

Programa de Formación Continua 2010

Sociedad de Cardiología de Corrientes

**“Síndromes genéticos: QT largo”
(QTL)**

Dr. Ignacio Reyes. Corrientes



“Síndromes genéticos: QT largo”

Enf. de los canales:

Síndrome de Brugada. (SB)

Síndrome de QT largo congénito. (QTL)

Síndrome de QT corto

Taquicardia ventricular adrenérgica

Enf. del músculo:

Miocardiopatía Hipertrófica. (MCH)

Displasia arritmogénica del VD



“Síndromes genéticos: QT largo”

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“Síndromes genéticos: QT largo”

Se trata de una mutación genética que afecta las proteínas que regulan la función de los canales iónicos (membrana celular). Bloqueo de la salida de K^+ o ingreso tardío de Na^+ , aumento intracelular de iones positivos, demora repolarización ventricular y prolongación del intervalo QT

Romano Ward: (70-90%)
Autosómico dominante

Jerwell Lange-Nielsen: (10%)
Autosómico recesivo



“Síndromes genéticos: QT largo”

| Tipo | Locus | Gen | Proteína | Corriente | Efecto | Frecuencia (%) |
|---|----------|---------------------|---|-----------|--------|----------------|
| Romano-Ward (autosómico dominante) | | | | | | |
| SQTL1 | 11p15.5 | <i>KCNQ1/KVLQT1</i> | Principal, subunidad α I_{Ks} | K | ↓ | 30-35 |
| SQTL2 | 7q35-36 | <i>KCNH2/HERG</i> | Principal, subunidad α I_{Kr} | K | ↓ | 25-30 |
| SQTL3 | 3p21-p24 | <i>SCN5A</i> | Principal, subunidad α I_{Na} | I_{Na} | ↑ | 5-10 |
| SQTL4 | 4q25-q27 | <i>ANKB</i> | Accesoria, anquirina- β | Na/Ca | ↑ | < 1 |
| SQTL5 | 21q22.1 | <i>KCNE1/minK</i> | Accesoria, subunidad β I_{Ks} | K | ↓ | < 1 |
| SQTL6 | 21q22.1 | <i>KCNE2/MIRP1</i> | Accesoria, subunidad β I_{Kr} | K | ↓ | < 1 |
| SQTL7 ^a | 17q23 | <i>KCNJ8</i> | Principal, subunidad α Kir 2.1 | K | ↓ | < 1 |
| SQTL8 ^b | 12p13.3 | <i>CACNA1</i> | Principal, subunidad α Ca _v 1.2 | Ca tipo L | ↑ | < 1 |
| SQTL9 | 3p25 | <i>CAV3</i> | Accesoria, caveolina 3 | Na | ↑ | < 1 |
| SQTL10 | 11q23 | <i>SCN4B</i> | Accesoria, subunidad β 4 I_{Na} | Na | ↑ | < 1 |
| Jervell-Lange-Nielsen (autosómico recesivo) | | | | | | |
| JLN1 | 11p15.5 | <i>KCNQ1/KVLQT1</i> | Principal, subunidad α I_{Ks} | K | ↓ | > 90,5 |
| JLN2 | 21q22.1 | <i>KCNE1/minK</i> | Accesoria, subunidad β I_{Ks} | K | ↓ | < 0,5 |

^aSíndrome de Andersen-Tawil.

^bSíndrome de Timothy.



“Síndromes genéticos: QT largo”

- Muerte súbita recuperada
- Síncope
- Evaluación familiar
- Hallazgo ECG.

“Síndromes genéticos: QT largo”

KVLQT1

HERG
(I_{Kr})

SCN5A
(I_{Na})

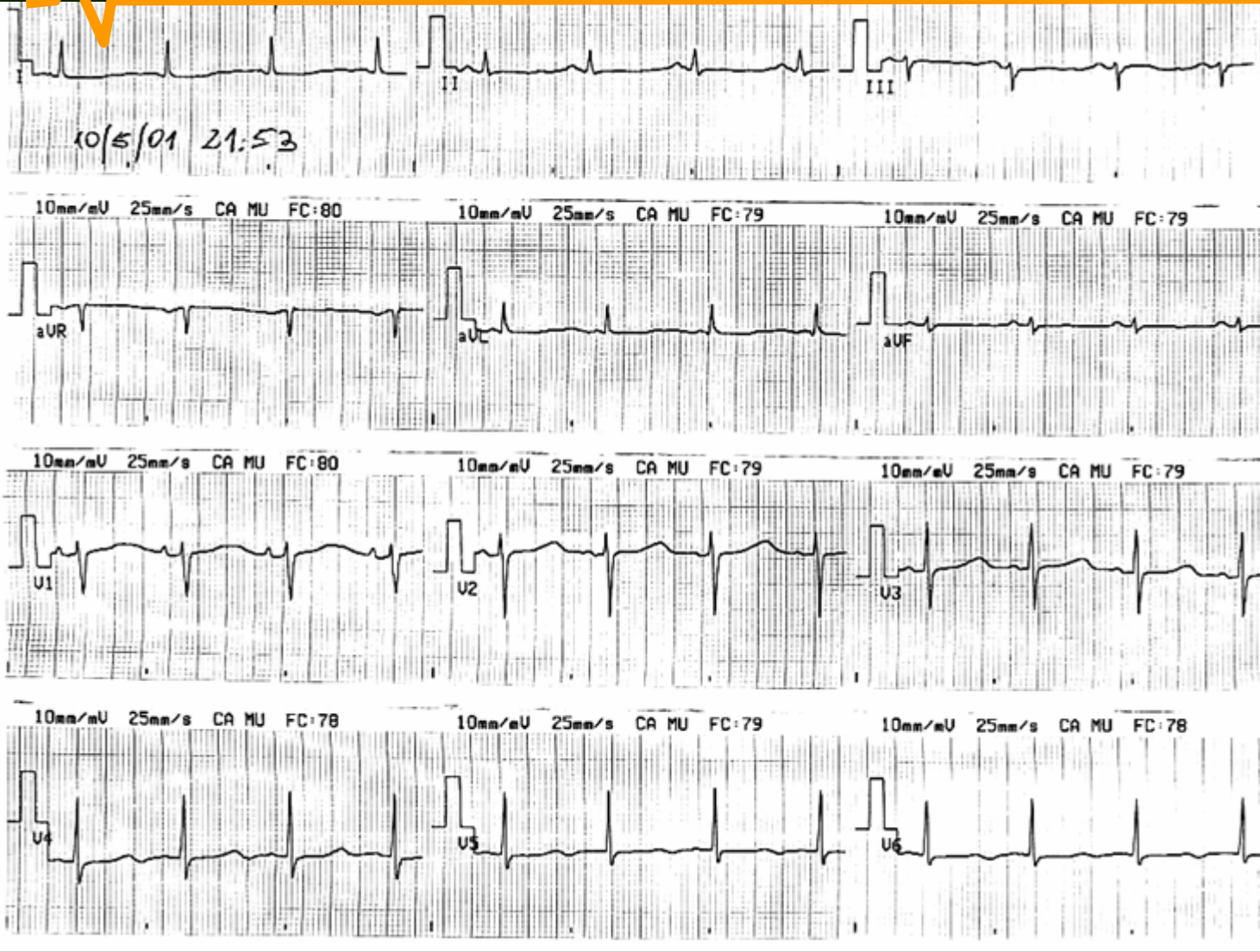


LQT1: Ondas T que arrancan tempranamente luego de la onda R, son de baja amplitud y base ancha.

LQT2: Ondas T tardías y baja amplitud.

LQT3: Ondas T tardías y alta amplitud. Alargamiento a expensas del segmento isoelectrico

“Síndromes genéticos: QT largo”



QTm= 0.56 seg

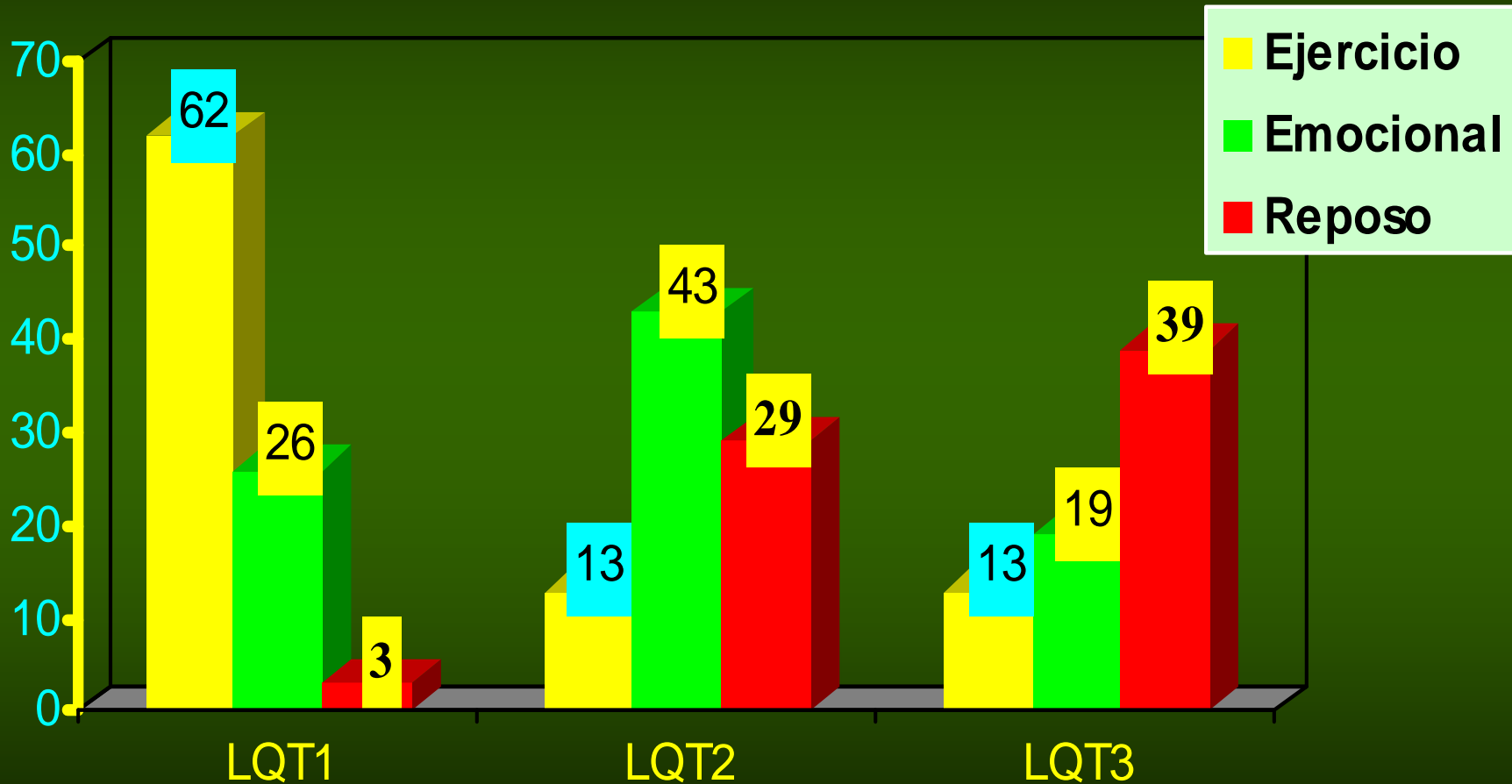
R-R= 0.76 seg

$$\sqrt{0.76} = 0.87$$

$$\frac{0.56}{0.87} = 0.64$$

“Síndromes genéticos: QT largo”

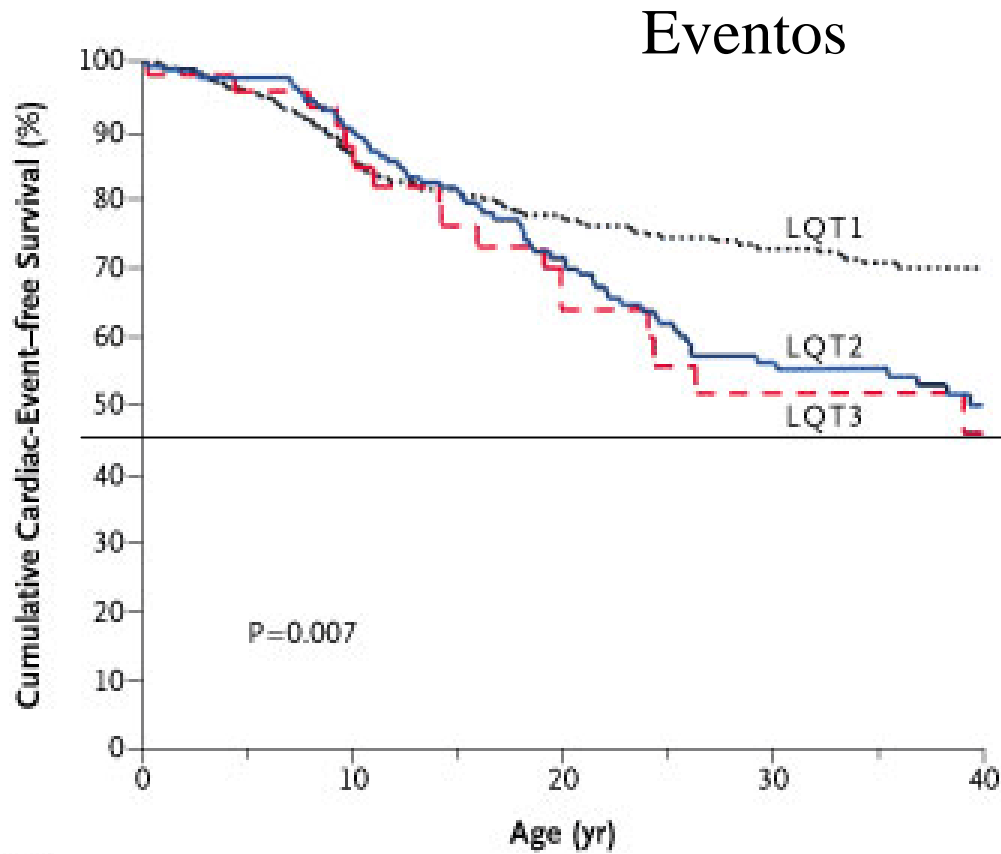
Estratificación del riesgo



Schwartz PJ, Priori SG, Spazzolini C, Moss AJ, Vincent GM, Napolitano C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation*. 2001;103:89-95

“Síndromes genéticos: QT largo”

Estratificación del riesgo



| No. at Risk | 0 | 10 | 20 | 30 | 40 |
|-------------|-----|-----|-----|-----|-----|
| LQT1 | 355 | 249 | 192 | 146 | 100 |
| LQT2 | 176 | 130 | 187 | 57 | 34 |
| LQT3 | 49 | 30 | 20 | 9 | 7 |

PC y/o MS

LQT1 10 %

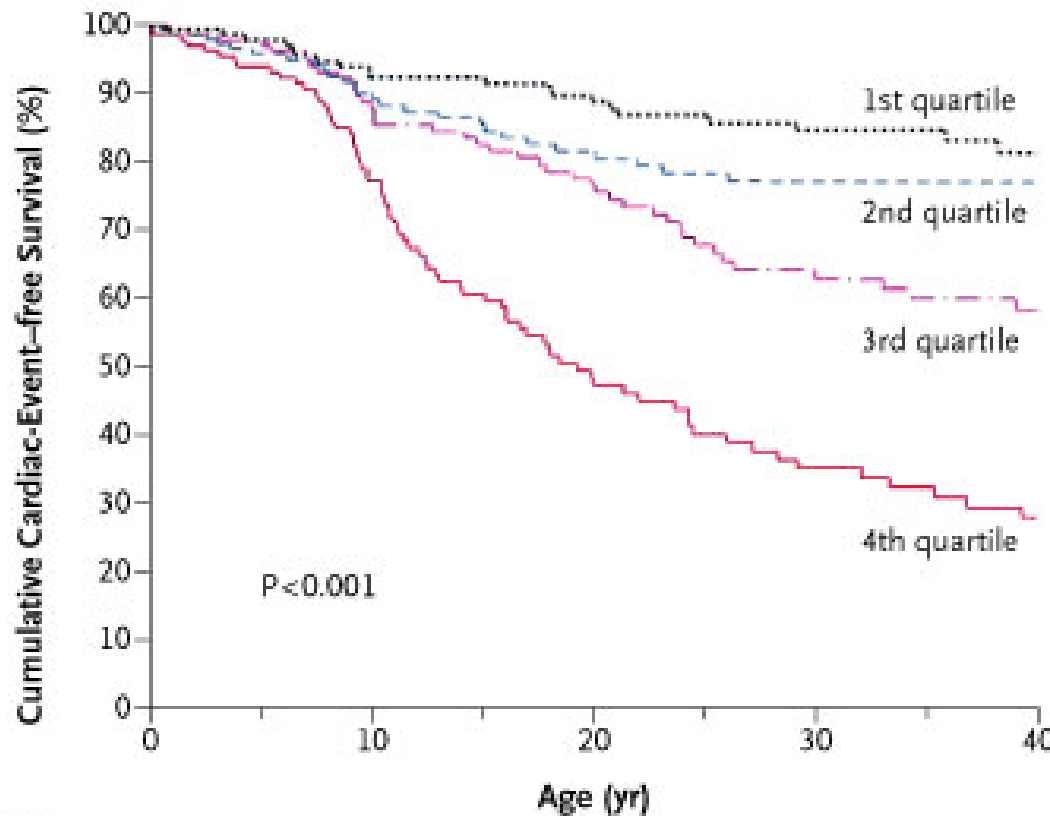
LQT2 20 %

LQT3 16.4 %

“Síndromes genéticos: QT largo”

Estratificación del riesgo

Sobrevida sin eventos



< 446 msec

< 447-468 msec

< 469-498 msec

> 498 msec

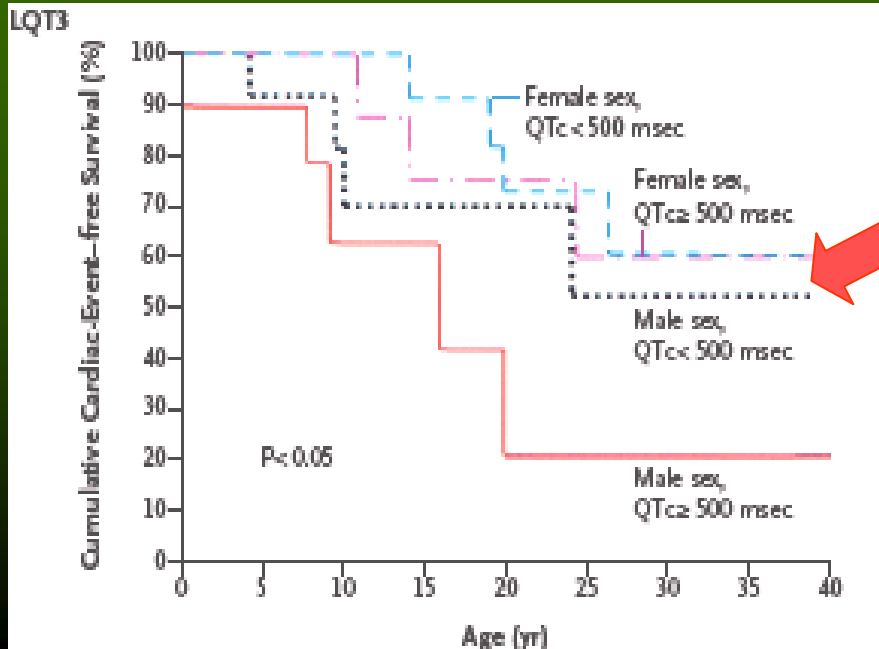
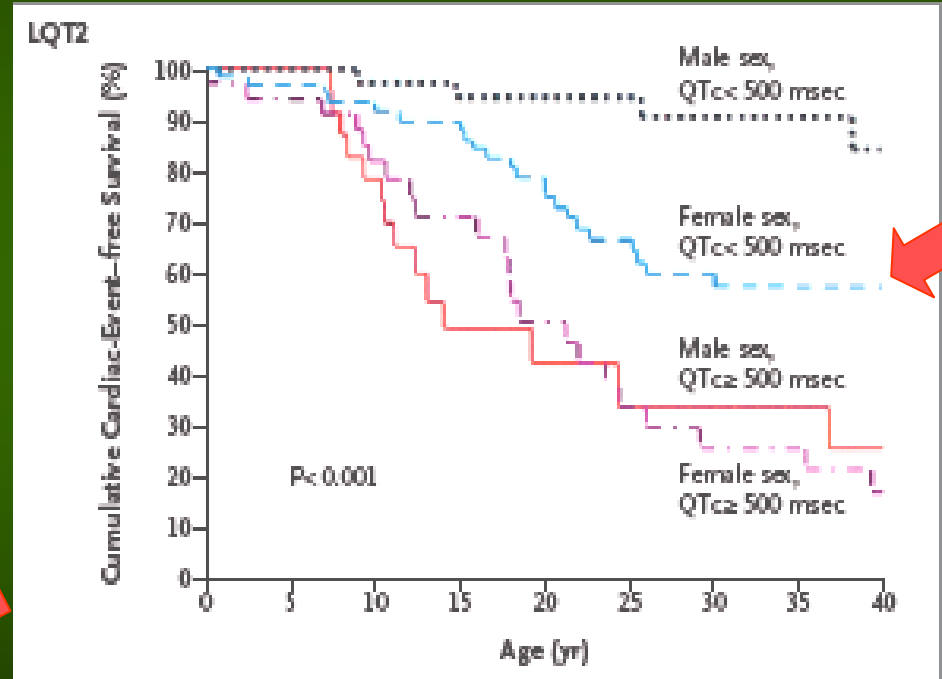
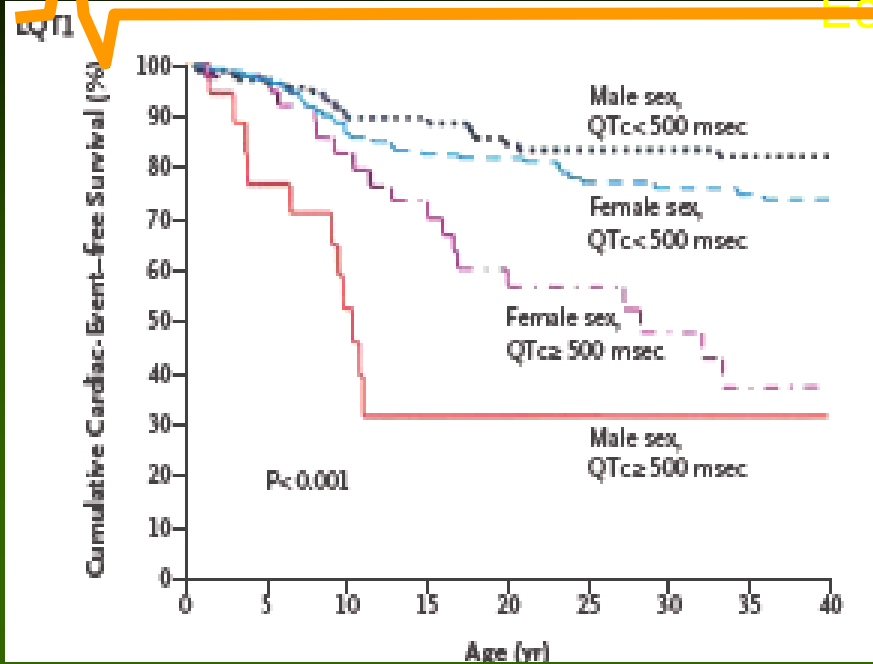
No. at Risk

| | | | | | |
|--------------|-----|-----|----|----|----|
| 1st quartile | 148 | 112 | 96 | 76 | 45 |
| 2nd quartile | 150 | 104 | 80 | 62 | 45 |
| 3rd quartile | 140 | 103 | 78 | 49 | 33 |
| 4th quartile | 142 | 92 | 45 | 28 | 18 |

“Síndromes genéticos: QT largo”

Estratificación del riesgo

Sobrevida sin eventos



Risk Stratification in the Long-QT Syndrome.
Silvia G. Priori, M.D., Ph.D., Peter J. Schwartz, M.D., Carlo Napolitano
N Engl J Med 2003;348:1866-74

“Síndromes genéticos: QT largo”

Estratificación del riesgo

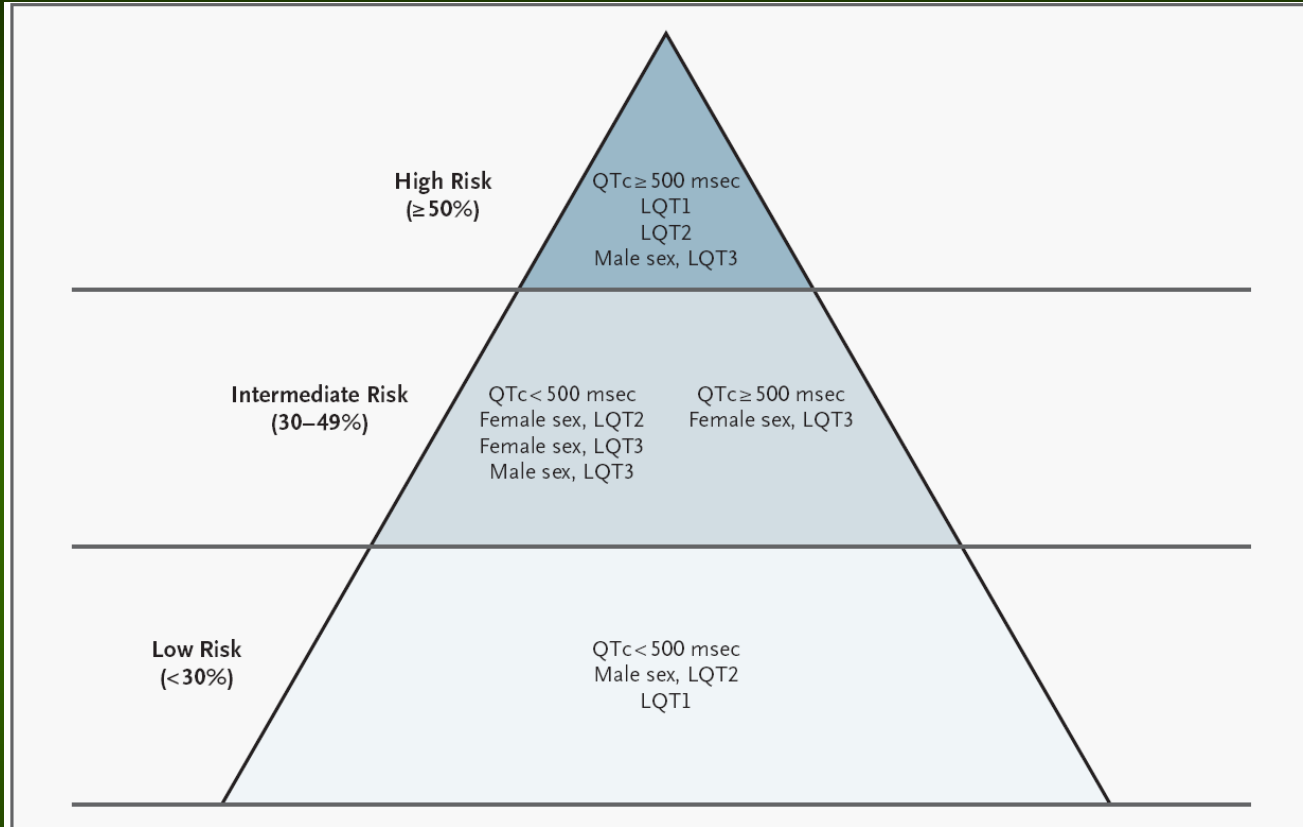


Figure 4. Proposed Scheme for Risk Stratification among Patients with the Long-QT Syndrome According to Genotype and Sex.

The risk groups have been defined on the basis of the probability of a first cardiac event (syncope, cardiac arrest, or sudden death) before the age of 40 years and before therapy. A probability of 50 percent or higher defines the high-risk group, a risk of 30 to 49 percent the intermediate-risk group, and a risk below 30 percent the low-risk group.

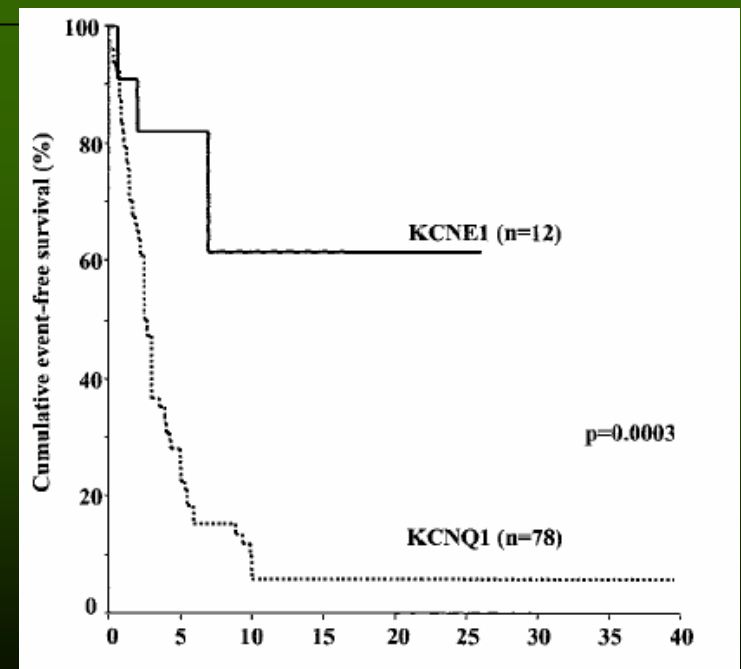
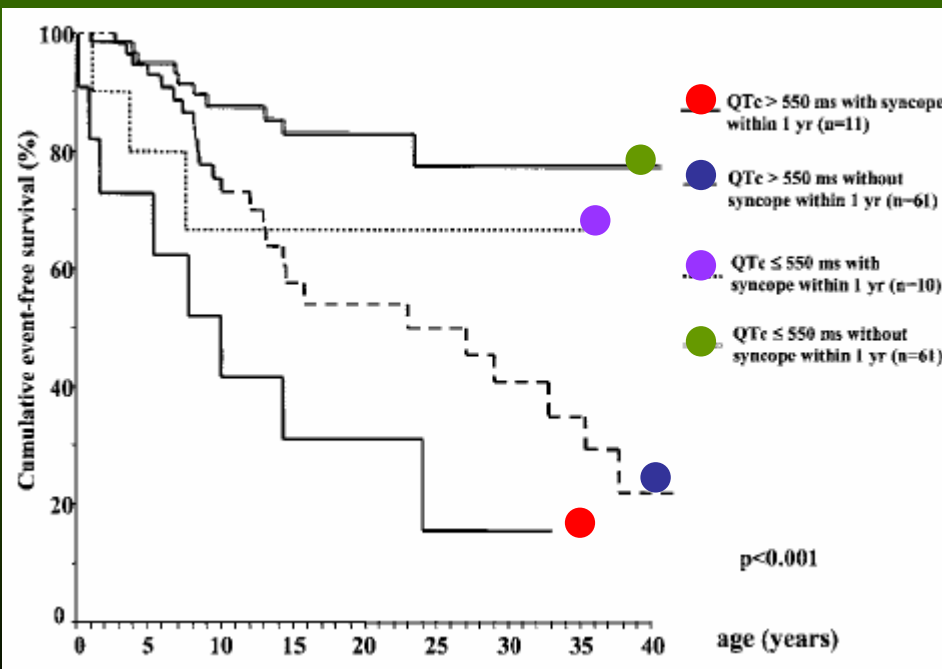
“Síndromes genéticos: QT largo”

Estratificación del riesgo

The Jervell and Lange-Nielsen Syndrome Natural History, Molecular Basis, and Clinical Outcome

Peter J. Schwartz, MD; Carla Spazzolini, DVM; Lia Crotti, MD; Jørn Bathen, MD; Jan P. Amlie, MD; Katherine Timothy, RN; Maria Shkolnikova, MD; Charles I. Berul, MD; Maria Bitner-Glindzicz, MD; Lauri Toivonen, MD; Minoru Horie, MD; Eric Schulze-Bahr, MD; Isabelle Denjoy, MD

Sincope 1er año y QT





“Síndromes genéticos: QT largo”

Estratificación del riesgo: Síncope

Risk of Fatal Arrhythmic Events in Long QT Syndrome Patients After Syncope

Christian Jons, MD,* Arthur J. Moss, MD,* Ilan Goldenberg, MD,* Judy Liu, MS,* Scott McNitt, MS,* Wojciech Zareba, MD, PhD,* Ming Qi, MD,† Jennifer L. Robinson, MS*

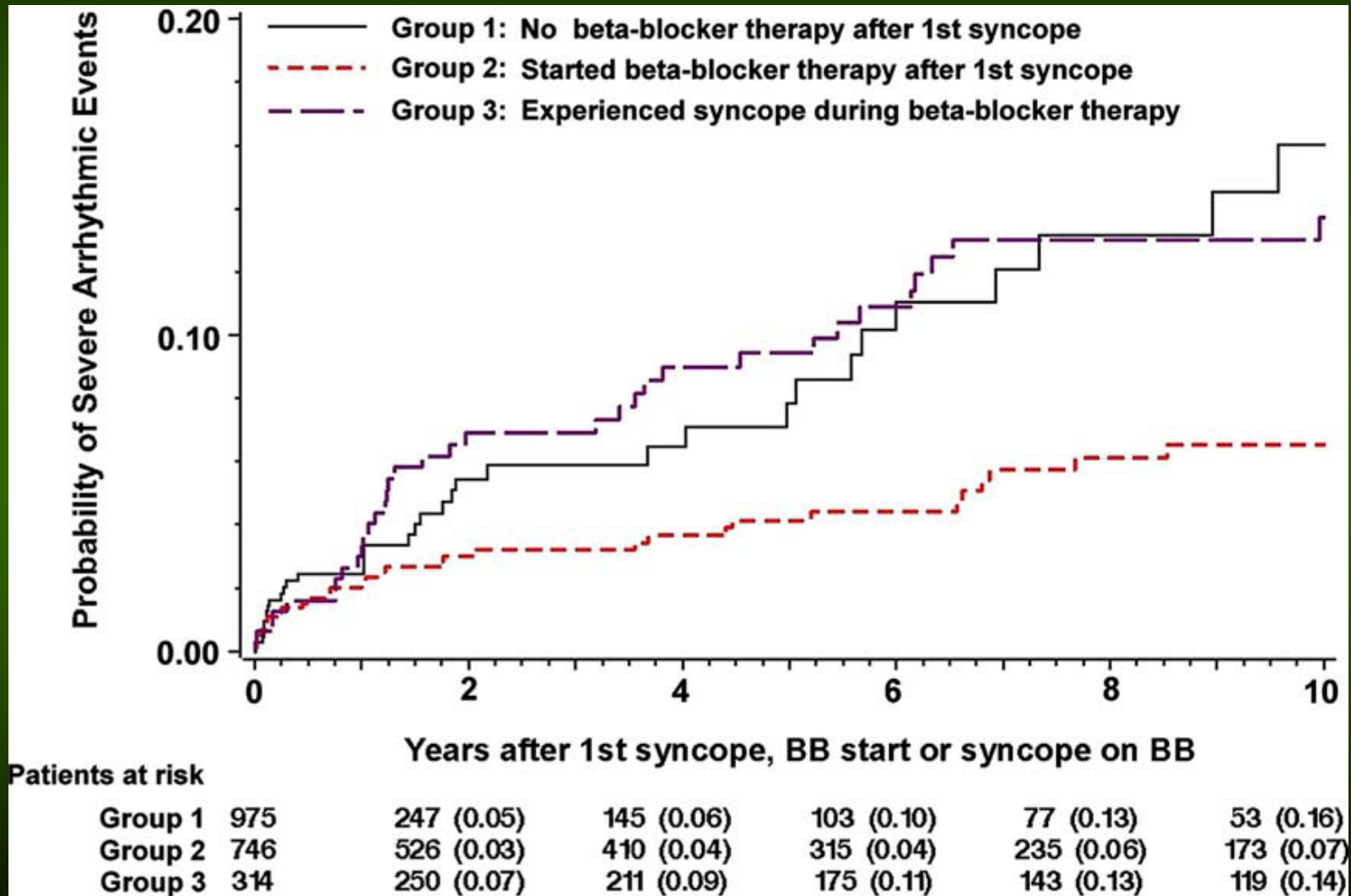
Rochester, New York

| | |
|--------------------|---|
| Objectives | The aim of this study was to identify risk factors for fatal arrhythmias in long QT syndrome (LQTS) patients presenting with syncope. |
| Background | Syncope is highly predictive for future fatal arrhythmias in the LQTS. However, there are no data regarding risk stratification and management strategies in the high-risk subset of LQTS patients presenting with syncope. |
| Methods | A total of 1,059 LQTS patients with a corrected QT interval ≥ 450 ms presenting with syncope as a first symptom were drawn from the International LQTS Registry. Cox proportional hazards regression was used to identify risk factors for a severe arrhythmic events comprising aborted cardiac arrest, appropriate implantable cardioverter-defibrillator therapy, and sudden cardiac death. |
| Results | The lowest risk was found in patients with only 1 syncopal episode occurring before the start of beta-blocker therapy. In contrast, patients experiencing syncope after starting beta-blocker therapy had a 3.6-fold increase in the risk of severe arrhythmic events ($p < 0.001$) relative to this low-risk group and displayed a risk of severe arrhythmic events similar to that of patients not treated with beta-blockers. Multiple syncopal episodes occurring before initiation of beta-blocker therapy were associated with an intermediate risk (hazard ratio: 1.8, $p < 0.001$). The risk of syncope during beta-blocker therapy is high during childhood in both sexes but is higher in women than in men (hazard ratio: 2.3, $p < 0.001$). |
| Conclusions | Patients with syncope during beta-blocker therapy are at high risk of life-threatening events, and implantable cardioverter-defibrillator therapy should be considered in these patients. The risk of beta-blocker failure is highest in young children and in women. (J Am Coll Cardiol 2010;55:783–8) © 2010 by the American College of Cardiology Foundation |

“Patients with syncope during beta-blocker therapy are at high risk of life-threatening events, and implantable cardioverter-defibrillator therapy should be considered in these patients. The risk of beta-blocker failure is highest in young children and in women”.

“Síndromes genéticos: QT largo”

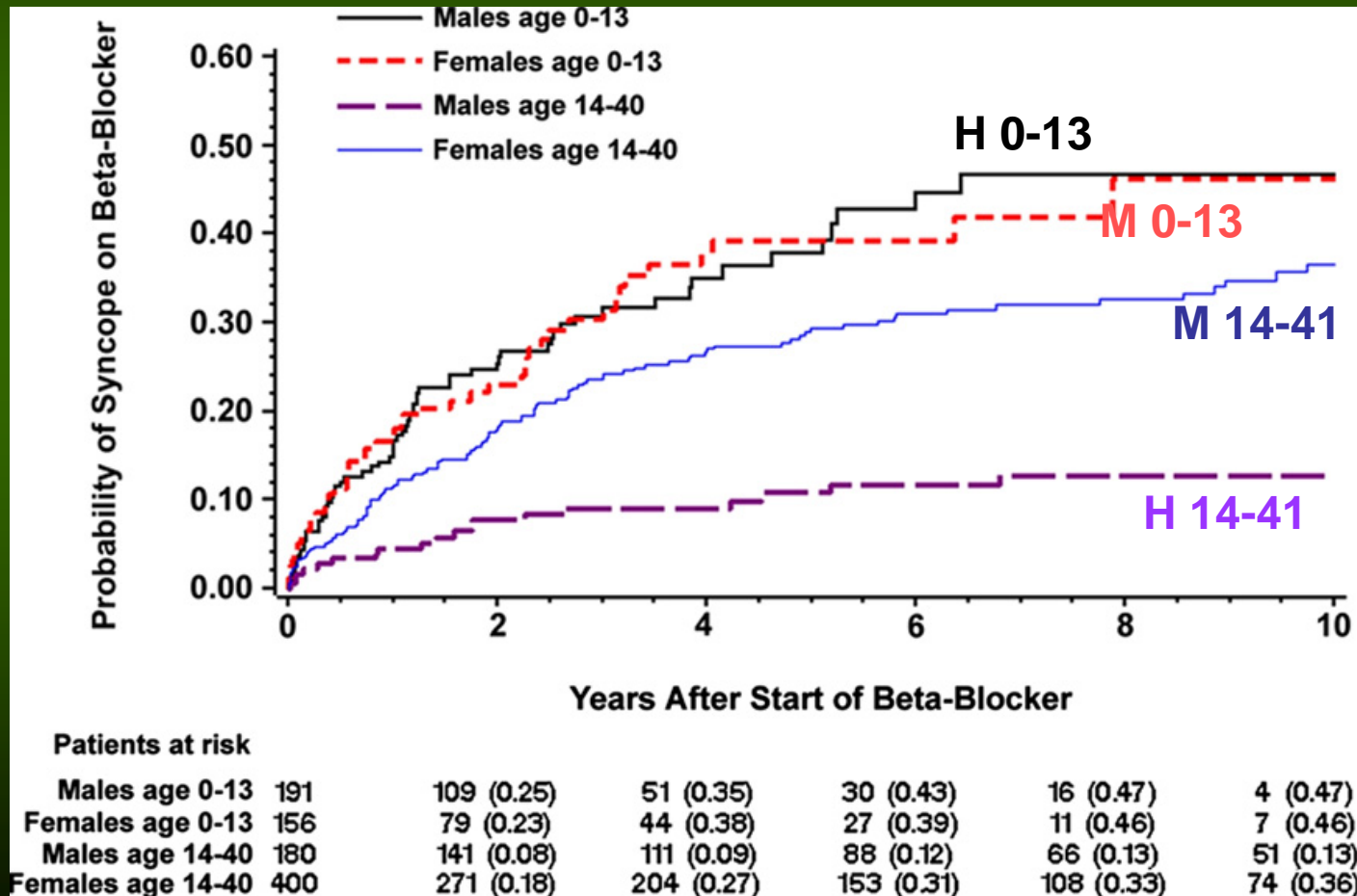
Estratificación del riesgo: síncope



“Síndromes genéticos: QT largo”

Estratificación del riesgo: síncope

Risk of the First Syncope Event on Beta-Blocker Treatment From the Start of Beta-Blocker Treatment or From the 14th Birthday



“Síndromes genéticos: QT largo”

Estratificación del riesgo: edad (adolesc)

Figure. Cox Model–Based Time to First Aborted Cardiac Arrest or Sudden Cardiac Arrest Between Ages 10 and 20 Years for Females with Long-QT Syndrome

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 |

Even the *Between the ages of 10 and 12 years, the risk of aborted cardiac arrest or sudden cardiac death is significantly higher in males than in females. †β-Blocker therapy was significantly associated with a lower risk of aborted cardiac arrest or sudden cardiac death in females with long-QT syndrome.

on the sexes. the past 2 years.

| Sinc | < 2 años | >2 años |
|------|----------|---------|
| 1 | 11.7 | 2.7 |
| > 1 | 18 | 5.8 |



“Síndromes genéticos: QT largo”

Estratificación del riesgo: edad

Long-QT Syndrome After Age 40

Ilan Goldenberg, MD; Arthur J. Moss, MD; James Bradley, MS; Slava Polonsky, MS; Derick R. Peterson, PhD; Scott McNitt, MS; Wojciech Zareba, MD, PhD; Mark L. Andrews, BBA; Jennifer L. Robinson, MS; Michael J. Ackerman, MD, PhD; Jesaia Benhorin, MD; Elizabeth S. Kaufman, MD; Emanuela H. Locati, 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

Background—Previous studies that assessed the risk of life-threatening cardiac events in patients with congenital long-QT syndrome (LQTS) have focused mainly on the first 4 decades of life, whereas the clinical course of this inherited cardiac disorder in the older population has not been studied.

Methods and Results—The risk of aborted cardiac arrest or death from age 41 through 75 years was assessed in 2759 subjects from the International LQTS Registry, categorized into electrocardiographically affected (corrected QT interval [QTc] ≥ 470 ms), borderline (QTc 440 to 469 ms), and unaffected (QTc < 440 ms) subgroups. The affected versus unaffected adjusted hazard ratio for aborted cardiac arrest or death was 2.65 ($P < 0.001$) in the age range of 41 to 60 years and 1.23 ($P = 0.31$) in the age range of 61 to 75 years. The clinical course of study subjects displayed gender differences: Affected LQTS women experienced a significantly higher cumulative event rate (26%) than borderline (16%) and unaffected (12%) women ($P = 0.001$), whereas event rates were similar among the 3 respective subgroups of men (29%, 26%, and 27%; $P = 0.16$). Recent syncope (< 2 years in the past) was the predominant risk factor in affected subjects (hazard ratio 9.92, $P < 0.001$), and the LQT3 genotype was identified as the most powerful predictor of outcome in a subset of 871 study subjects who were genetically tested for a known LQTS mutation (hazard ratio 4.76, $P = 0.02$).

Conclusions—LQTS subjects maintain a high risk for life-threatening cardiac events after age 40 years. The phenotypic expression of affected subjects is influenced by age-specific factors related to gender, clinical history, and the LQTS genotype. (*Circulation*. 2008;117:2192-2201.)



“Síndromes genéticos: QT largo”

Estratificación del riesgo

2759 (779) Pctes. 41-75 años

...“ At present, ICD implantation should be considered as a primary prevention measure in high-risk LQTS subjects who remain symptomatic despite -blocker therapy and as a secondary prevention measure in LQTS subjects who experience ACA ...”

“Síndromes genéticos: QT largo”

Tratamiento

Association of Long QT Syndrome Loci and Cardiac Events Among Patients Treated With β -Blockers

N° = 355

Silvia G. Priori, MD, PhD

Carlo Napolitano, MD, PhD

Peter J. Schwartz, MD

Massimiliano Grillo, MD

Raffaella Bloise, MD

Elena Ronchetti, PhD

Cinzia Moncalvo, MD

Chiara Tulipani, MD

Alessia Veia, MD

Georgia Bottelli, BS

Janni Nastoli, BS

Context Data on the efficacy of β -blockers in the 3 most common genetic long QT syndrome (LQTS) loci are limited.

Objective To describe and assess outcome in a large systematically genotyped population of β -blocker-treated LQTS patients.

Design, Setting, and Patients Consecutive LQTS-genotyped patients (n=335) in Italy treated with β -blockers for an average of 5 years.

Main Outcome Measures Cardiac events (syncope, ventricular tachycardia/torsades de pointes, cardiac arrest, and sudden cardiac death) while patients received β -blocker therapy according to genotype.

Results Cardiac events among patients receiving β -blocker therapy occurred in 19 of 187 (10%) LQ1 patients, 27 of 120 (23%) LQ2 patients, and 9 of 28 (32%) LQ3 patients ($P < .001$). The risk of cardiac events was higher among LQ2 (adjusted relative risk, 2.81; 95% confidence interval [CI], 1.50-5.27; $P = .001$) and LQ3 (adjusted relative risk, 4.00; 95% CI, 2.45-8.03; $P < .001$) patients than among LQ1 patients, suggesting inadequate protection from β -blocker therapy. Other important predictors of risk were a QT interval corrected for heart rate that was more than 500 ms in patients receiving therapy (adjusted relative risk, 2.01; 95% CI, 1.16-3.51; $P = .01$) and occurrence of a first cardiac event before the age of 7 years (adjusted RR, 4.34; 95% CI, 2.35-8.03; $P < .001$).

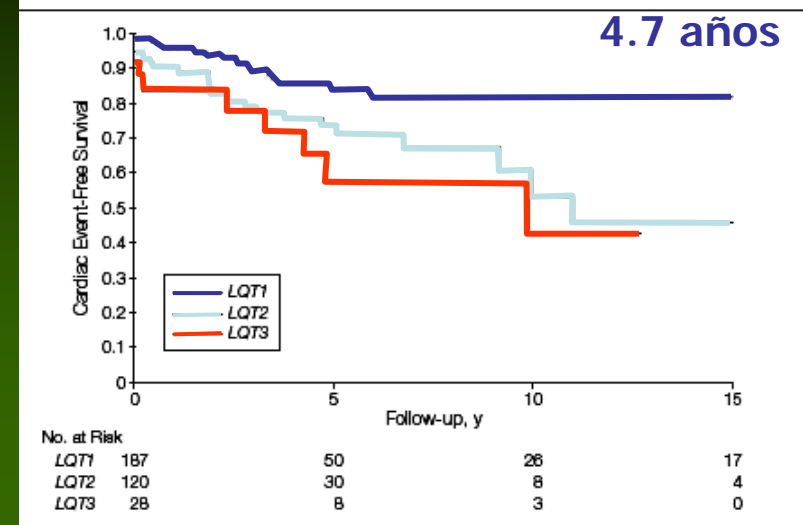
Conclusion Among patients with genetic LQTS treated with β -blockers, there is a high rate of cardiac events, particularly among patients with LQ2 and LQ3 genotypes.

JAMA. 2004;292:1341-1344

www.jama.com

LONG QT SYNDROME (LQTS) IS A genetic disease characterized by prolonged ventricular repolarization, syncope, ventricular arrhythmias, and sudden death,¹⁻³ often precipitated by emotion or exercise. Primarily according to nonrandomized trial

Kaplan-Meier Analysis of Event-Free Survival



Kaplan-Meier analysis of cumulative cardiac event-free survival in genotyped long QT syndrome patients receiving β -blockers according to the genetic variant of the disease (log-rank $P < .001$). The definition of events includes syncope, cardiac arrest, and sudden cardiac death. LQ1 indicates long QT syndrome type 1; LQ2, long QT syndrome type 2; LQ3, long QT syndrome type 3.

| | LQ1 | LQ2 | LQ3 |
|------------|-----|-----|-----|
| Event | 10% | 23% | 32% |
| CA Pre Tx | 2.1 | 8.3 | 18 |
| CA Post Tx | 1.1 | 6.6 | 14 |

Caso 1 J.A.

**Mujer de 67 años, HTA. DBT tipo 2
sin antecedentes de angor**

**Desde 1990 recibe Amiodarona por FA.
En 1998 CVE por FA.**

El 09/05/01 palpitaciones, disnea y síncope.

El 10/05/01: ingresa a nuestro centro,

ECG

Caso 1 J.A.

INTERNACION

ECG: Torsión de punta.

Durante la internación: Recurrentes episodios de Torsión de punta.

Presentó 3 episodios de FA de alta respuesta con descompensación, que requirieron CVE.

?

**Se suspendió amiodarona y se implantó
MCP transitorio.**

- **Laboratorio: Na 140, K 3.0, Mg 2.71, Ca 6.7, Troponina T < 0.01. CPK 55, CK MB (12/21).**
- **Eco 2D: AO 37, AI 55, VIDD 46, S 12, PP 11, Fey 64%, motilidad parietal normal; cavidades derechas normales.**
- **Cinecoronariografía: Arteria Coronarias Normales, Función Sistólica conservada, IM leve-moderada; Presión Fin Diástole: 13 mmHg.**

Caso 1 J.A.

El 23/05/01 se implantó marcapasos definitivo VVIR y se realizó ablación del nodo AV. (FA alta respuesta).

Se programó a 80 lpm frecuencia mínima, y se agregó Atenolol 50 mgrs.

En el seguimiento 12-07-01 “síncope”

Ya suspendimos amio, ablacionamos el nodo, implantamos MCP, tiene BB y sigue con síncope y TP.

Que hacer???????

Modificar la programación del marcapasos?

Modificar la terapéutica antiarrítmica?

Implantar un CDI?

Otro.

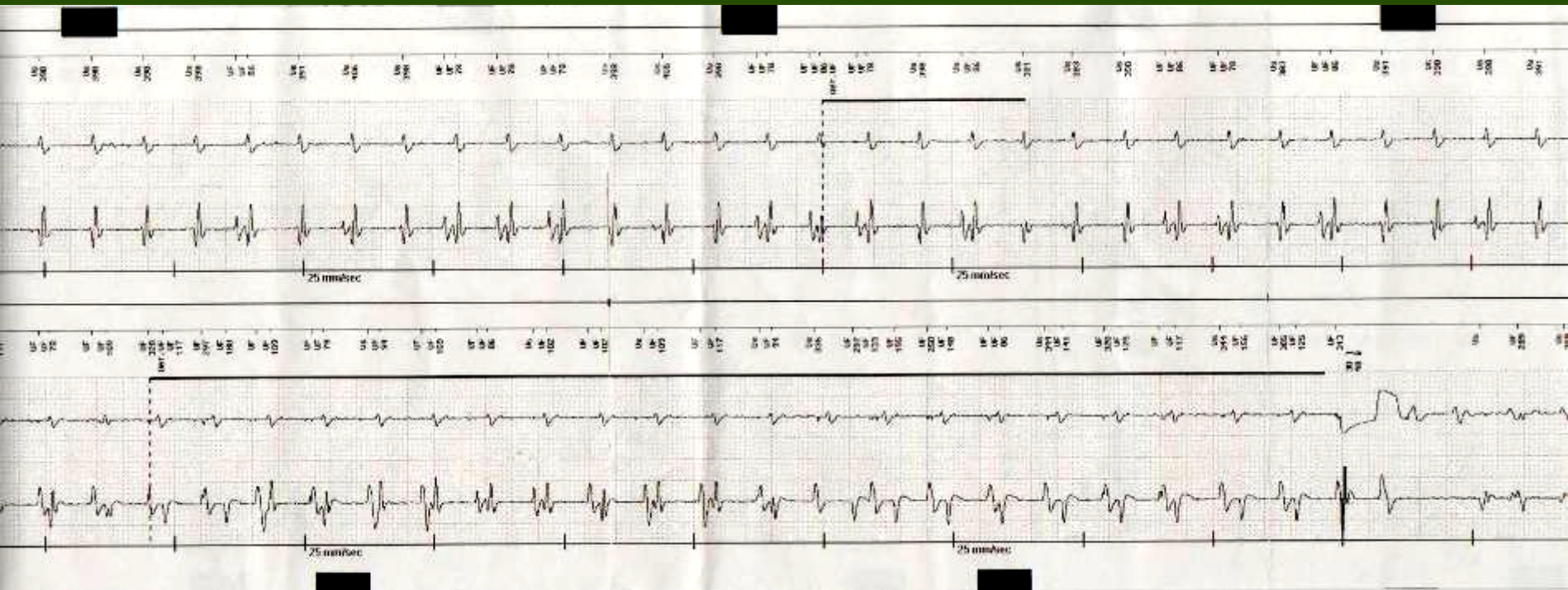
EI 31/08/01 se implanta CDI.

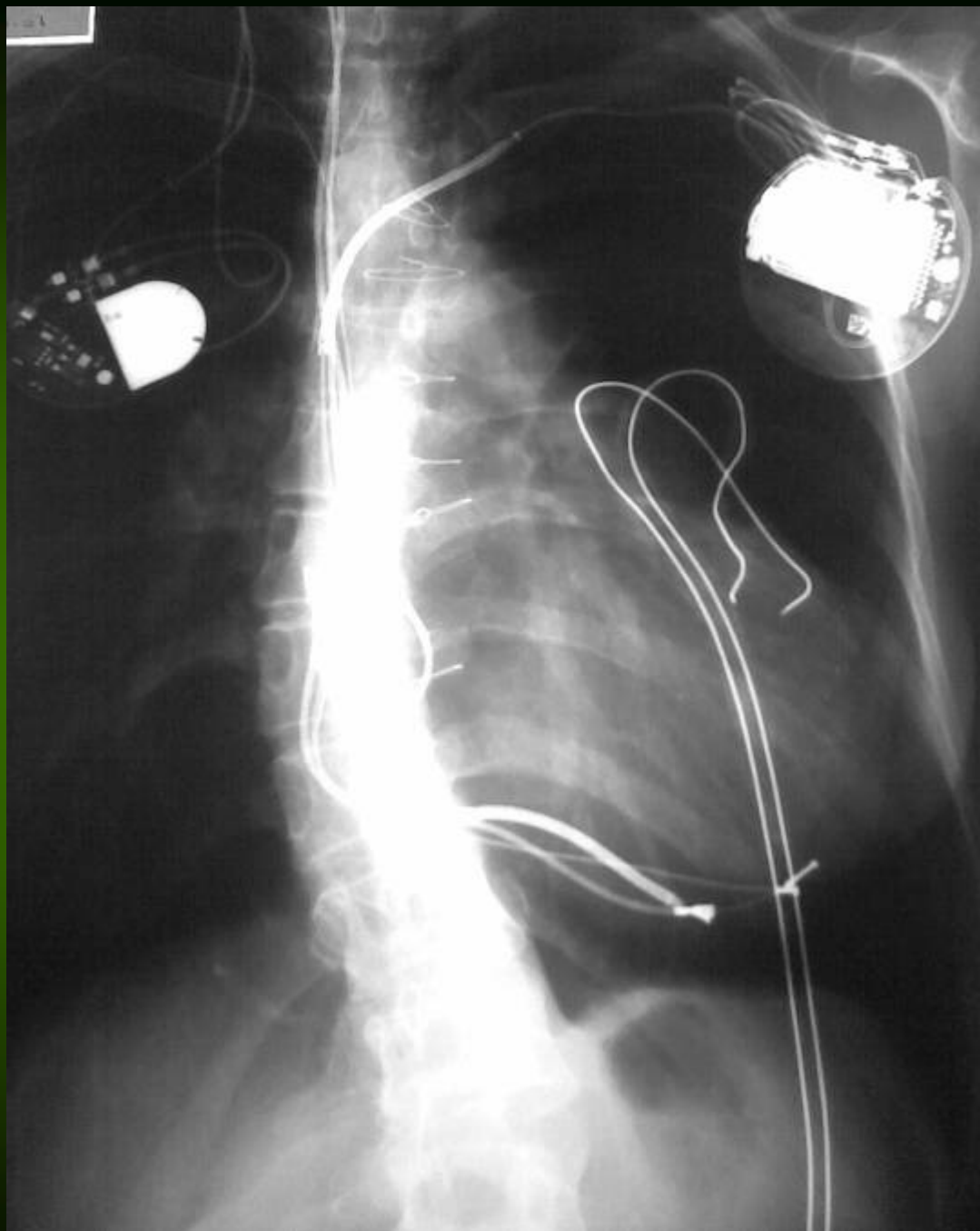
**EI 11/09/01 descarga apropiada
por torsión de
punta, con presíncope.**

**Al mes del implante, internación en su
ciudad
por IC, le suspendieron el atenolol.
Días después tuvo 6 descargas apropiadas
en 3-4
días (todas por torsión de punta).**

Reingresa

**Se reprogramó el CDI, con criterio de
detección mas
"duro" para diagnosticar FV. (16/40).
Se indicó Bisoprolol**





“Síndromes genéticos: QT largo”

Tratamiento

ACC/AHA/ESC Practice Guidelines

ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death

A Report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to

Table 2. Guidelines for Management of the Long-QT Syndrome.*

| Recommendation | Level of Evidence† | Comment |
|--|--------------------|---|
| No participation in competitive sports | I | Includes patients with the diagnosis established by means of genetic testing only |
| Beta-blockers | I | For patients who have QTc-interval prolongation (>460 msec in women and >440 msec in men) |
| Implantable cardioverter–defibrillator | IIa | For patients with a normal QTc interval |
| | I | For survivors of cardiac arrest |
| | IIa | For patients with syncope while receiving beta-blockers |
| | IIb | For primary prevention in patients with characteristics that suggest high risk; these include LQT2, LQT3, and QTc interval >500 msec‡ |

de pointes, or cardiac arrest while receiving betablockers. (Level of Evidence: B)

2. Implantation of an ICD with the use of beta blockers may be considered for prophylaxis of SCD for patients in categories possibly associated with higher risk of cardiac arrest such as LQT2 and LQT3 and who have reasonable expectation of survival with a good functional status for more than 1 y. (Level of Evidence: B)

Muchas gracias !!!!