Long QT syndrome

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History

Jervell A & Lange-Nielsen F

" Congenital deaf-mutism, functional heart-disease with prolongation of the QT interval and sudden death "
Am Heart 1957

Romano C

" Aritmie cardiache rare dell'eta pediatrica »
Clin Pediatr 1963

Ward OC

" A new familial cardiac syndrome in children «
J Irish Med Assoc 1964

What about the definition ?

TABLE 1. 1985 LQTS Diagnostic Criteria

Major	Minor
Prolonged QT interval (QT_c >440 msec)	Congenital deafness
Stress-induced syncope	Episodes of T-wave alternans
Family members with LQTS	Low heart rate (in children)
	Abnormal ventricular repolarization

(Schwartz, Am Heart J 1985)

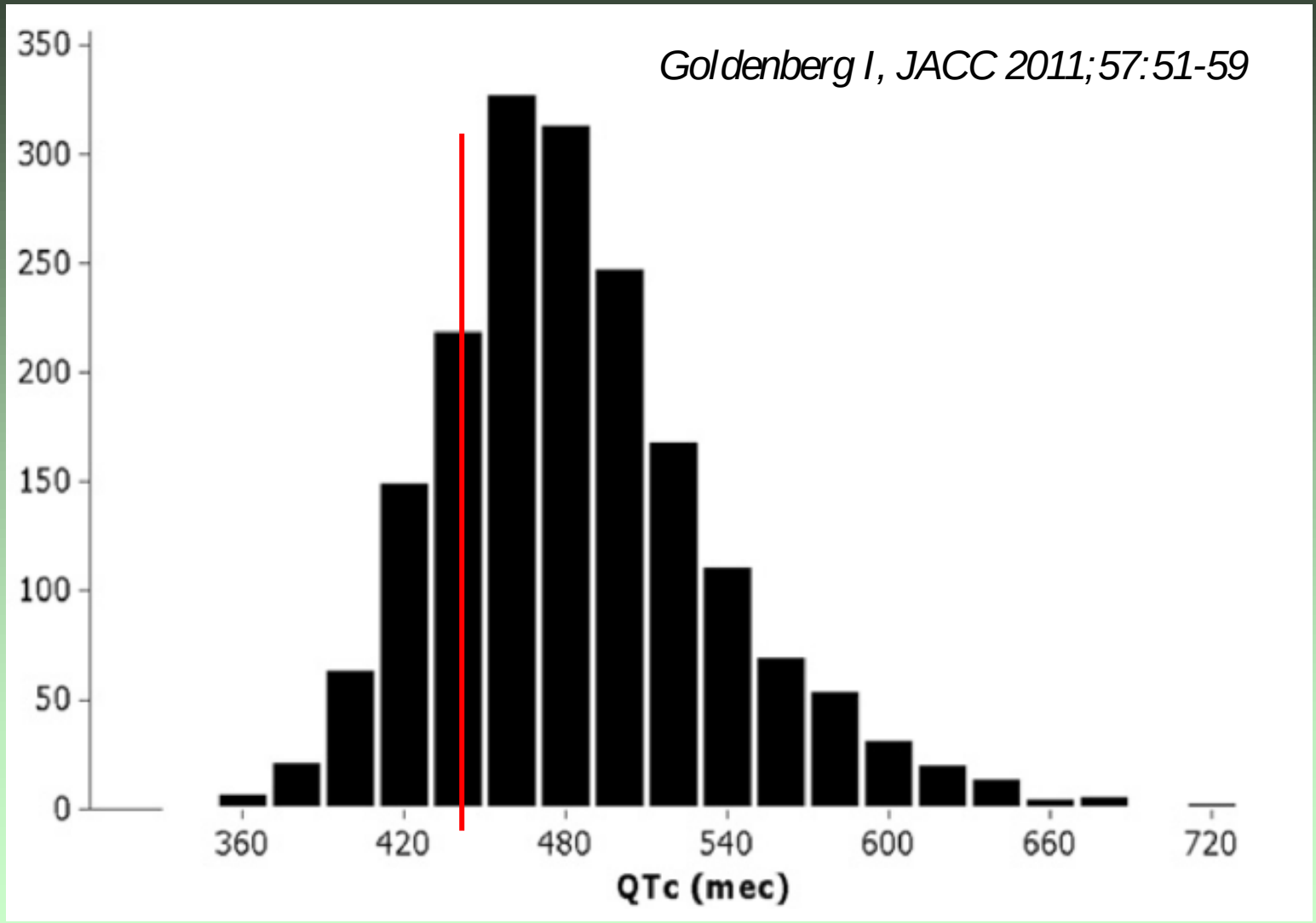
(Schwartz, Circulation 1993)

Good specificity
by poor sensitivity

TABLE 2. 1993 LQTS Diagnostic Criteria

		Points
ECG findings*		
A.	QT_c†	
	≥480 $msec^{1/2}$	3
	460-470 $msec^{1/2}$	2
	450 $msec^{1/2}$ (in males)	1
B.	Torsade de pointes‡	2
C.	T-Wave alternans	1
D.	Notched T wave in three leads	1
E.	Low heart rate for age§	0.5
Clinical history		
A.	Syncope‡	
	With stress	2
	Without stress	1
B.	Congenital deafness	0.5
Family history‖		
A.	Family members with definite LQTS#	1
B.	Unexplained sudden cardiac death below age 30 among immediate family members	0.5

What about the definition ?



25% of genotyped LQT have … normal QTc (same for LQT1, 2 or 3)

What about the definition ?

currently

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

1. LQTS is diagnosed:
   a. In the presence of an LQTS risk score ≥3.5 in the absence of a secondary cause for QT prolongation *and/or*
   b. In the presence of an unequivocally pathogenic mutation in one of the LQTS genes *or*
   c. In the presence of a QT interval corrected for heart rate using Bazett's formula (QTc) ≥500 ms in repeated 12-lead electrocardiogram (ECG) and in the absence of a secondary cause for QT prolongation.

2. LQTS can be diagnosed in the presence of a QTc between 480–499 ms in repeated 12-lead ECGs in a patient with unexplained syncope in the absence of a secondary cause for QT prolongation and in the absence of a pathogenic mutation.

What about the definition ?

currently

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

1. LQTS is diagnosed:
   a. In the presence of an LQT
      absence of a secondary ca
      and/or
   b. In the presence of an u
      mutation in one of the LQT
   c. In the presence of a QT inte
      using Bazett's formula (QTc)
      lead electrocardiogram (ECG
      secondary cause for QT prol

2. LQTS can be diagnosed in the
   480–499 ms in repeated 12-le
   unexplained syncope in the abs
   for QT prolongation and in the
   mutation.

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Some help ?

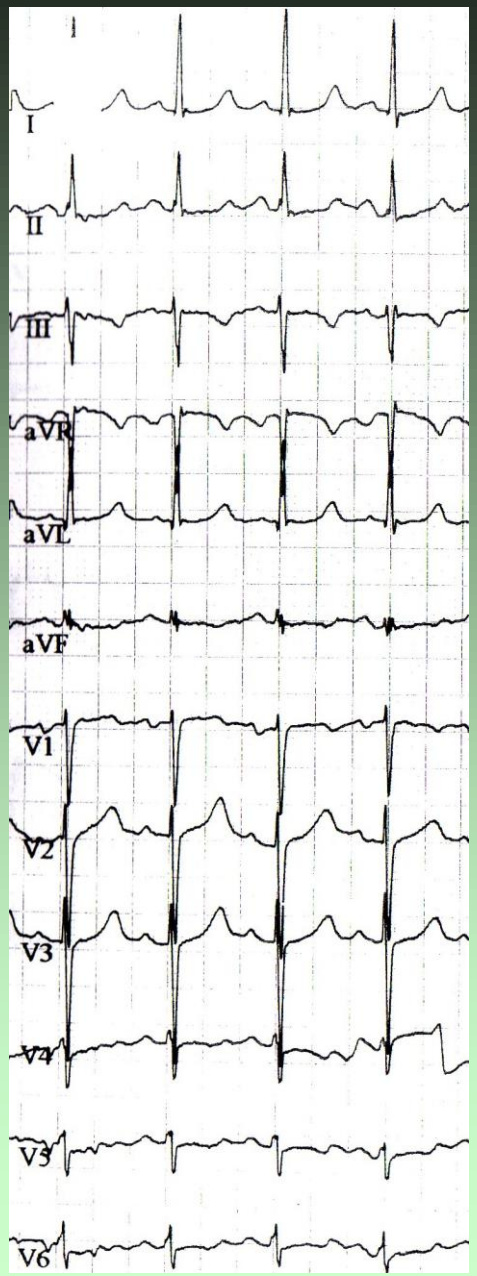
Treadmill

4 min recovery: QTc > 445 ms

Swan H, JACC 1999

Sy RW, Circulation 2011

Horner RM, Heart Rhythm 2011



Valsalva, cold pressor test

Mitsutake A, Circulation 1981

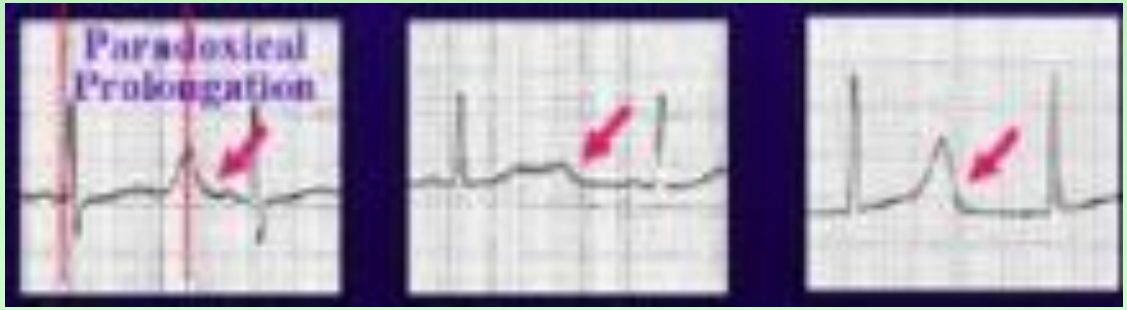
Standing ECG

Viskin S, et al. 2010

Epinephrin test

Ackerman, Mayo Clin Proc 2002

Shimizu, Heart Rhythm 2004



How to measure QT ?

1. Measurement

II, V2 or V5-V6 (or lead with longest QT) 50 mm/sec
« Surawicz technique »
Stable sinus rythm between 50 and 80 bpm
Otherwise averaged 3-5 beats

2. Correction

Bazett formula
$QTc = QT\ (ms) / \sqrt{RR\ (sec)}$

Long QT is not an always easy diagnosis !

on 902 physicians asked to measure QT interval ...

	LQTS	LQTS	Control	Control
Correct results (%)	QT	QTc	QT	QTc
Arrhythmia specialists	73%	73%	91%	72%
Cardiologists	75%	53%	67%	48%
Non-cardiologists	68%	32%	61%	31%

Correct diagnosis of real long QT

> 80 % électrophysiologists

< 50 % cardiologists

< 40 % non cardiologists

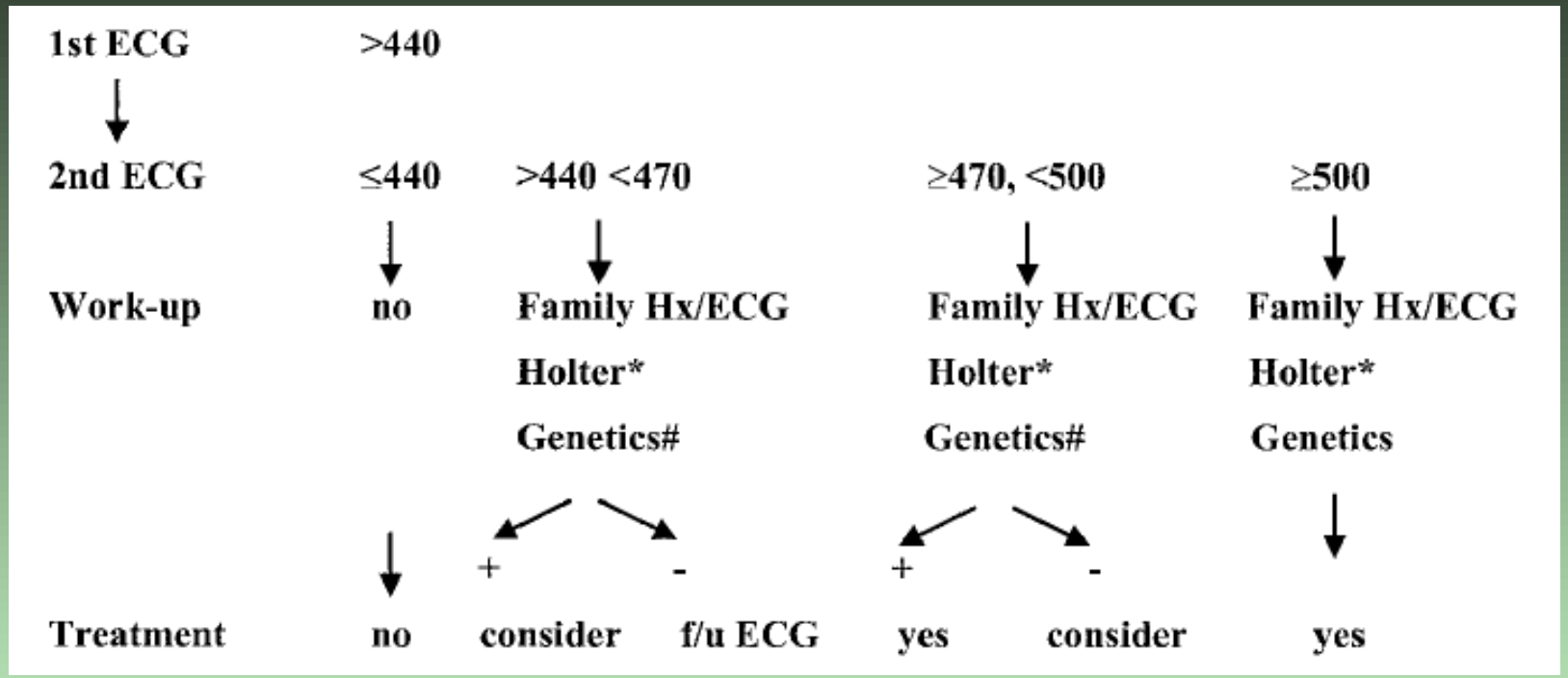
Correct diagnosis of any QT (normal or abnormal)

62 % électrophysiologists

< 25 % cardiologists and non cardiologists

Viskin S et al., Heart Rhythm 2005

And in newborns ?



repeated ECG + bradycardia + family ECG/history + Holter + genetic

Guidelines for the interpretation of the neonatal electrocardiogram.
Eur Heart J. 2002 Sep;23(17):1329-44.

Epidemiology

prevalence > 1/2000 living births
(based on QTc > 460 ms and positive genotype)
(Schwartz P, Circulation 2009)

First event chilhood, teen, young adults (< 40 yo)

Mean age SD 21 years old but persisting risk with age + + +

One of the causes of SIDS (10-15%) (LQT1, LQT3)

LQT = 20 % SD between 1 and 13 yo
LQT = 30 % SD between 13 and 20 yo

Moss AJ, et al. Circulation1995;92:2929-2934

ECG

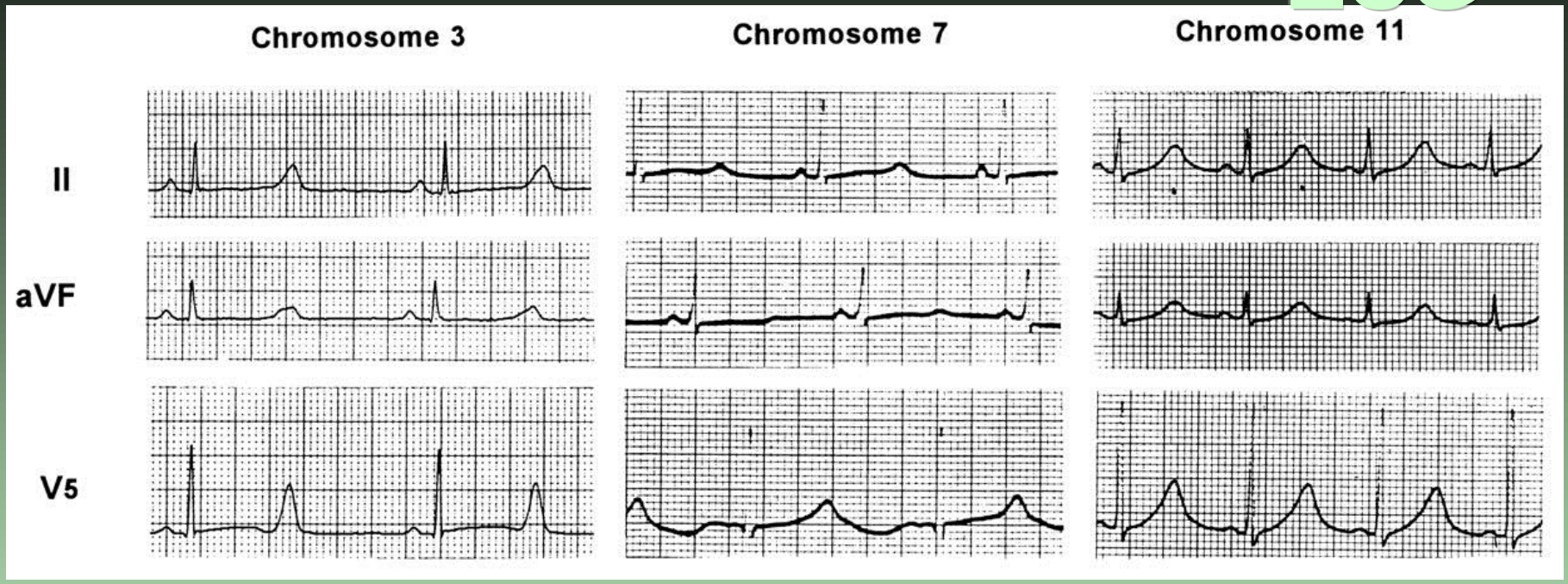
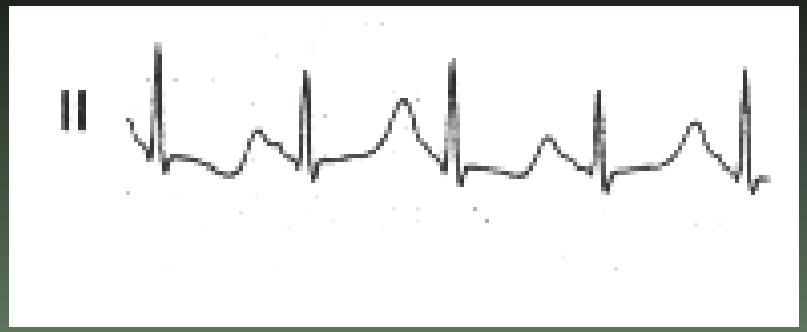


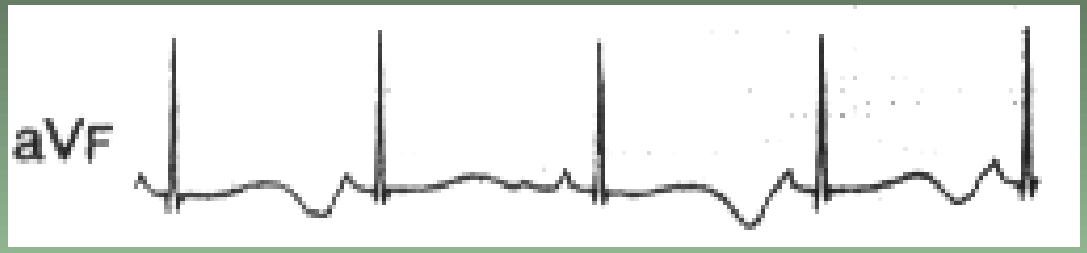
TABLE 4. Sensitivity and Specificity of Genotype Identification by Other Cardiologists

Genotype Identification	LQT1	LQT2	LQT3
Individual ECG evaluation (n=146), %			
Sensitivity	61 (54–69)	62 (55–71)	33 (27–39)
Specificity	71 (63–78)	87 (85–90)	98 (96–100)
Family-grouped ECG evaluation (n=29), %			
Sensitivity	77 (64–82)	79 (58–92)	54 (33–83)
Specificity	81 (78–83)	88 (71–100)	100 (100)

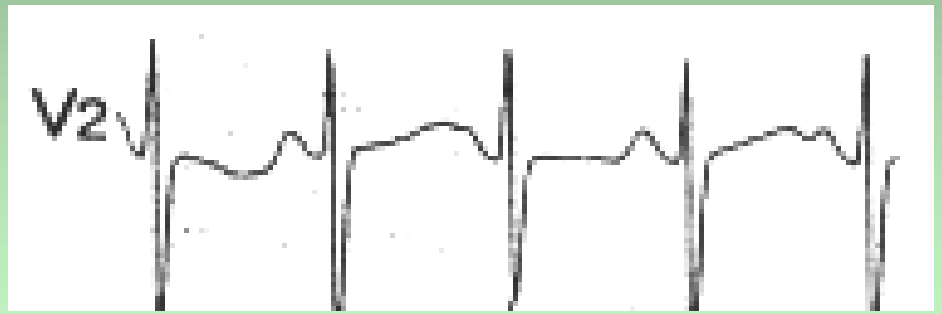
Zhang L, et al. Circulation 2000;102:2849-2855

ECG





(Shimizu, PACE 1996)



T wave alternans highly predictive of torsades-de-pointes

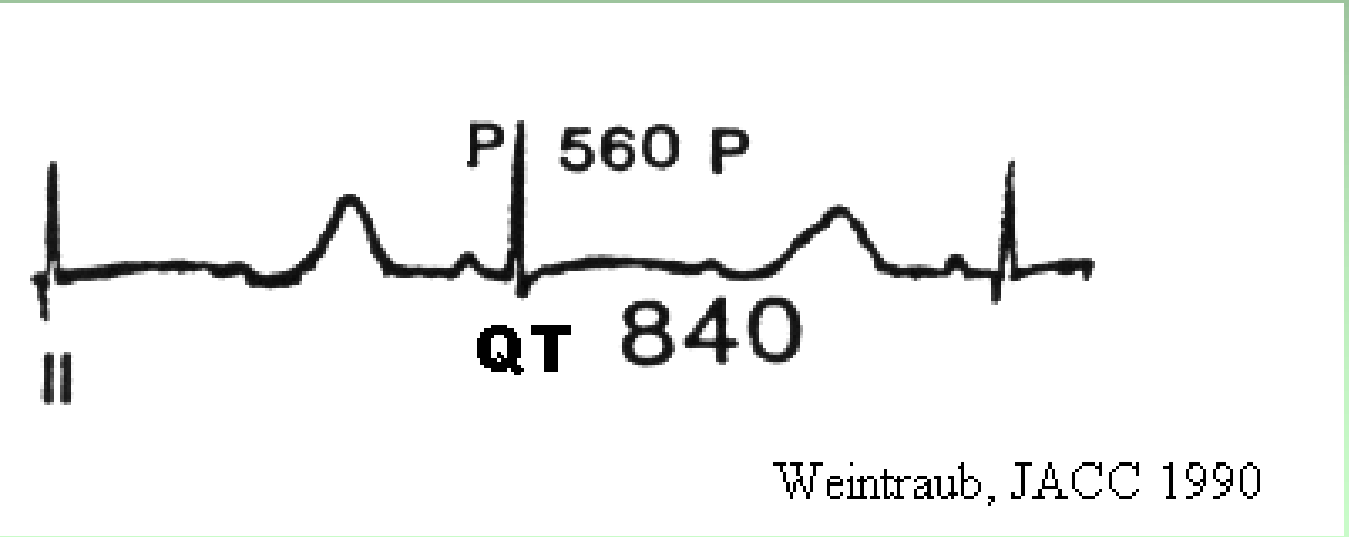
(Zareba, JACC 1994)

Other arrhythmias

Sinus node bradycardia / sick sinus syndrome (pauses)

1/3 patients (LQT 3 and LQT 4)

Atrial arrhythmias (Afib, atrial salvos)



AV block and « pseudo » AV block (neonates) (LQT 2 and LQT 3)

Genetical heterogeneity

GENE	LOCUS	PROTEIN
Long QT Syndrome		
Major LQTS Genes		
KCNQ1 (LQT1)	11p15.5	I_{Ks} potassium channel α subunit (K_vLQT1, K_v7.1)
KCNH2 (LQT2)	7q35-36	I_{Kr} potassium channel α subunit (HERG, K_v11.1)
SCN5A (LQT3)	3p21-p24	Ca… sodium channel α subunit (Na_v1.5)
Minor LQTS Genes (listed alphabetically)		
AKAP9	7q21-q22	…tiao
CACNA1C	12p13.3	Voltage gated L-type calcium channel (Ca_v1.2)
CALM1	14q32.11	Calmodulin
CALM2	2p21	Calmodulin
CAV3	3…	Caveolin-3
KCNE1		K_v7.1 potassium channel beta subunit (MinK)
KCNE2	…2.1	K_v11.1 potassium channel beta subunit (MiRP1)
KCNJ5	…q24.3	Potassium inwardly-rectifying channel (Kir3.4)
SCN4B	11q23.3	Sodium channel beta 4 subunit
SNTA1	20q11.2	Syntrophin-alpha 1
Ankyrin-B Syndrome		
ANK2	4q25-q27	Ankyrin B
Andersen-Tawil Syndrome		
KCNJ2 (ATS1)	17q23	I_{K1} potassium channel (Kir2.1)
Timothy Syndrome		
CACNA1C	12p13.3	Voltage gated L-type calcium channel (CaV1.2)

> 90%

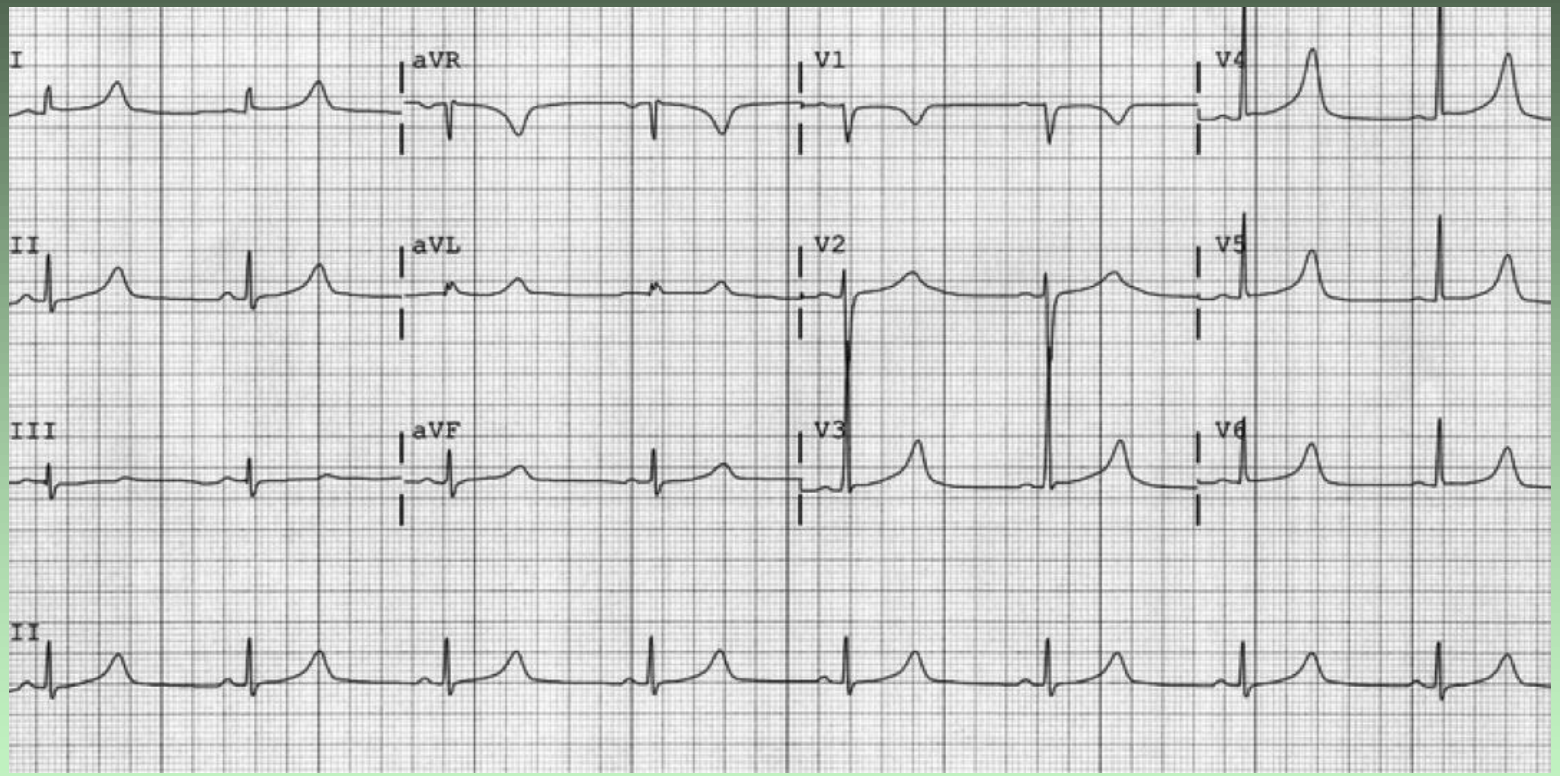
20% without (known) mutation

From_Tester DJ, Ackerman MJ. Methodist Debakey Cardiovasc J. 2014

LQT 1

(Keating et al., Science 1991)

Mutation KCNQ1 (11p15.5) **α subunit IK_s**



50 % genotyped families or cases *(Khan et al., Am Heart J 2002, Splawsky, Priori)*

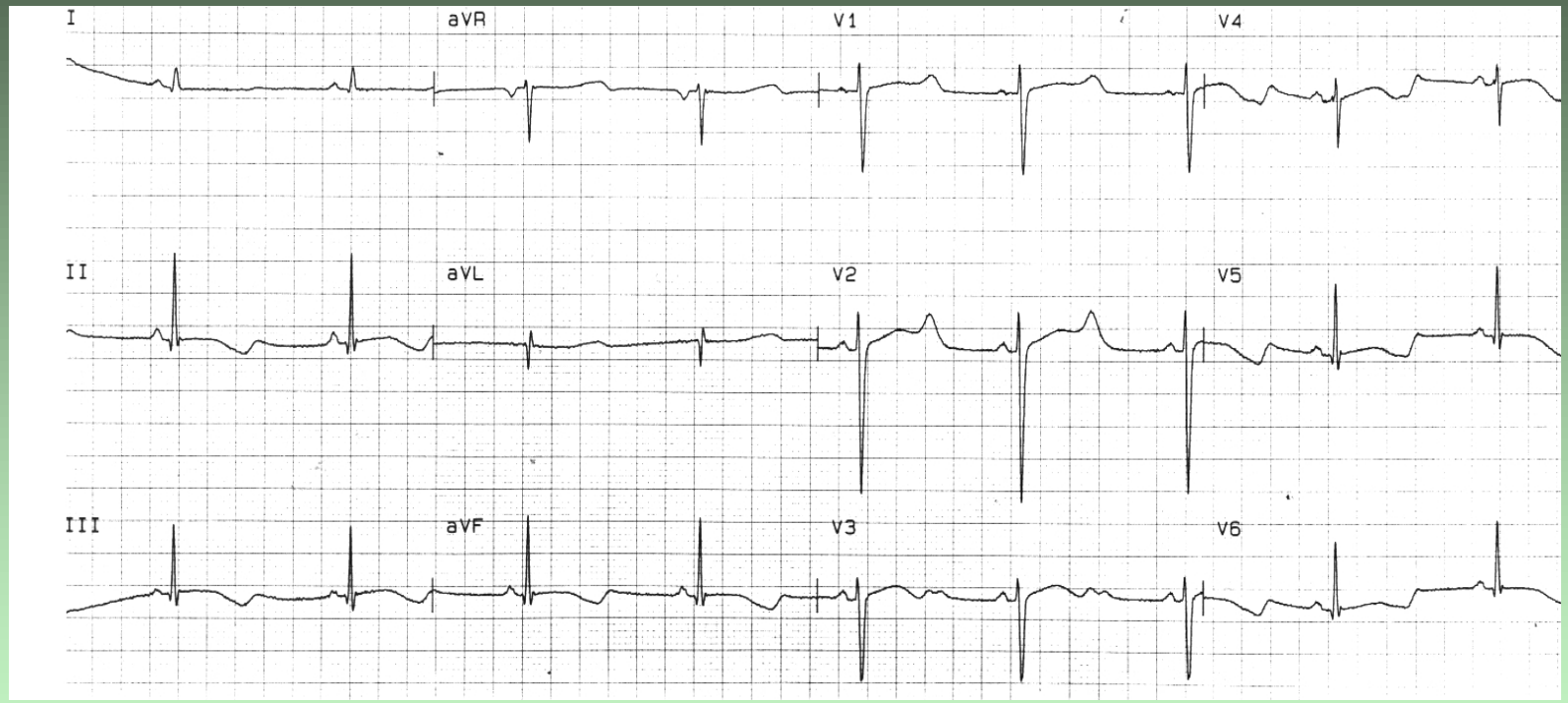
Ample assymetrical T wave (large base)

Arrhythmias: at exercice (swimming) or emotion/stress > 95 %

LQT 2

(Curran ME et al., Cell 1995)

Mutation KCNQ2 (HeRG) **(7q35-36)** **α subunit IK_R**



30/45 % genotyped families or cases *(Khan et al., Am Heart J 2002, Splawsky, Priori)*

Noched/flat T wave

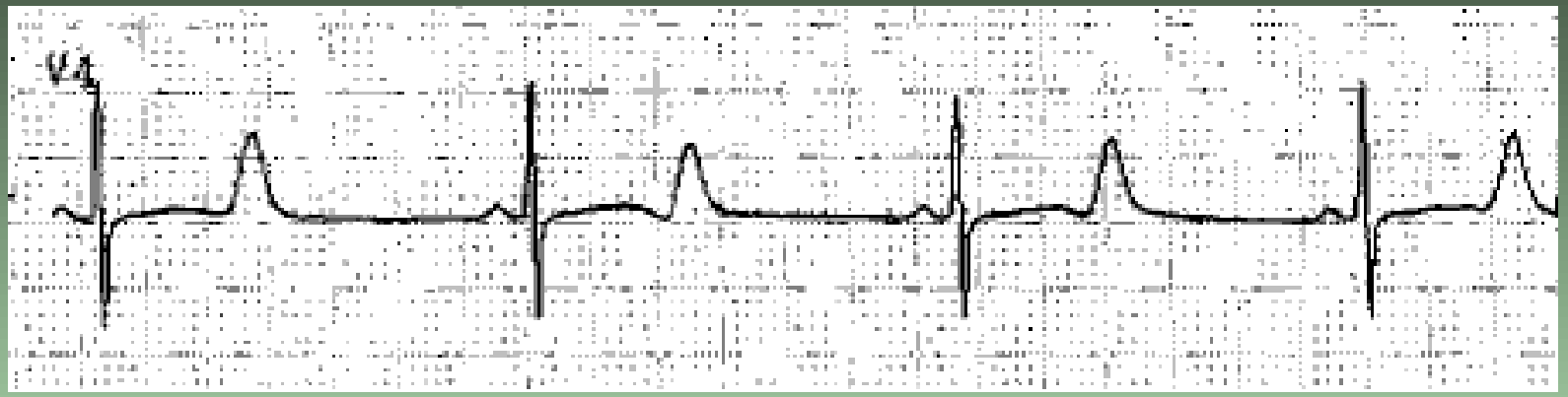
Arrhythmias: exercice 15 %, stress (sounds) 35 %

rest (stress ? noise ? dream ? arousal ?) 50 %

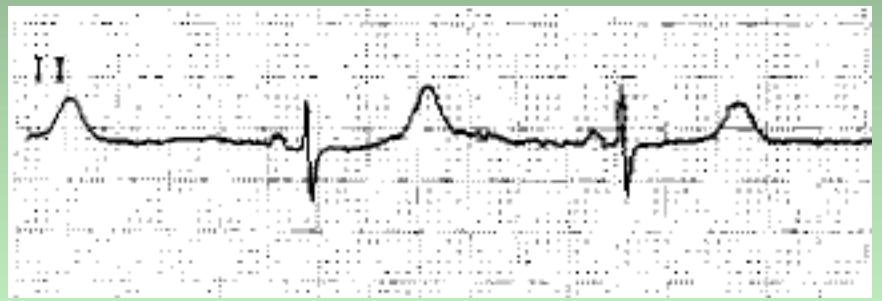
LQT 3

(Wang Q et al., Cell 1995)

Mutation SCN5A (3p21-24) α subunit IN_A



Ample T wave and long ST segment



5/15 % genotyped families or cases *(Khan et al., Am Heart J 2002, Splawsky, Priori)*

Arrhythmias: 3/4 at rest (pause dependant)

Andersen-Tawill syndrome (LQT 7)

(Plaster NM et al., Cell 2001)

K sensitive-periodic paralysis

Malformations

Arrhythmias:

PVC, bidirectional VT

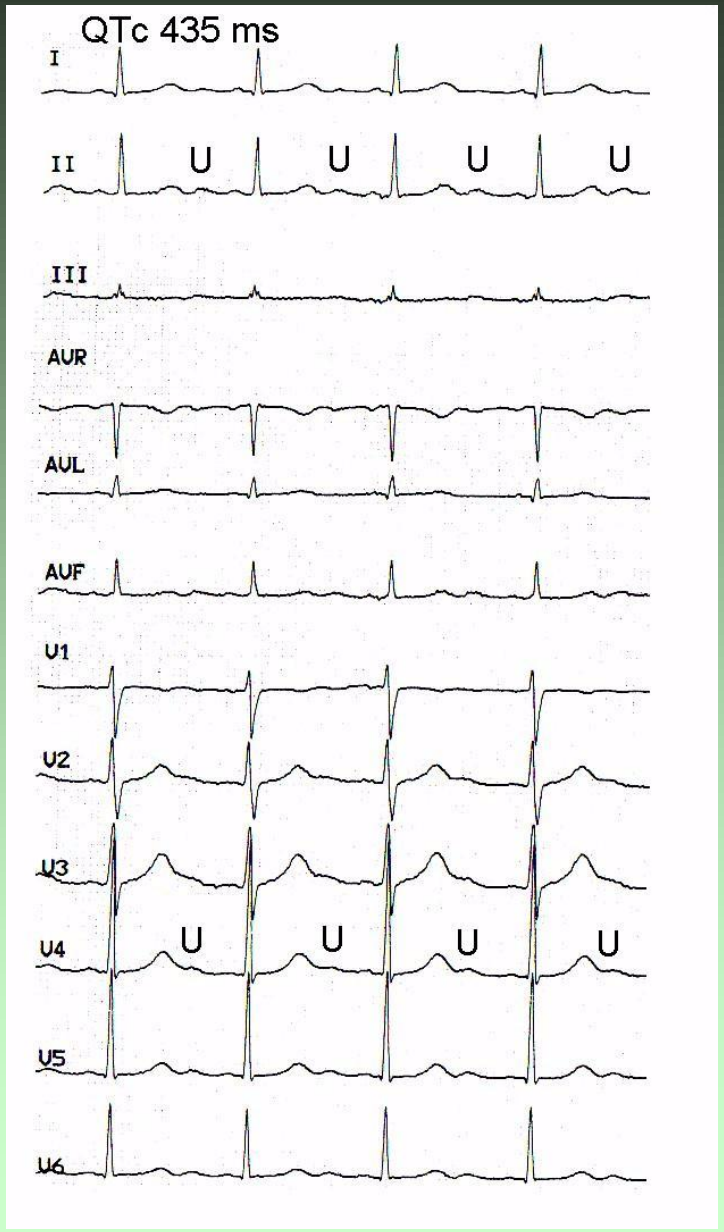
Torsades de pointes

SD more exceptional

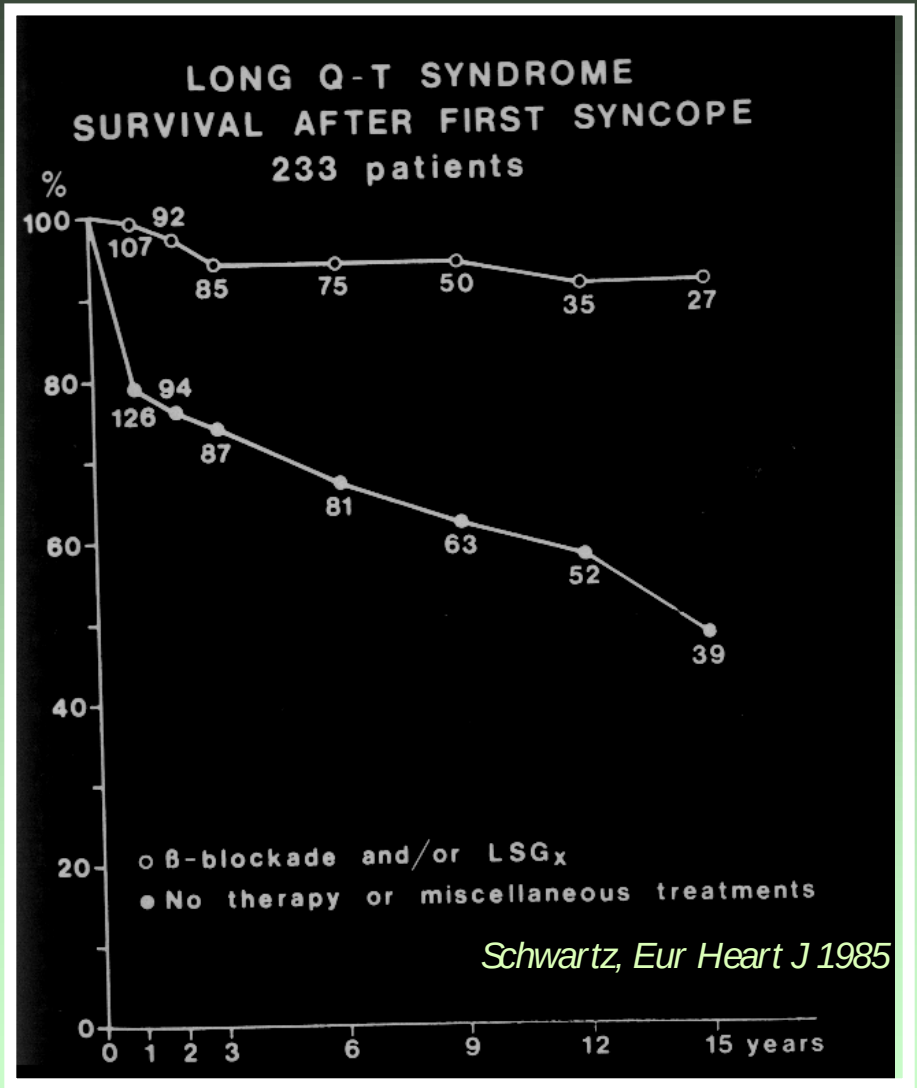
especially when hypoK

Mutation on KCNJ2 (17q23) (IK1)

« Normal » QT and U waves



Prognosis and risk stratification



Mortality in symptomatic untreated patients

5 % yearly

(Schwartz Am H J 1975, Eur H J 1985)

Ten times lower when treated

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risk Stratification in the Long-QT Syndrome

Silvia G. Priori, M.D., Ph.D., Peter J. Schwartz, M.D.,
Carlo Napolitano, M.D., Ph.D., Raffaella Bloise, M.D., Elena Ronchetti, Ph.D.,
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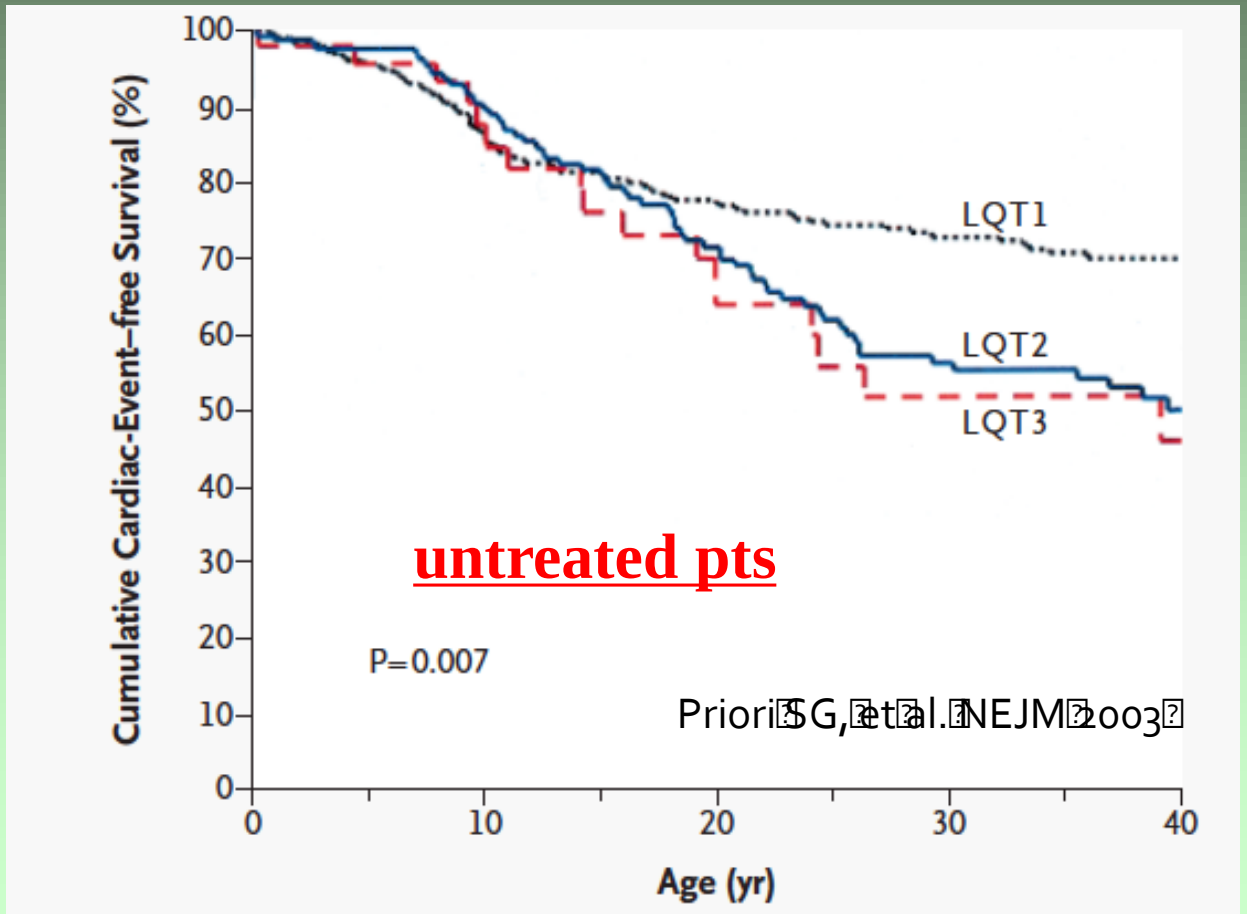

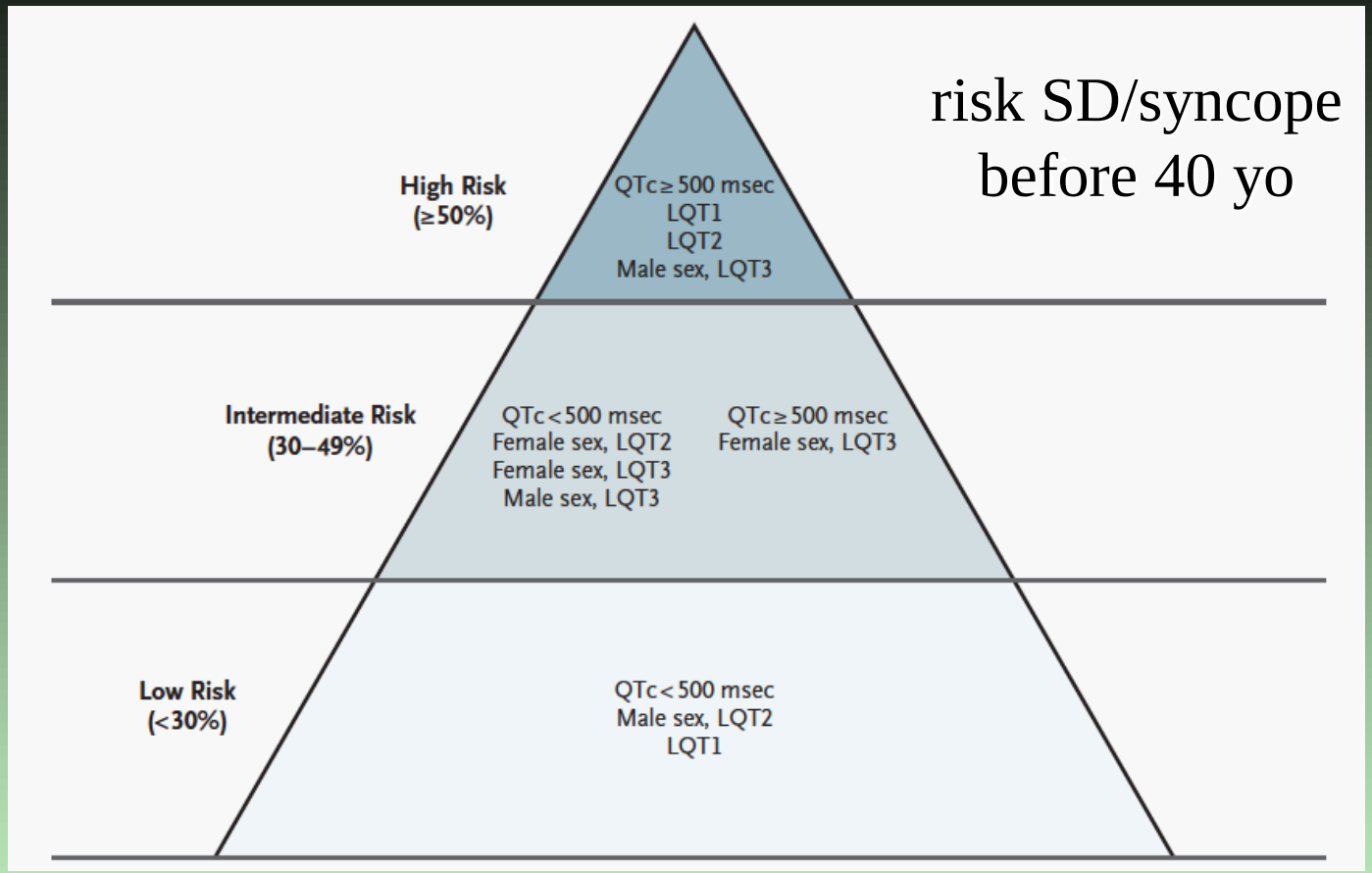

risk SD/syncope before 40 yo

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Prognosis and risk stratification

Populations at high risk

- Jervell-Lange Nielsen
- Timothy syndrome
- QTc > 500 ms
- first event during childhood
- specific mutations
    - missense mutations cytoplasmic loop (LQT1)
    - dominant-negative ion current effects (LQT2)
    - missense mutations pore loop (men LQT2)
    - specific mutations ((KCNQ1-A341V)
    - > 1 mutation

Populations at low risk

- specific mutations
    - missense mutations C terminal (LQT1)
- asymptomatic LQT1 males

Management of long QT patients

Life style modifications

- avoid any QT lengthening-drug
- avoid any K, Mg or Ca depletion
- avoid competitive sport and intense physical activity
- avoid swimming without supervision (LQT1)
- avoid sudden loud noises (LQT2)

Competition possible ?

-asymptomatic and no familial sudden deaths
-borderline QTc
-under BB therapy
-automated external defibrillator available
-no LQT1

Management of long QT patients

Medical therapy

Beta-blockers

decrease symptoms (0,31 vs 0,97 events/year)
decrease mortality (6 % at 3 years, 9 % at 15 years)

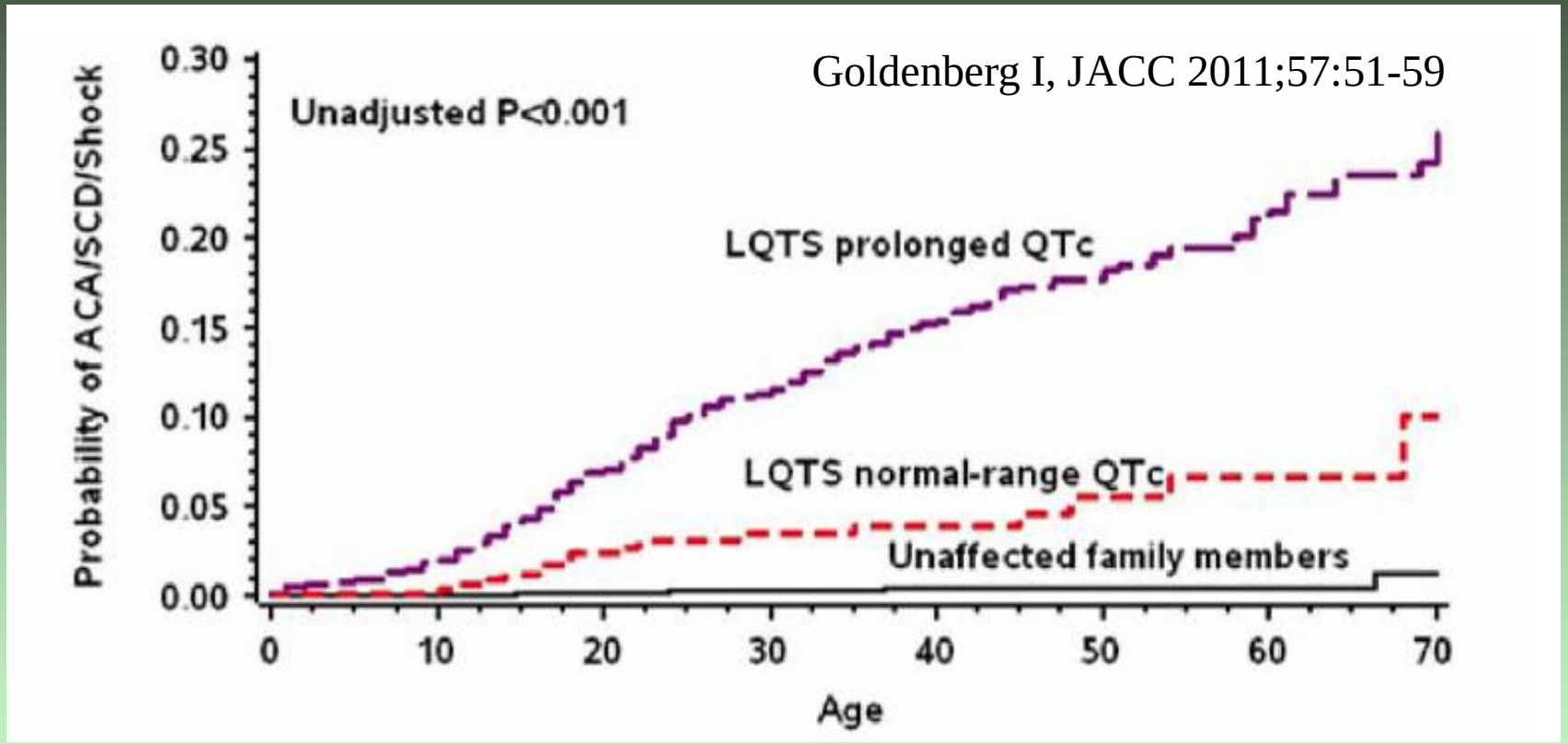
No randomized trial

Full dosing when possible

avoid metoprolol

propanolol 2-3 mg/kg (child)
nadolol 2-3 mg/kg (child)

BB even for normal QT in genotyped + pts



Still a place for pace-maker ?

(DDD without algorithms allowing pauses)

. severe symptomatic bradycardia under BB ?

. Bradycardia-induced arrhthmias ?

. sick sinus syndrome ? (LQT 3, LQT 4)

Currently only with ICD

Newborn or young children with 2/1 AV block ?

Left cardiac sympathetic denervation

(lower half left stellate gg + left T2-T4)

Surgically (left supraclavicular) or minimally invasive (videoscopy)
Experienced centers

not a perfect therapy

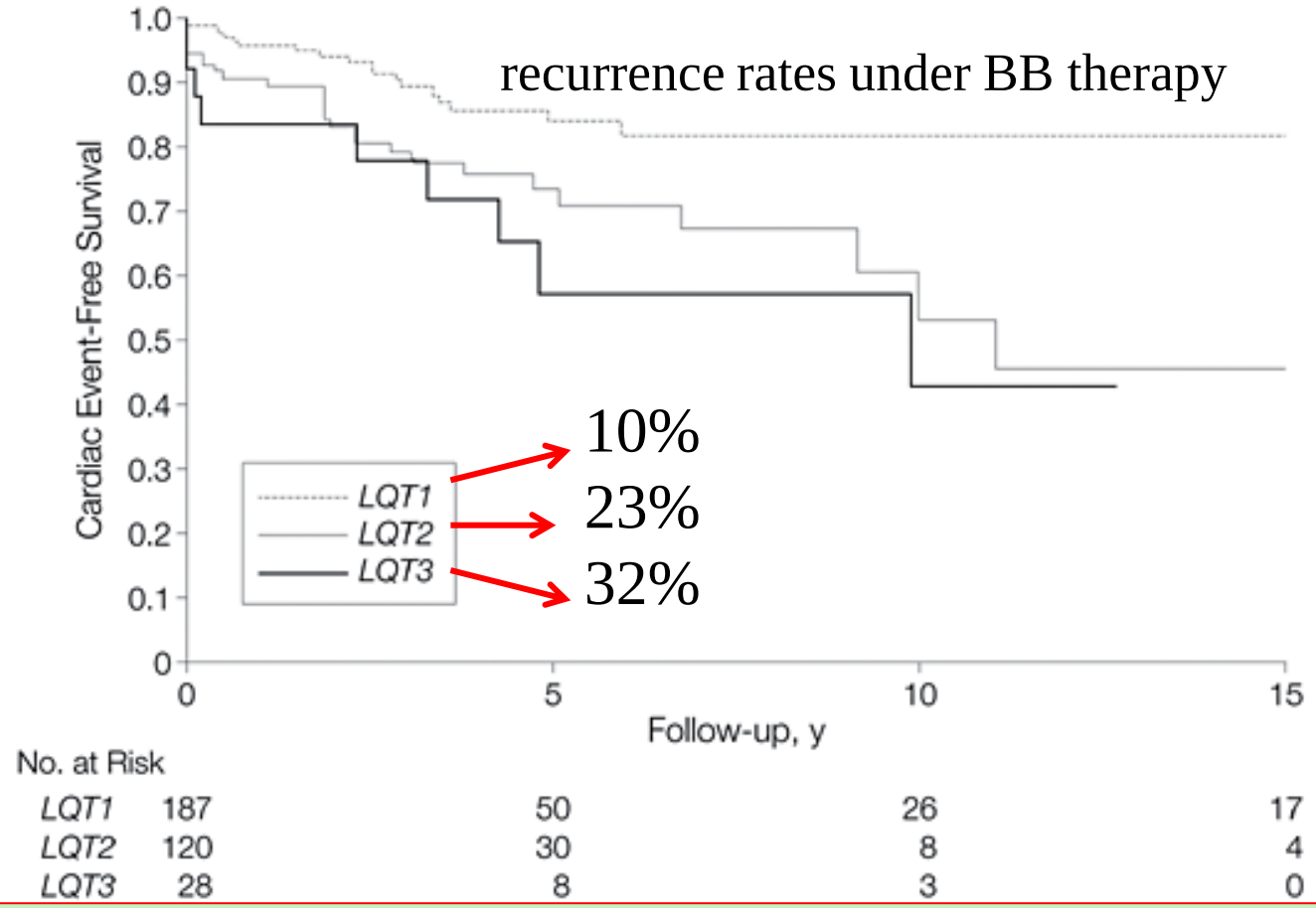
7% SD and 50% symptoms

Schwartz P, et al. Circulation. 2004;109:1826-33

- CI to BB
- high risk children/infants instead of ICD
- syncope despite BB ?
- Electrical storm despite BB

However …

Priori S, et al. JAMA 2004



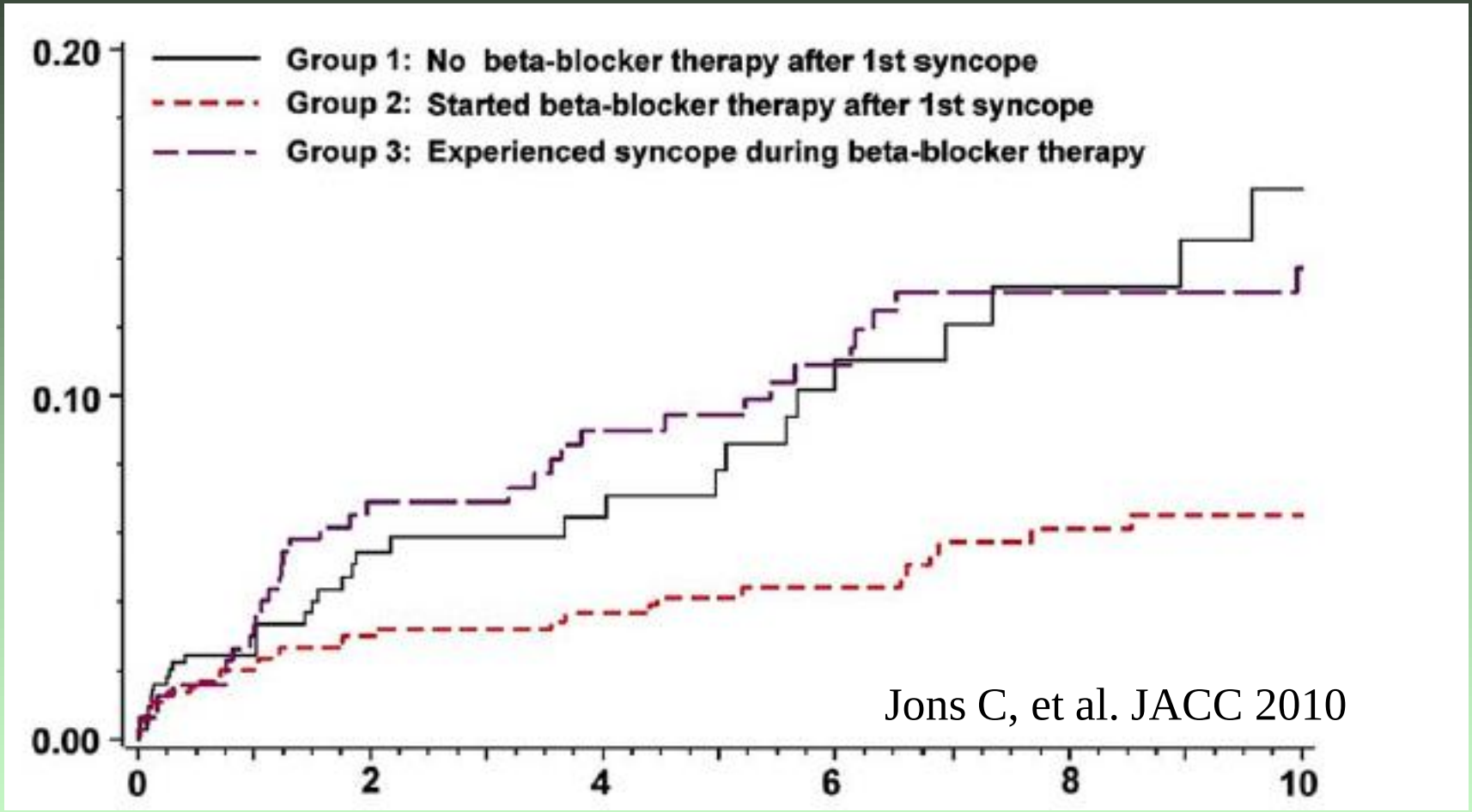
24 % SD in high risk patients (SD, syncope despite BB)

(Dorostkar, Circulation 1999)

32 % SD/syncope at 5 years in symptomatic pts treated by BB

(Moss, Circulation 2000)

However …



LQT with syncope

ICD

No control study

High risk patients (SD or recurring syncope under BB)

1.3 % mortality at 3 years vs 14 % at 8 years without ICD

(Zareba, JCE 2003)

keep the BB !!!!

ICD

Who Are the Long-QT Syndrome Patients Who Receive an Implantable Cardioverter-Defibrillator and What Happens to Them?

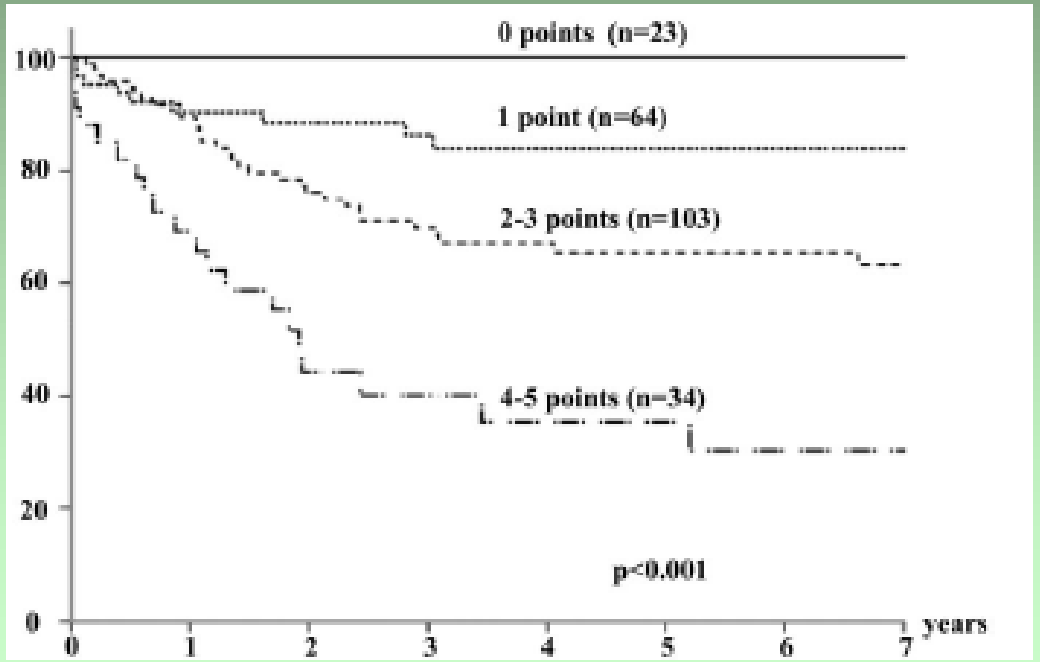
Circulation. 2010

Data From the European Long-QT Syndrome Implantable Cardioverter-Defibrillator (LQTS ICD) Registry

Peter J. Schwartz, MD; Carla Spazzolini, DVM, MS; Silvia G. Priori, MD, PhD; Lia Crotti, MD, PhD; Alessandro Vicentini, MD; Maurizio Landolina, MD; Maurizio Gasparini, MD; Arthur A.M. Wilde, MD; Reinoud E. Knops, MD; Isabelle Denjoy, MD; Lauri Toivonen, MD; Gerold Mönnig, MD; Majid Al-Fayyadh, MD; Luc Jordaens, MD; Martin Borggrefe, MD; Christina Holmgren, MD; Pedro Brugada, MD, FAHA; Luc De Roy, MD; Stefan H. Hohnloser, MD; Paul A. Brink, MD

233 implanted LQT patients (30 +/- 17 yo) FU 4.5 ans

11 % inappropriate th
25% complications
3 % death (non-arrhythmic)
28% appropriate shock

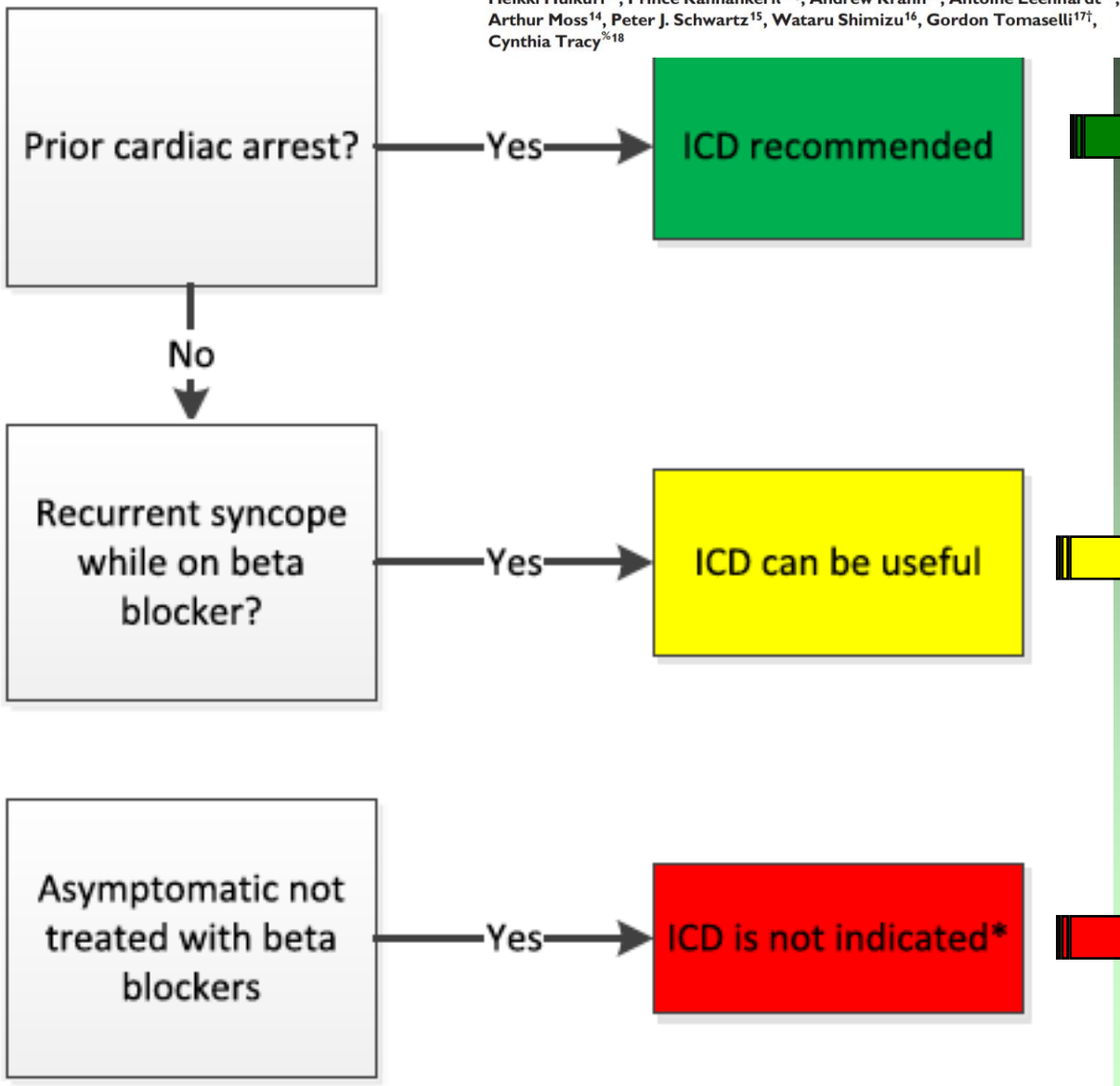


Score risk

- *cardiac arrest*
- *symptoms despite BB*
- *QTc > 500 ms*
- *implantation < 20 yo*

Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes

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



BB/LSCD in LQT1 if CI ICD (infants)

symptomatic JLN or multiple mutations

?

very high risk patients with CI BB