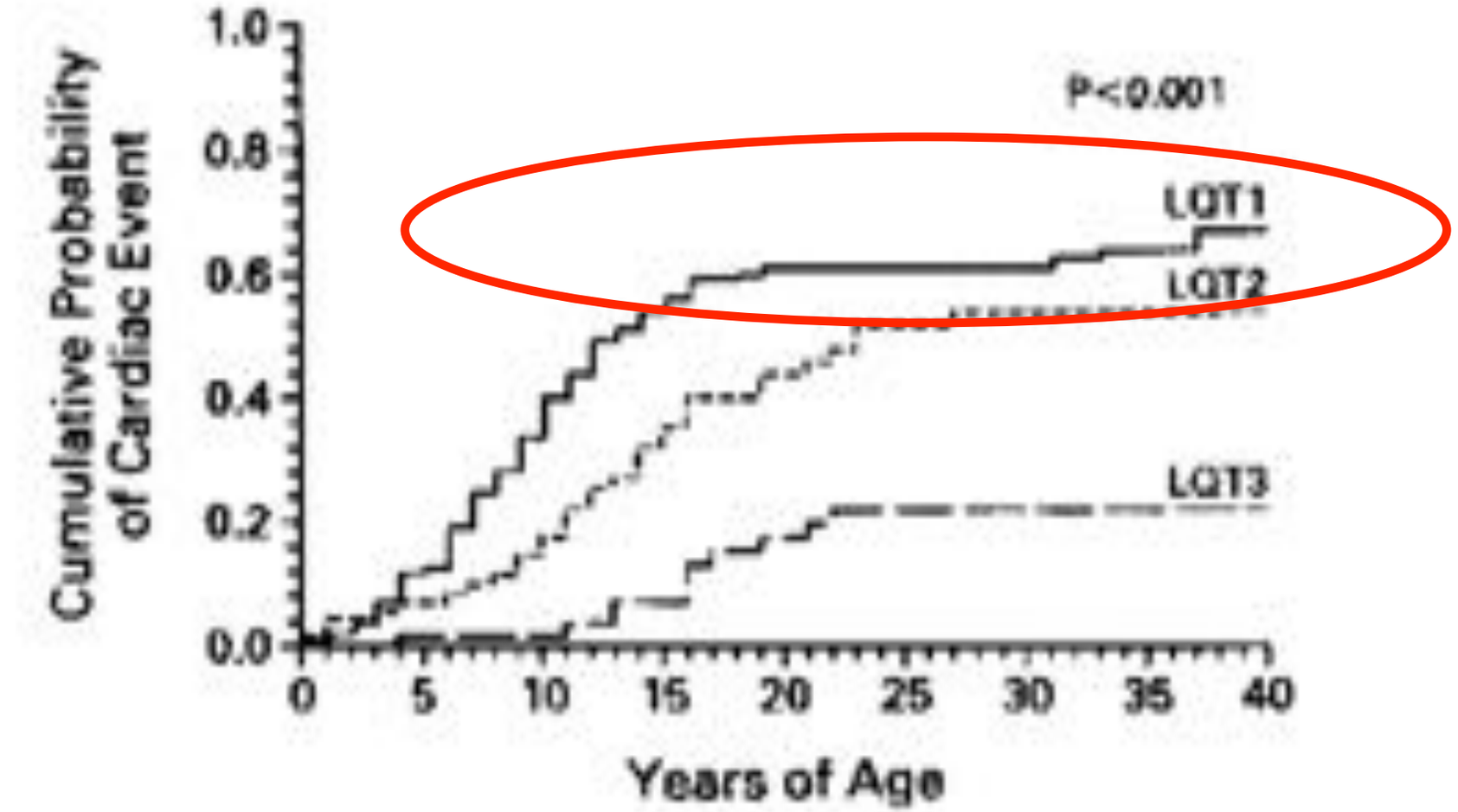
When should an ICD be considered?

- ♥ JLNS patient with a long QTc (>500msec)
- ♥ LQT2 pt with QTc > 550
- ♥ LQT3 pt with QTc > 500
- ♥ Torsades de Pointes, T-wave alternans
- ♥ rarely LQT1!
- ♥ Family history of (a)SCD is not a riskfactor

Class	Beta-blocker Recommendations
Class I	Beta-blockers **are recommended** for patients with a diagnosis of LQTS who are: • Asymptomatic with QTc ≥ 470 ms, *and/or* • Symptomatic for syncope or documented VT/VF .
Class IIa	Beta-blockers **can be useful** in patients with a diagnosis of LQTS who are asymptomatic with QTc ≤ 470ms

But in who treatment is not needed?

Long QT syndrome, focus on LQT1

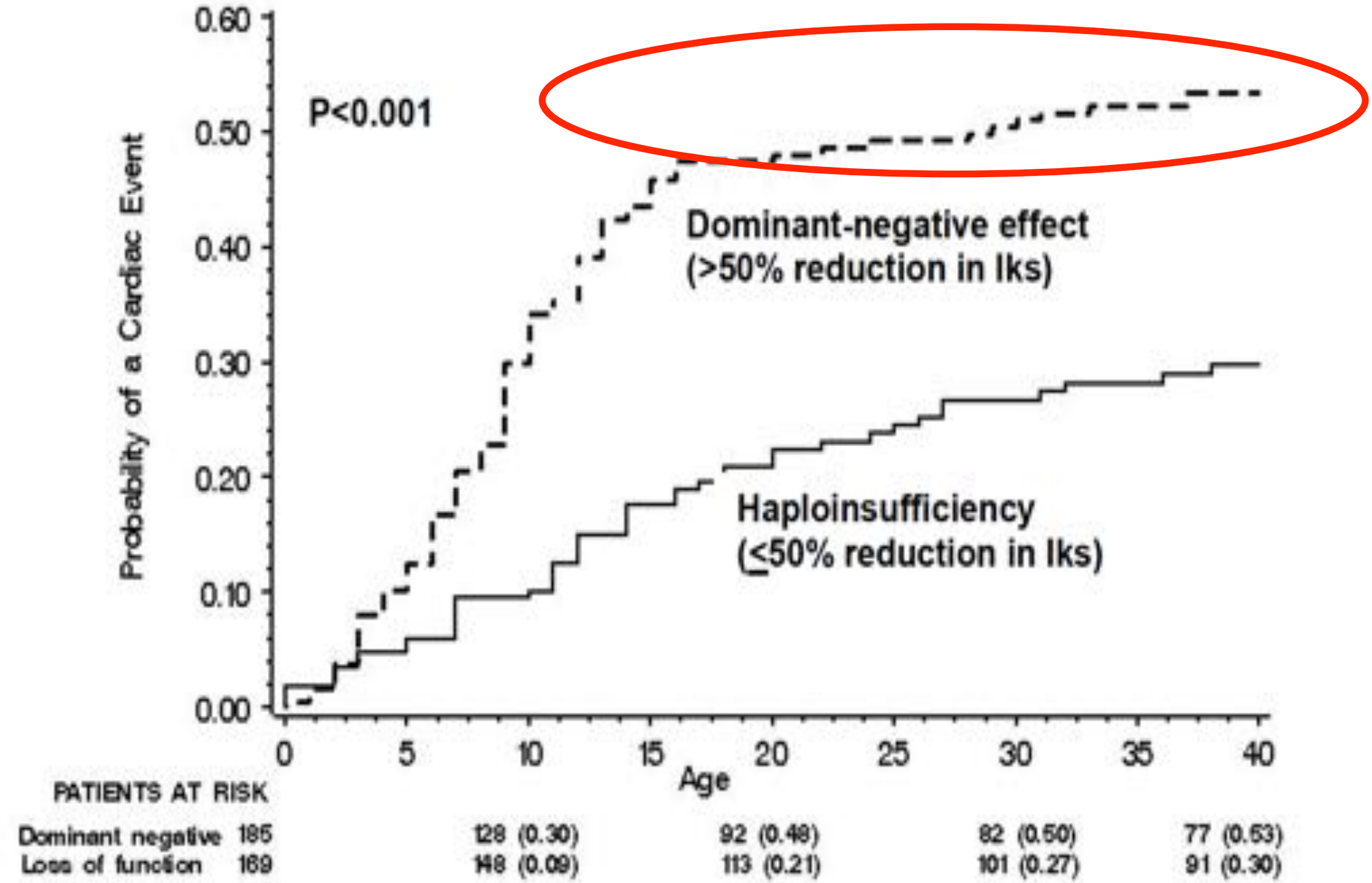


No. of Subjects					
LQT1 group	112	72	36	27	19
LQT2 group	72	56	29	16	11
LQT3 group	62	56	38	24	16

The LQT registry

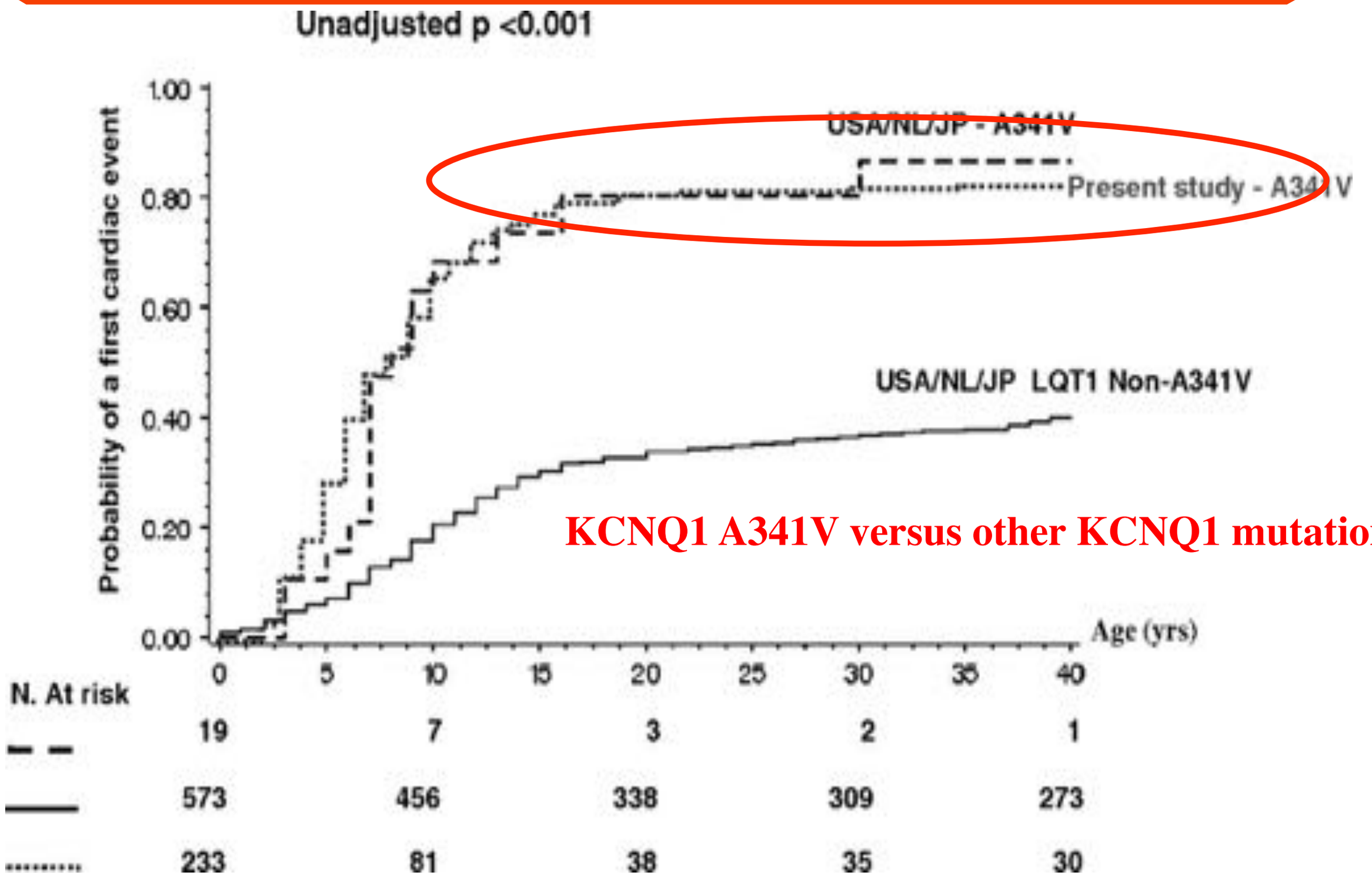
Zareba et al. NEJM 1998; 339: 960-5.

Long QT syndrome, focus on LQT1



Moss, Shimizu, Wilde et al. Circulation 2007

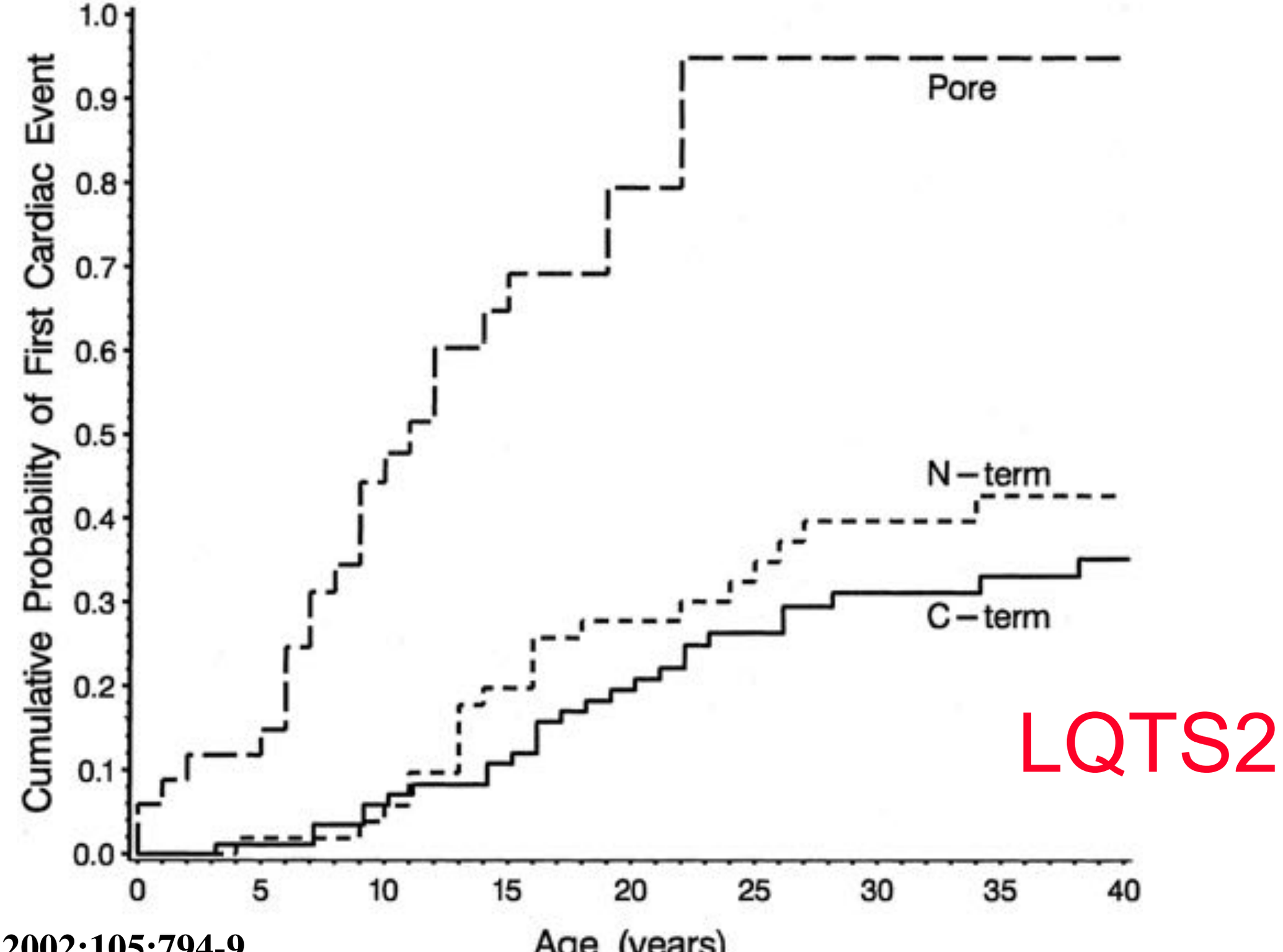
Long QT syndrome, focus on LQT1



KCNQ1 A341V versus other KCNQ1 mutations

Crotti et al, Circulation 2007

Mutation dependent prognosis (LQTS2)



Circulation 2002;105:794-9

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Low risk: asymptomatic LQT1 adult (QTc < 500?)

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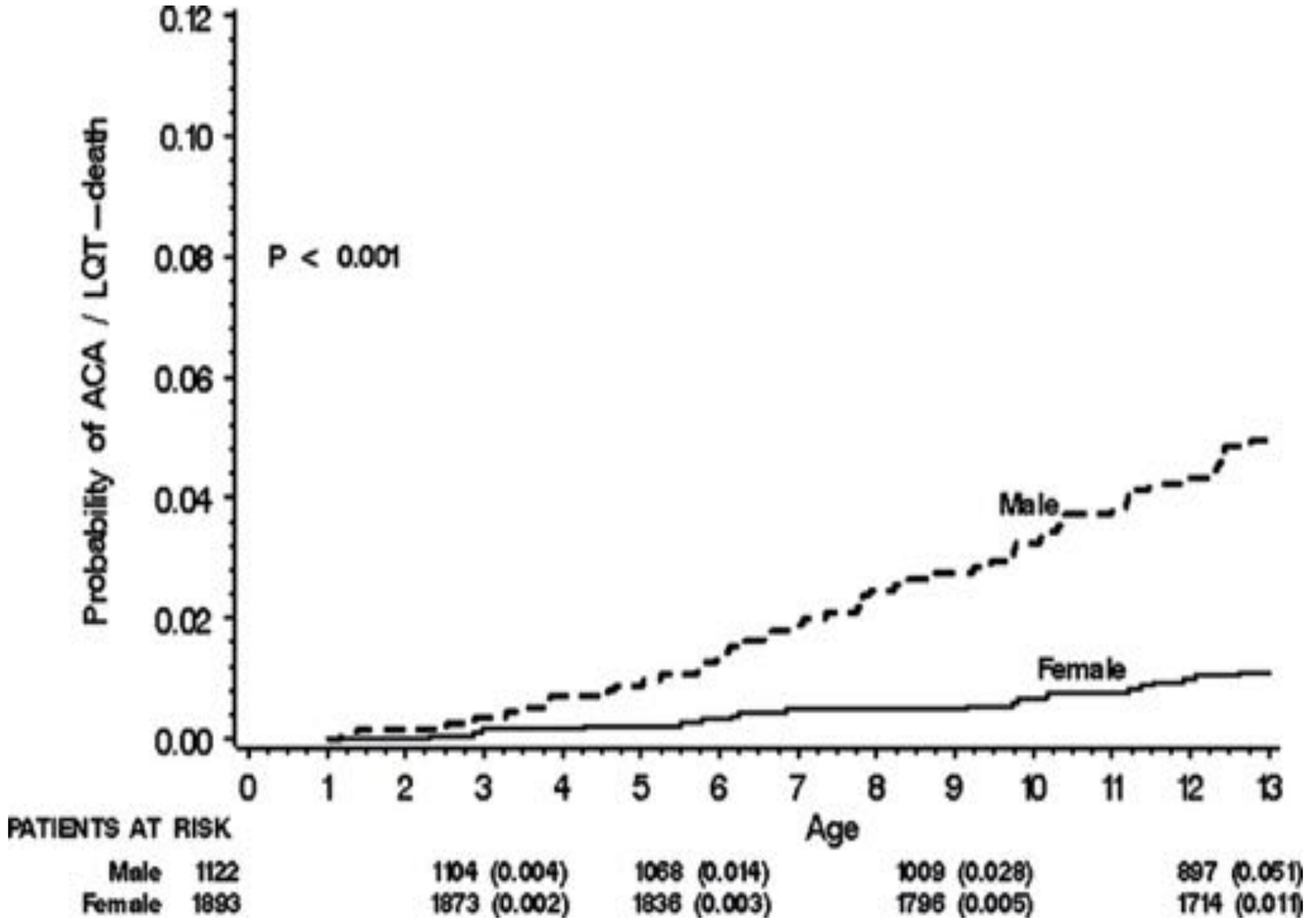
Low risk: asymptomatic LQT1 adult (QTc < 500?)

Risk Factors for Aborted Cardiac Arrest and Sudden Cardiac Death in Children With the Congenital Long-QT Syndrome

Ilan Goldenberg, MD; Arthur J. Moss, MD; Derick R. Peterson, PhD; Scott McNitt, MS; Wojciech Zareba, MD, PhD; Mark L. Andrews, BBA; Jennifer L. Robinson, MS; Emanuela H. Locati, MD; Michael J. Ackerman, MD, PhD; Jesaia Benhorin, MD; Elizabeth S. Kaufman, MD; Carlo Napolitano, MD; Silvia G. Priori, MD, PhD; Ming Qi, MD; Peter J. Schwartz, MD; Jeffrey A. Towbin, MD; G. Michael Vincent, MD; Li Zhang, MD

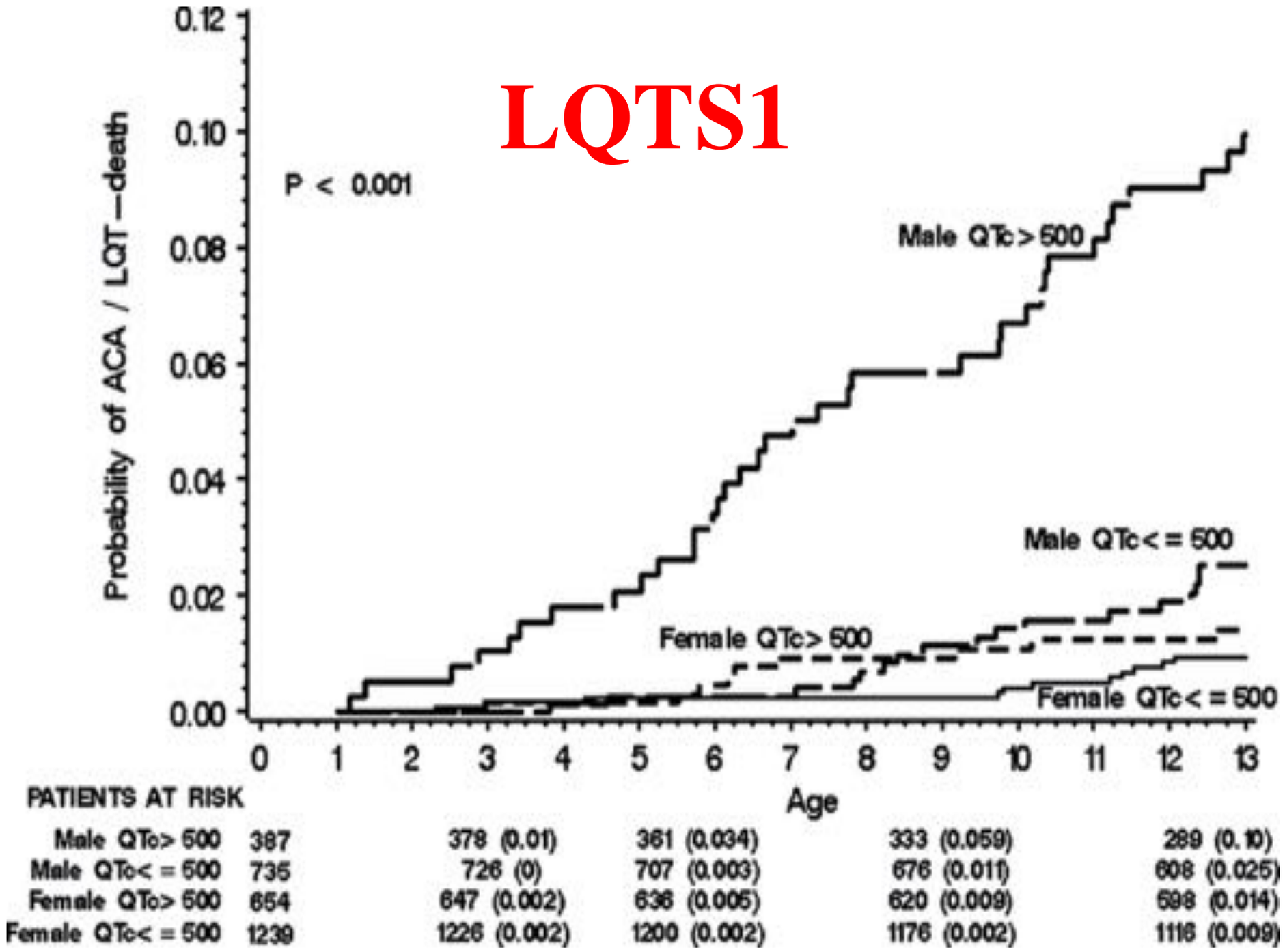
(Circulation 2008;117:2184-2191)

Figure 1. Kaplan–Meier estimates of the probability of ACA or SCD by gender (values in parentheses are event rates).



Goldenberg I et al. Circulation 2008;117:2184-2191

Figure 2. Kaplan–Meier estimates of the probability of ACA or SCD by gender and QTc subgroups (values in parentheses are event rates).



Goldenberg I et al. Circulation 2008;117:2184-2191

Beta-Blocker Efficacy in High-Risk Patients With the Congenital Long-QT Syndrome Types 1 and 2: Implications for Patient Management

ILAN GOLDENBERG, M.D., JAMES BRADLEY, M.D., M.P.H., ARTHUR MOSS, M.D., SCOTT McNITT, M.S., SLAVA POLONSKY, M.S., JENNIFER L. ROBINSON, M.S., MARK ANDREWS, B.B.A., WOJCIECH ZAREBA, M.D., PH.D., on behalf of the International LQTS Registry Investigators*

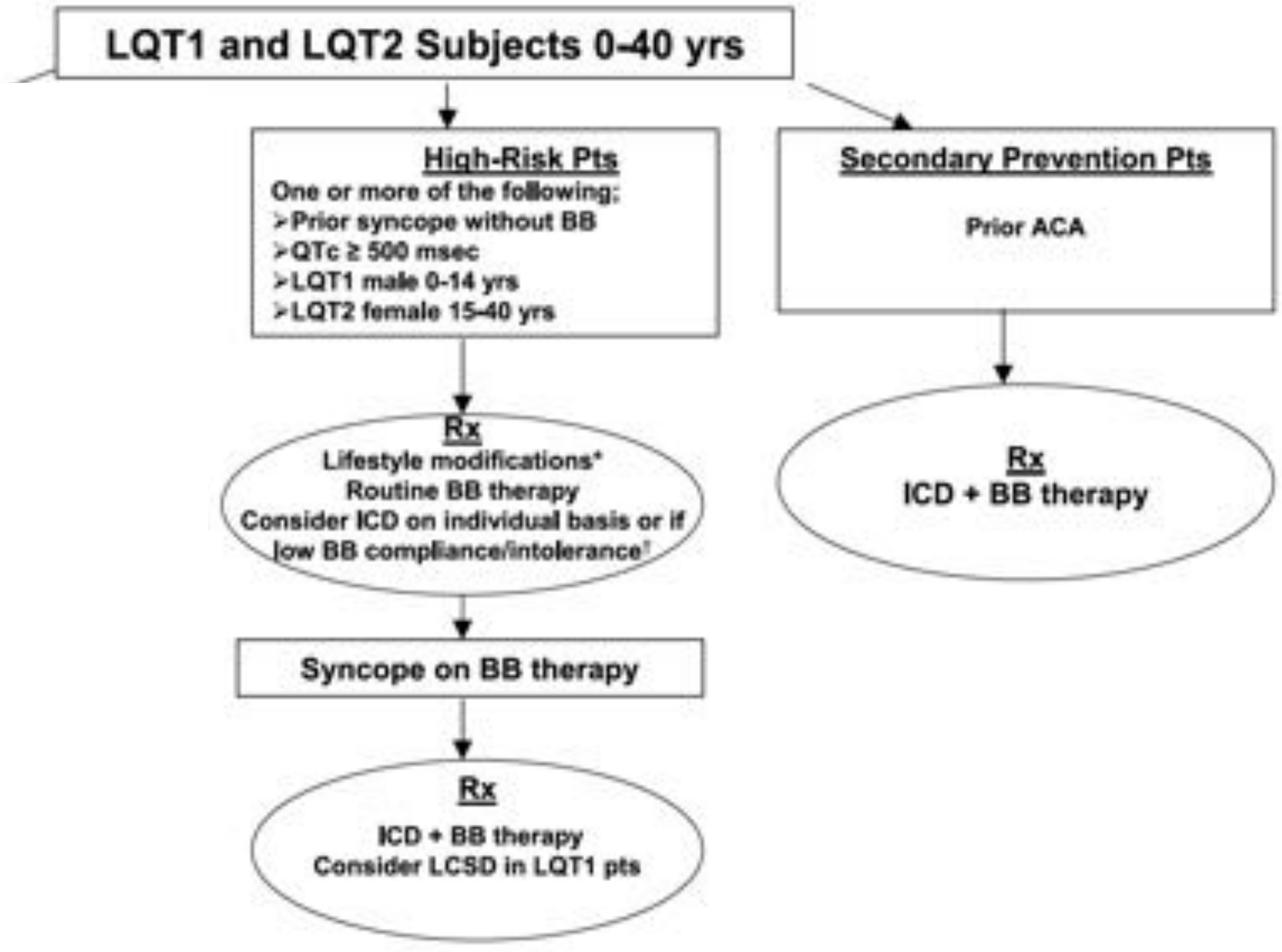
From the Cardiology Division, Department of Medicine, University of Rochester Medical Center, Rochester, New York, USA

β-Blockers for LQTS Types 1 and 2. *Background:* **Beta-blockers are the mainstay therapy in patients with the congenital long-QT syndrome (LQTS) types 1 and 2. However, limited data exist regarding the efficacy and limitations of this form of medical management within high-risk subsets of these populations.**

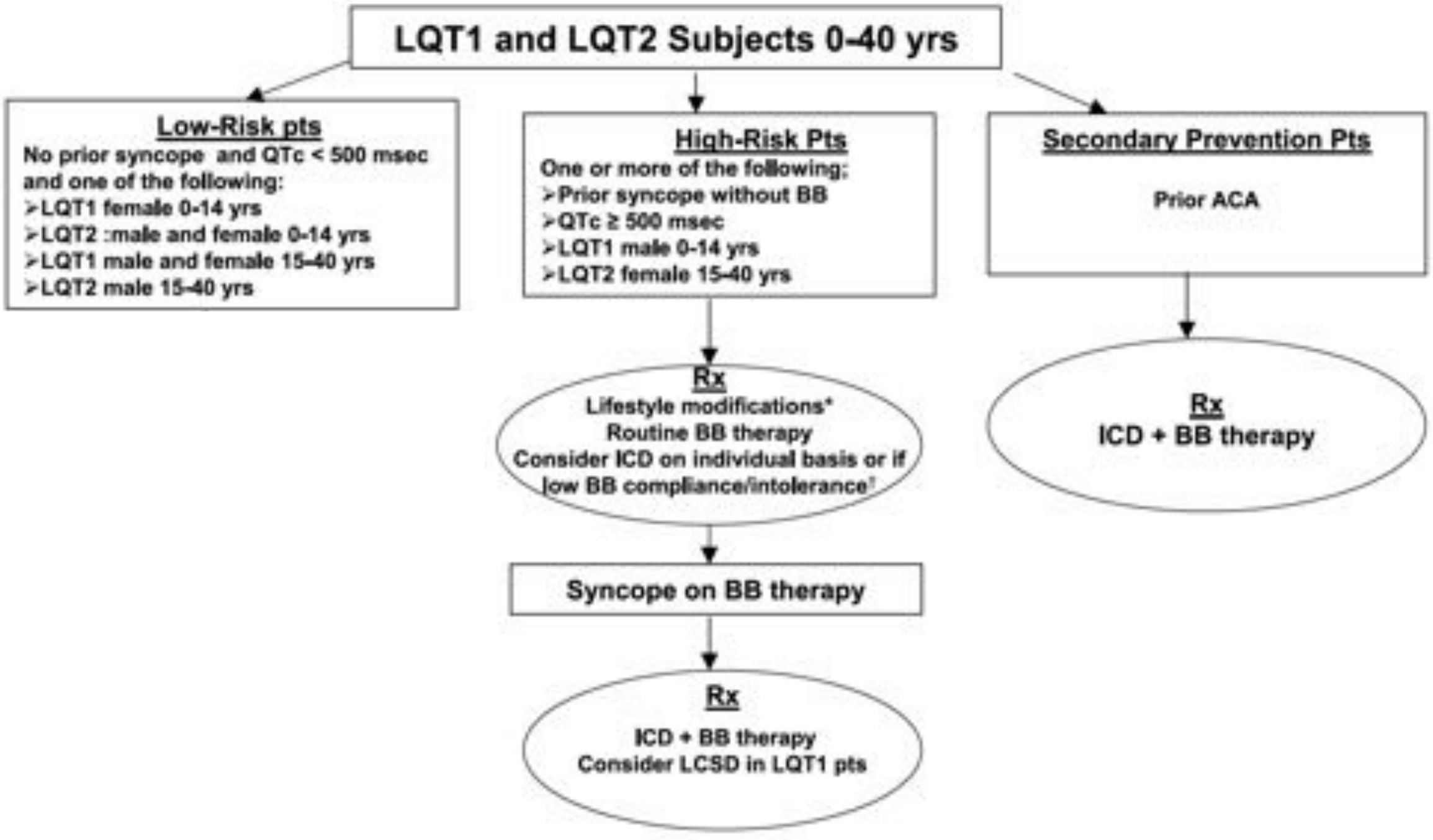
Methods and Results: **Multivariate analysis was carried out to identify age-related gender- and genotype-specific risk factors for cardiac events (comprising syncope, aborted cardiac arrest [ACA] or sudden cardiac death [SCD]) from birth through age 40 years among 971 LQT1 (n = 549) and LQT2 (n = 422) patients from the International LQTS Registry. Risk factors for cardiac events included the LQT1 genotype (HR = 1.49, P = 0.003) and male gender (HR = 1.31, P = 0.04) in the 0–14 years age group; and the LQT2 genotype (HR = 1.67, P < 0.001) and female gender (HR = 2.58, P < 0.001) in the 15–40 years age group. Gender–genotype subset analysis showed enhanced risk among LQT1 males (HR = 1.93, P < 0.001) and LQT2 females (HR = 3.28, P < 0.001) in the 2 respective age groups. Beta-blocker therapy was associated with a significant risk-reduction in high-risk patients, including a 67% reduction (P = 0.02) in LQT1 males and a 71% reduction (P < 0.001) in LQT2 females. Life-threatening events (ACA/SCD) rarely occurred as a presenting symptom among beta-blocker-treated patients. However, high-risk patients who experienced syncope during beta-blocker therapy had a relatively high rate of subsequent ACA/SCD (>1 event per 100 patient-years).**

Conclusions: **The present findings suggest that beta-blocker therapy should be routinely administered to all high-risk LQT1 and LQT2 patients without contraindications as a first line measure, whereas primary defibrillator therapy should be recommended for those who experience syncope during medical therapy.**
(J Cardiovasc Electrophysiol, Vol. 21, pp. 893-901, August 2010)

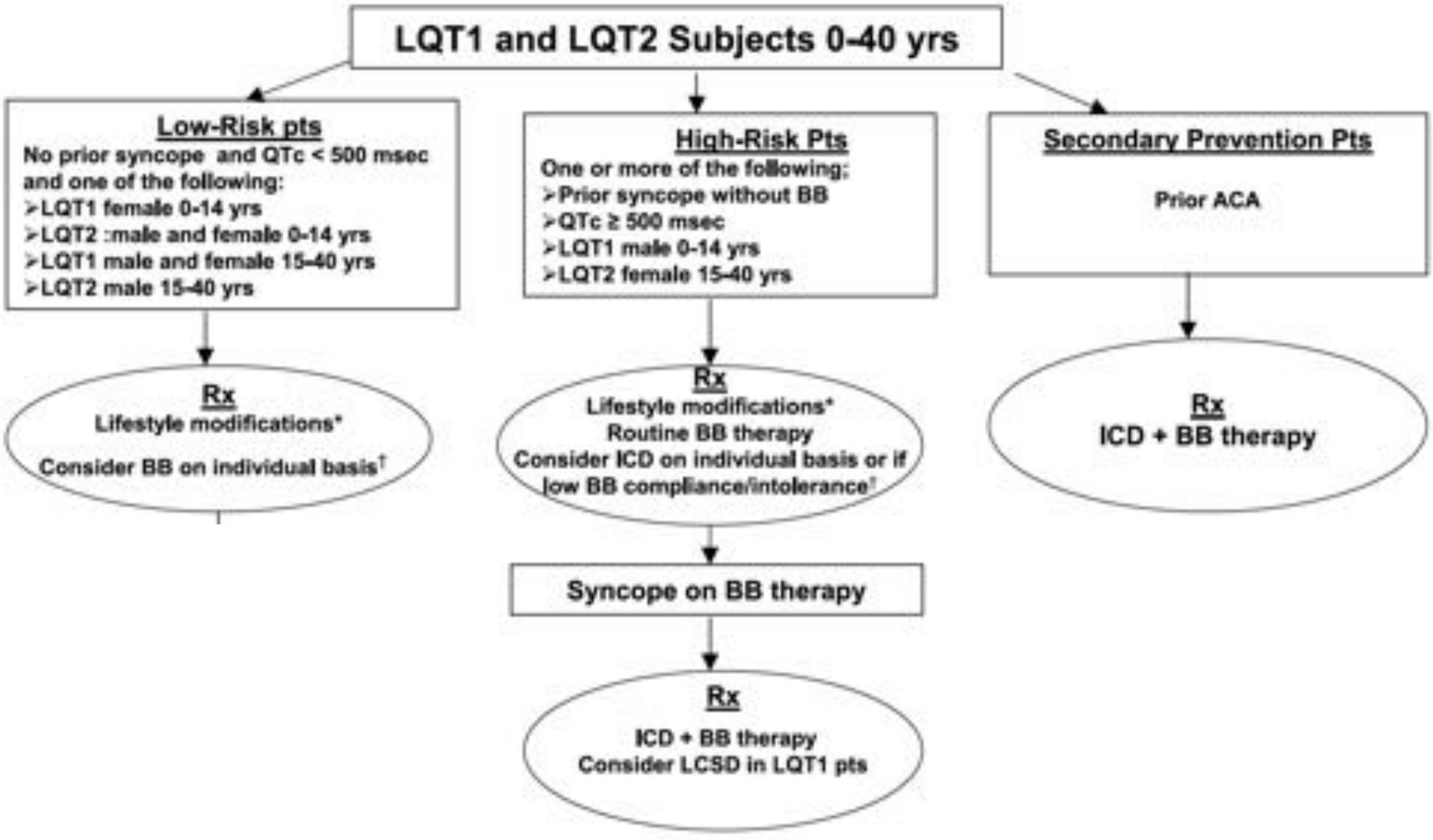
Proposed Management Strategy in LQT1 and LQT2 patients



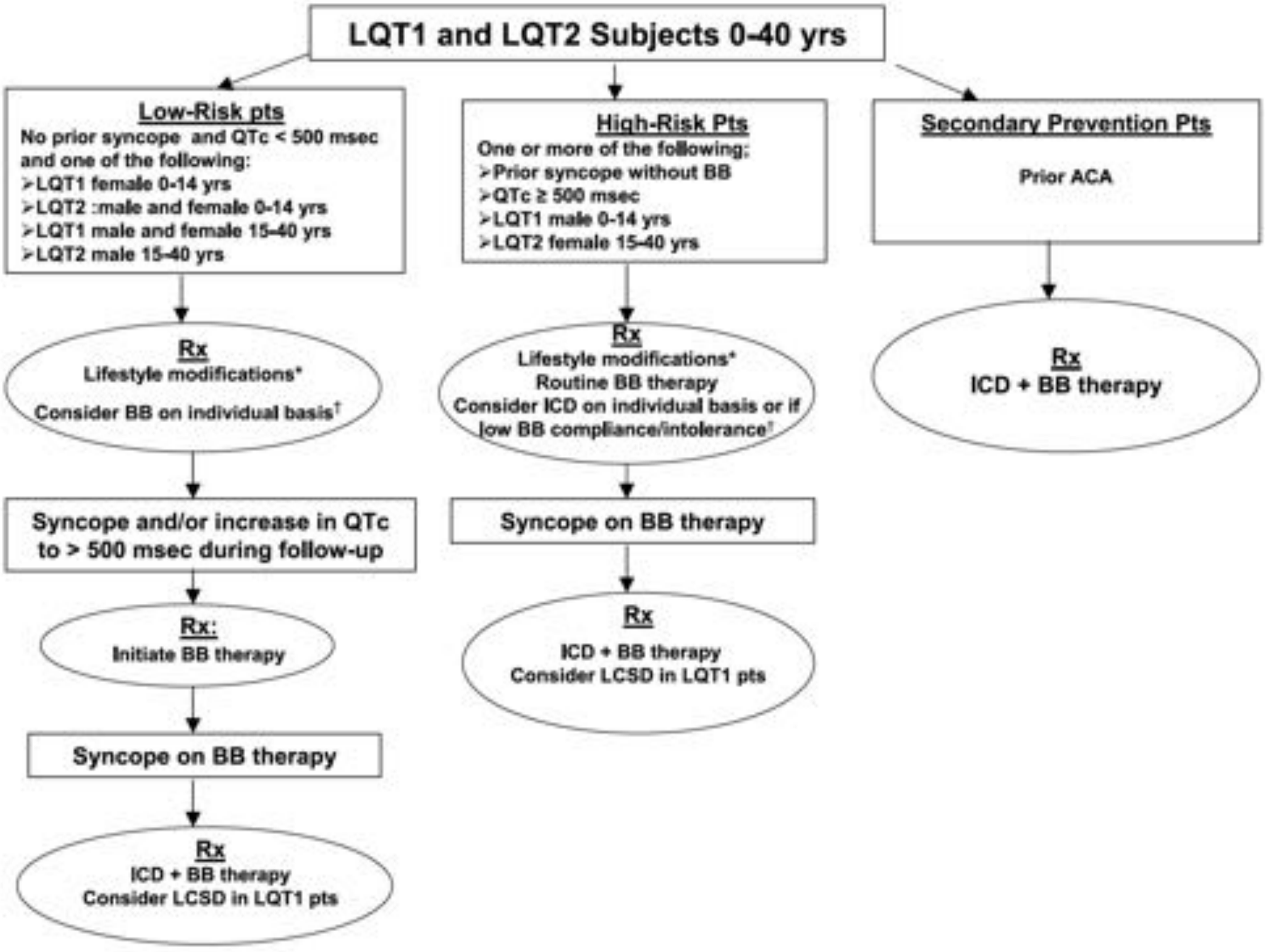
Proposed Management Strategy in LQT1 and LQT2 patients



Proposed Management Strategy in LQT1 and LQT2 patients



Proposed Management Strategy in LQT1 and LQT2 patients



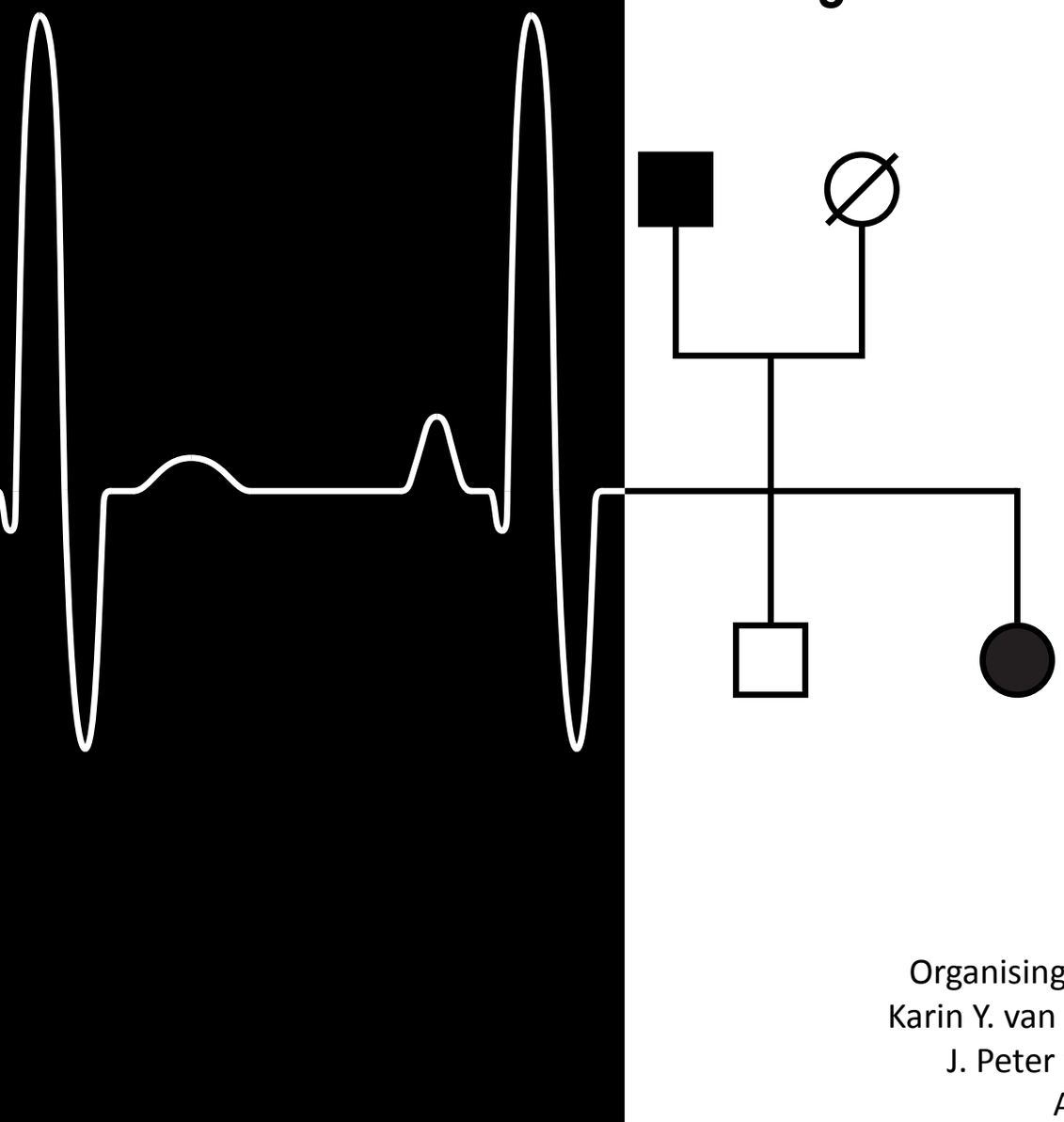
20 years

cardiogenetics in the Netherlands

Amsterdam, the Netherlands

December 4th 2015

For information and registration see www.20yrsCG.nl

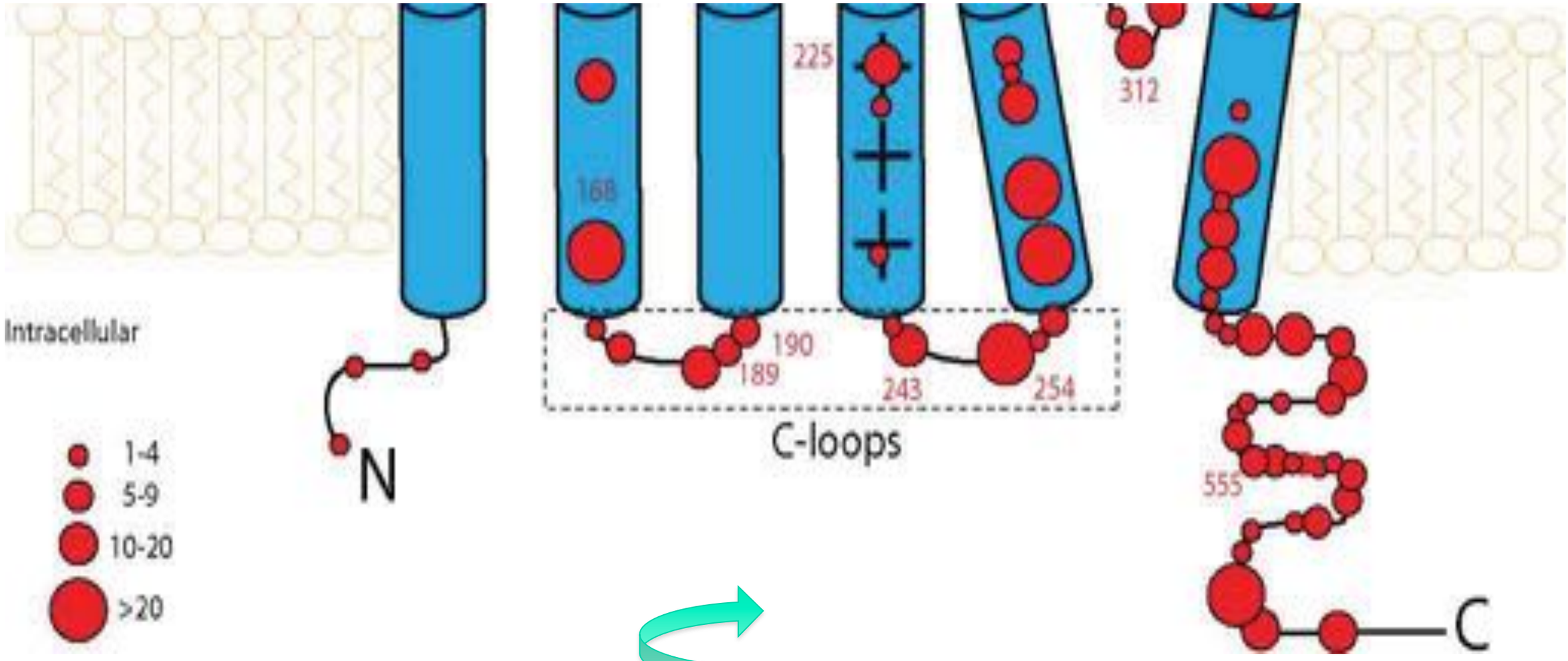


www.20yrsCG.nl

Organising committee:
Karin Y. van Spaendonck
J. Peter van Tintelen
Arthur Wilde

Thank you

Mutations sites in the KCNQ1 gene



Barsheshet ea, Circulation. 2012;125:1988-96.

ORIGINAL CONTRIBUTION

Risk of Aborted Cardiac Arrest or Sudden Cardiac Death During Adolescence in the Long-QT Syndrome

Jenny B. Hobbs, MD
Derick R. Peterson, PhD
Arthur J. Moss, MD
Scott McNitt, MS

Context Analysis of predictors of cardiac events in hereditary long-QT syndrome (LQTS) has primarily considered syncope as the predominant end point. Risk factors specific for aborted cardiac arrest and sudden cardiac death have not been investigated.

JAMA 2006;296:1249-1254

Risk during adolescence (10-20y)

- ♥ 2772 children followed between 10 and 20y
- ♥ 81 ACA and 45 SCD (4,5%)
- ♥ risk factors: syncope, QTc and gender (10-12)

JAMA 2006;296:1249-1254

Table 2. Time-Dependent Multivariable Cox Model: Risk of Aborted Cardiac Arrest or Sudden Cardiac Death (Ages 10-20 Years)

Factor	No. of Events	Hazard Ratio (95% Confidence Interval)	*P* Value
Recent syncope vs no syncope in past 10 y			
1 Syncopal event in past 2-10 y and no events within 2 y	9	2.7 (1.3-5.7)	<.01
≥2 Syncopal events in past 2-10 y and no events within 2 y	29	5.8 (3.6-9.4)	<.001
1 Syncopal event in past 2 y	26	11.7 (7.0-19.5)	<.001
≥2 Syncopal events in past 2 y	20	18.1 (10.4-31.2)	<.001
QTc ≥530 ms	51	2.3 (1.6-3.3)	<.001
Males aged 10-12 y vs age-matched females*	19	4.0 (1.8-9.2)	<.01
Time-dependent β-blocker therapy for those with recent syncope†	10	0.36 (0.2-0.7)	<.01

*Between the ages of 13 and 20 years, there was no significant difference in risk between the sexes.
†β-Blocker therapy was significant only among those who had experienced syncope in the past 2 years.

Does the genotype matter?