

PLACE

PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

ROMA

Centro Congressi
di Confindustria

Auditorium
della Tecnica

9^a Edizione

30 Settembre
1 Ottobre
2022



**Canalopatie e morte improvvisa:
Epidemiologia, stratificazione del rischio, terapia**

QT LUNGO

Prof.ssa Priori Silvia Giuliana, MD, PhD

University of Pavia

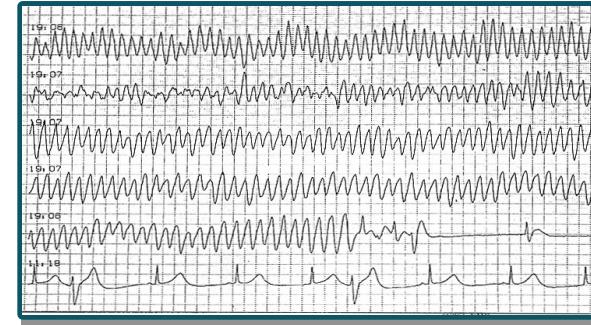
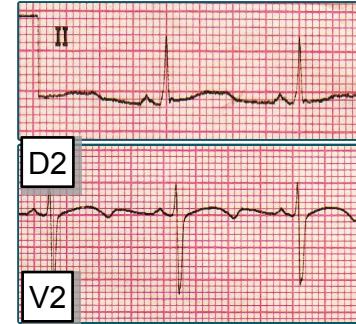
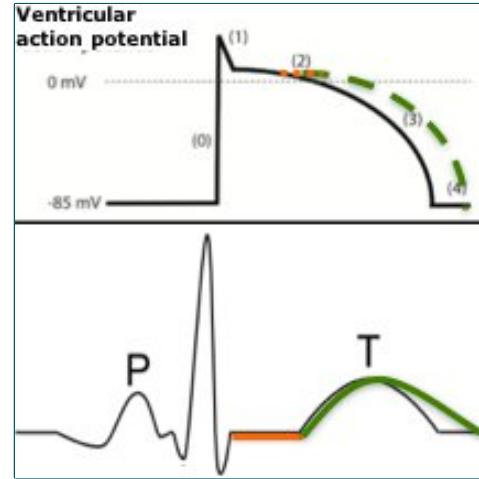
IRCCS ICS Maugeri, Pavia, Italy

Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain





Prolonged QT, Abnormal T wave Morphology, Polymorphic VT/TdP

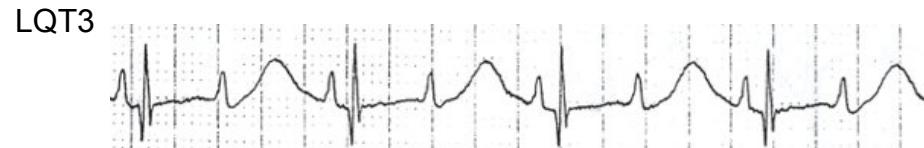
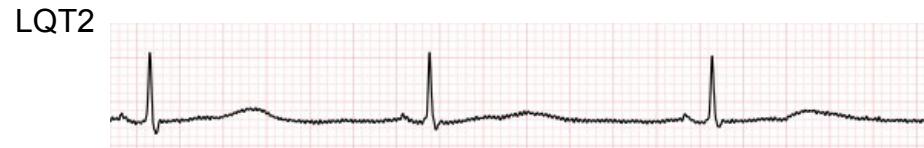


Self-limiting arrhythmia = Syncope



Long QT Syndrome: Epidemiology

- One of the **commonest** inherited arrhythmias syndromes with a prevalence:
1 in 2500



Zeppenfeld K et al.
2022 ESC Guidelines for the management of patients with ventricular
arrhythmias and the prevention of sudden cardiac death.
Eur Heart J. 2022 Aug 26;ehac262.

Diagnosis of LQTS



Recommendations	Class ^a	Level ^b
Diagnosis		
It is recommended that LQTS is diagnosed with either QTc ≥ 480 ms in repeated 12-lead ECGs with or without symptoms or LQTS diagnostic score >3 .	I	C
In patients with clinically diagnosed LQTS, genetic testing and genetic counselling are recommended.	I	C
It is recommended that LQTS is diagnosed in the presence of a pathogenic mutation, irrespective of the QT duration.	I	C
The LQTS diagnosis should be considered in the presence of a QTc ≥ 460 ms and <480 ms in repeated 12-lead ECGs in patients with an arrhythmic syncope in the absence of secondary causes for QT prolongation. 952,962,963	IIa	C

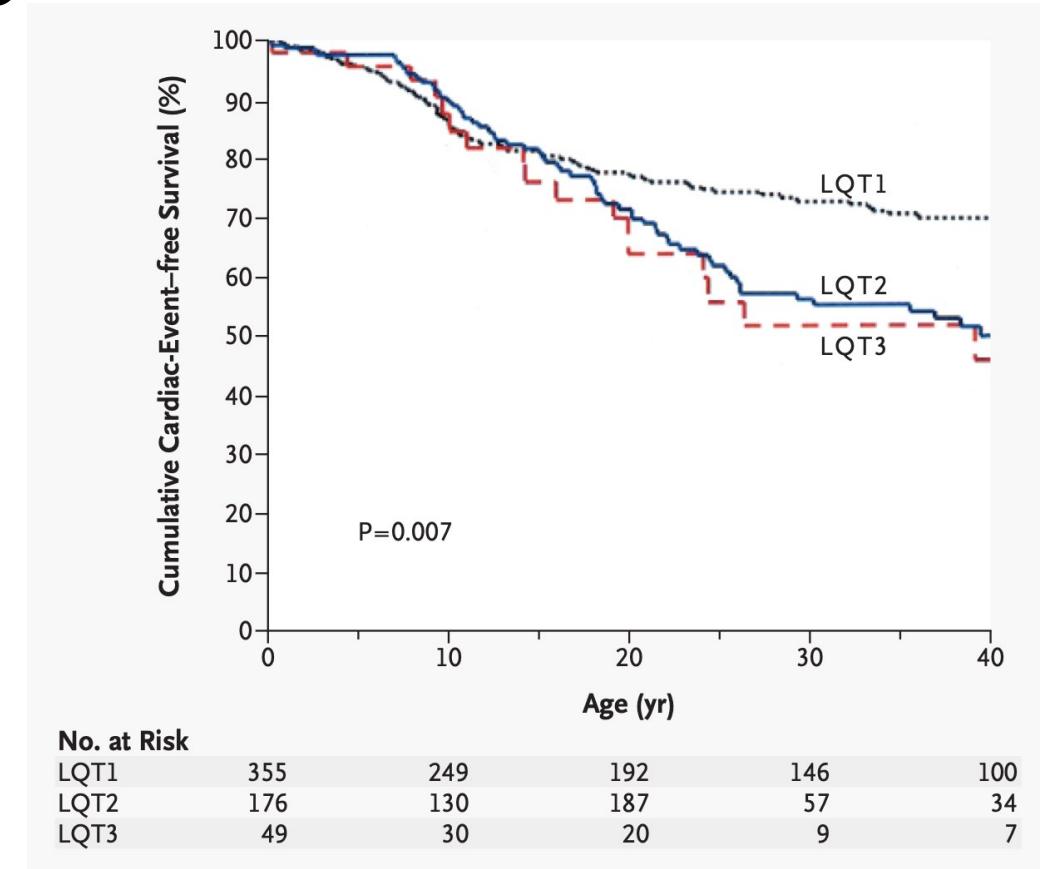
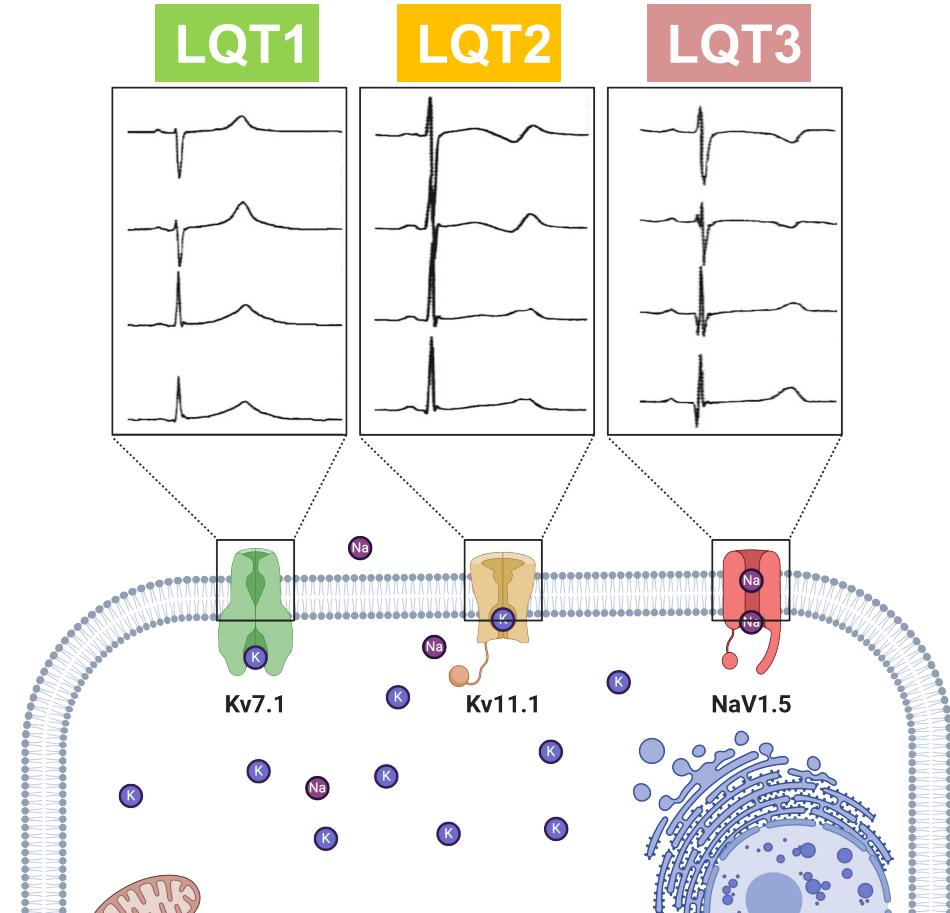
NEW!

“Overt LQTS”
 QTc ≥ 480 ms
 or
 QTc ≥ 460 ms with
 syncope

“Concealed LQTS”
 Mutation Carriers



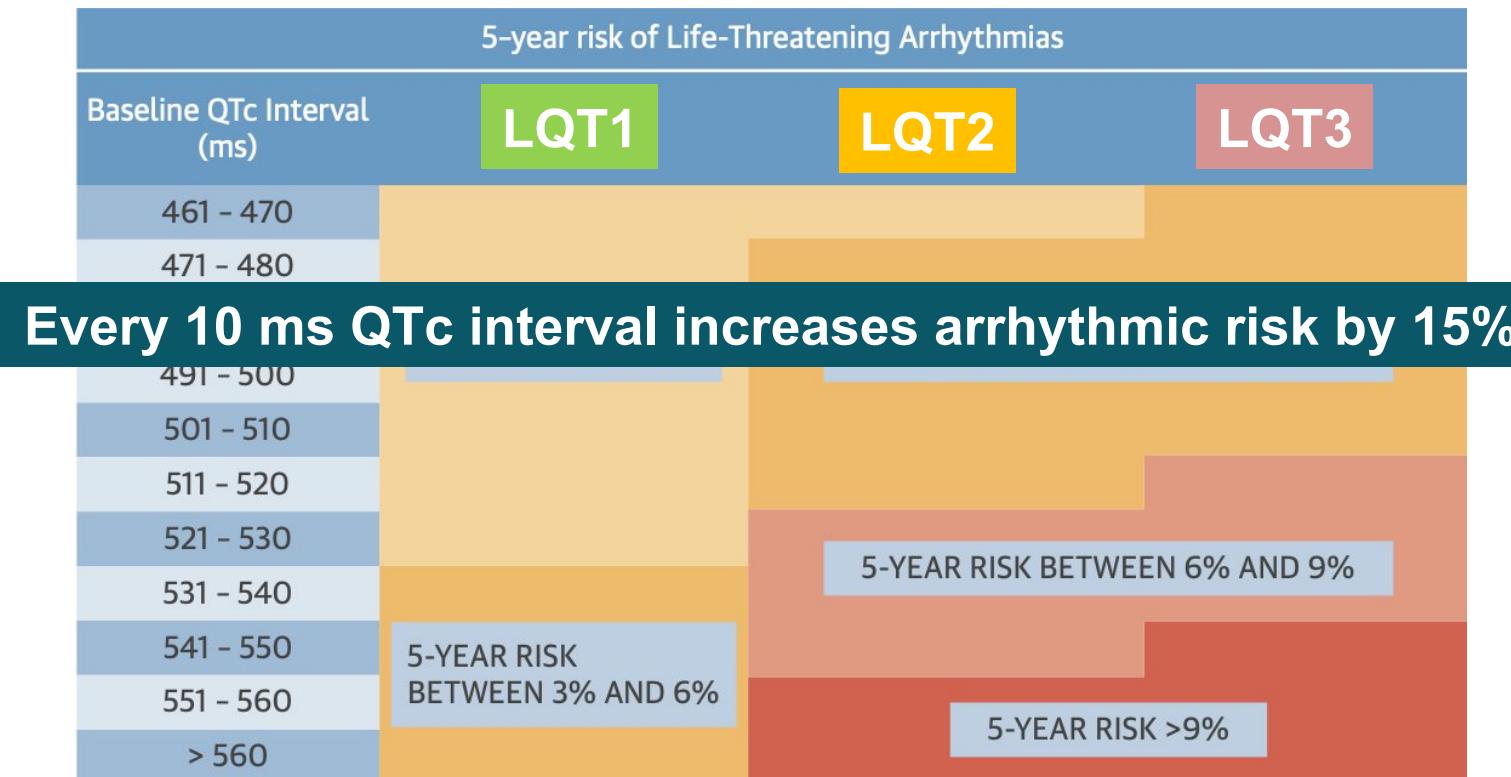
Role of Genotype in LQTS



Priori SG et al.
Risk stratification in the long-QT syndrome.
 N Engl J Med. 2003; 348(19):1866-74.



Genetics and the QT Interval: Strong Predictors of Outcome

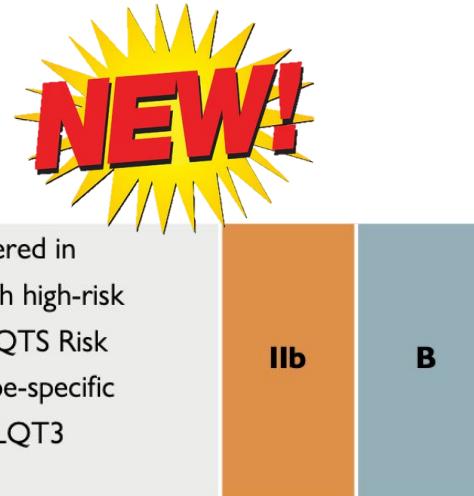


Mazzanti A et al.

Interplay Between Genetic Substrate, QTc Duration, and Arrhythmia Risk in Patients With Long QT Syndrome.
 J Am Coll Cardiol. 2018; 71(15):1663-1671.

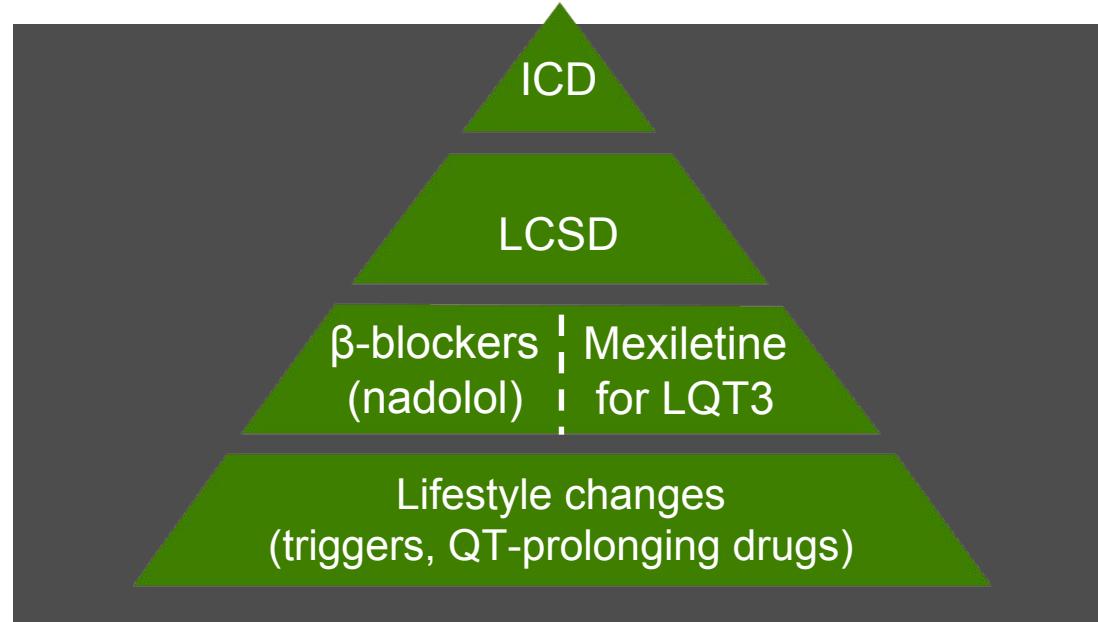
Zeppenfeld K et al.

2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.
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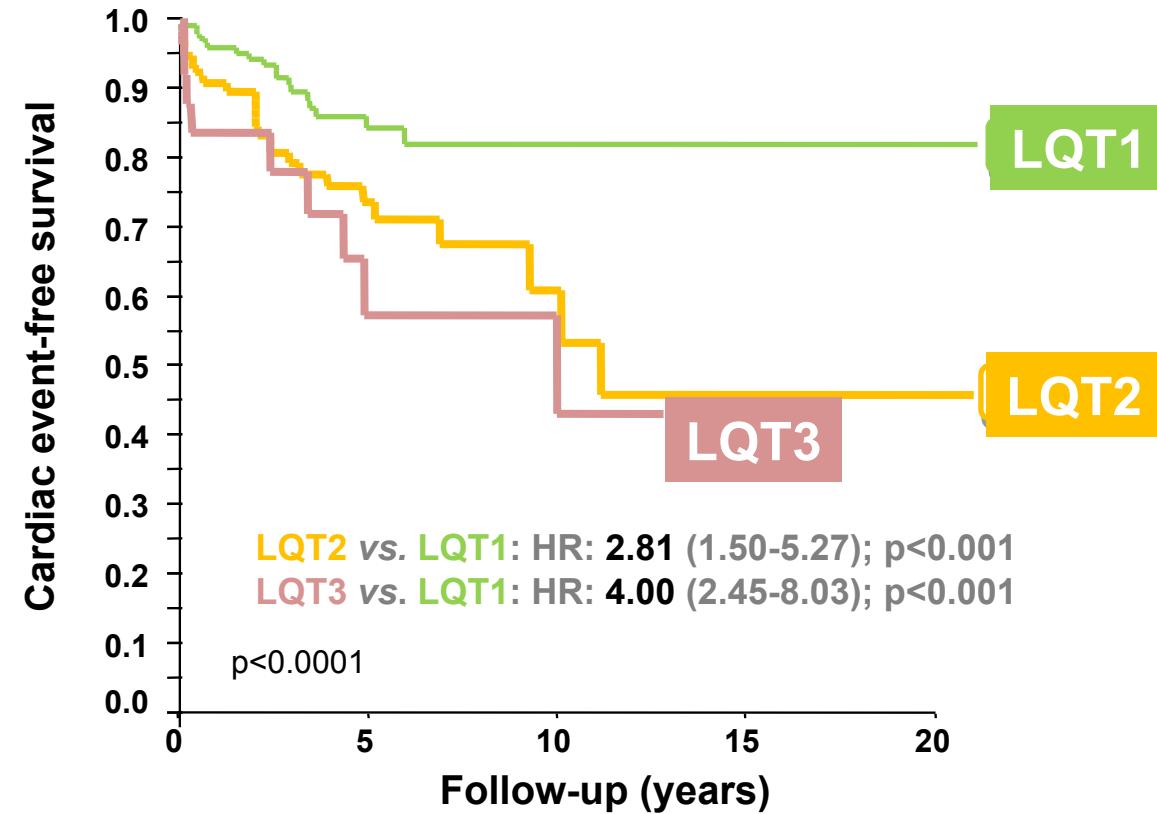
Remember! LQTS is a Treatable Disorder



Zeppenfeld K et al.
2022 ESC Guidelines for the management of patients with ventricular
arrhythmias and the prevention of sudden cardiac death.
Eur Heart J. 2022 Aug 26:ehac262.



Genotype-Specific Responses to BB Therapy



Priori SG et al.
Association of long QT syndrome loci and cardiac events among patients treated with beta-blockers.
JAMA. 2004; 292(11):1341-4.



Clinical Superiority of Nadolol

NEW!

Multivariable Cox Model

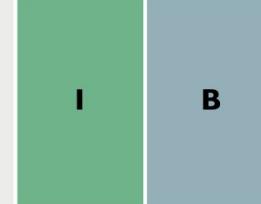
Effect of Drugs Independent of Genotype and QTc duration

Nadolol reduces risk by 62%

Propranolol reduces risk by 36% (n.s.)

	n	Events/PY	HR	95% CI	p Value
Sex					
Male	817	21/6,630	Ref.		
Female	893	47/7,694	1.70	1.00-2.88	0.048
LQTS genotype					
LQT1	963	15/7,913	Ref.		
LQT2	551	34/4,672	2.23	1.14-4.37	0.02
LQT3	196	19/1,739	4.00	1.89-8.47	< 0.001
Basal QTc, ms					
≤460	719	5/5,643	Ref.		
461-499	669	23/5,661	3.28	1.20-9.02	0.02
≥500	322	40/3,020	8.44	3.14-22.7	< 0.001
Syncope (time dependent)					
No	*	53/13,119	Ref.		
Yes		15/1,205	2.52	1.38-4.61	0.003
BB (time dependent)					
No BB		29/5,150	Ref.		
Nadolol		10/4,480	0.38	0.15-0.93	0.03
Propranolol		13/1,432	0.74	0.32-1.68	0.47
Selective		15/3,159	0.79	0.35-1.77	0.56
Episode of life-threatening arrhythmias before diagnosis					
No	1,639	54/13,635	Ref.		
Yes	71	14/689	2.56	1.24-5.29	0.01

Beta-blockers, ideally non-selective beta-blockers (nadolol or propranolol), are recommended in LQTS patients with documented QT interval prolongation, to reduce risk of arrhythmic events. [940,945,946](#)

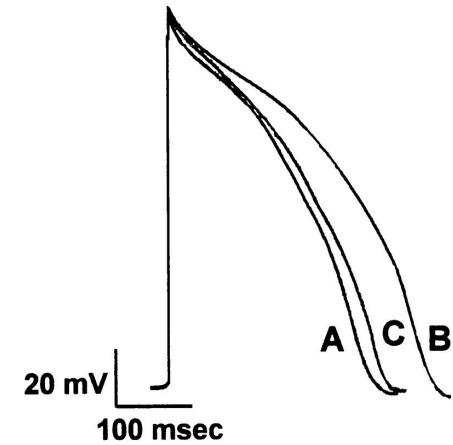
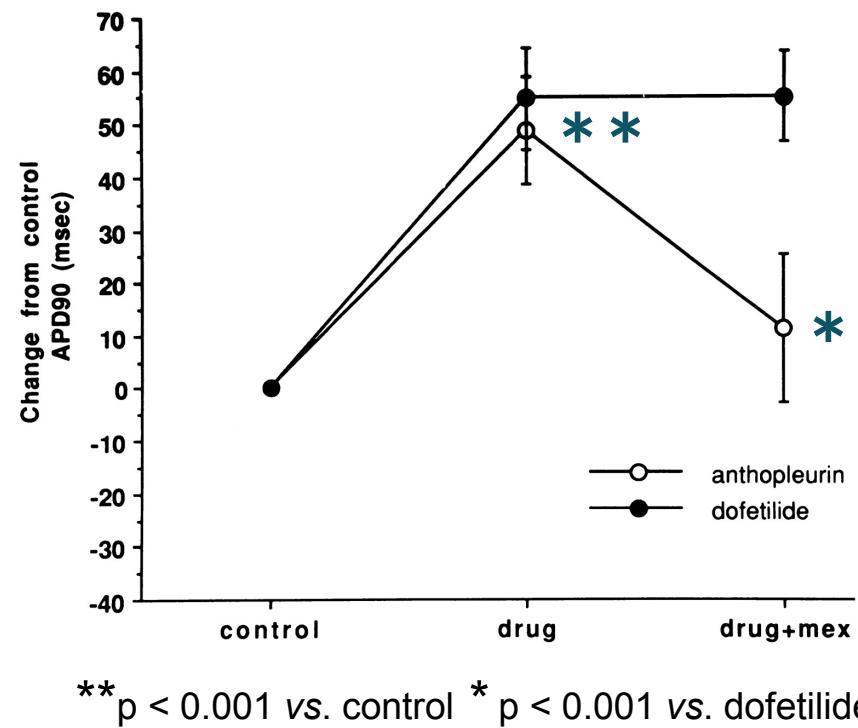


Zeppenfeld K et al. Eur Heart J. 2022 .



Mexiletine: From A Promise of a Gene-Specific Therapy...

LQT3 cellular model



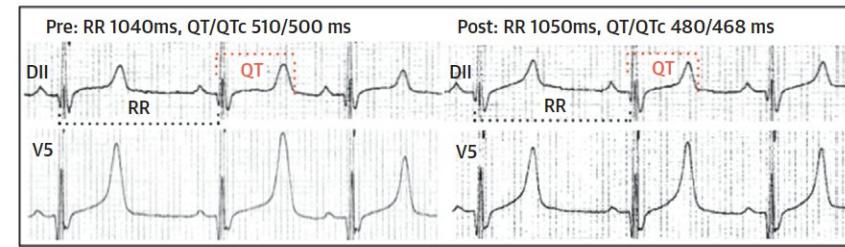
A: Control
 B: Anthopleurin
 C: Anthopleurin + Mexiletine

Priori SG et al.

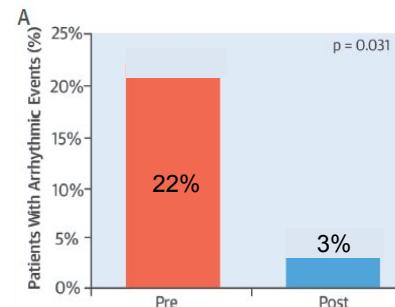
Differential response to Na⁺ channel blockade, beta-adrenergic stimulation, and rapid pacing in a cellular model mimicking the SCN5A and HERG defects present in the long-QT syndrome. Circ Res. 1996 Jun;78(6):1009-15.



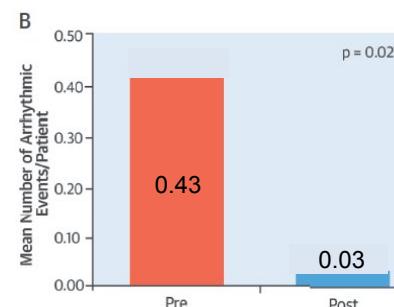
...To Clinical Evidence for Mexiletine use in LQT3...



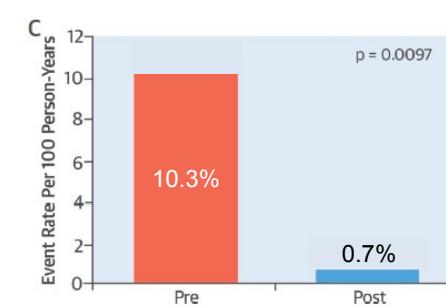
Shortens the QTc interval



Reduces the number of patients with events



Reduces the number of events per patient



Reduces the event rate

Mazzanti A et al.

Gene-Specific Therapy With Mexiletine Reduces Arrhythmic Events in Patients With Long QT Syndrome Type 3.
 J Am Coll Cardiol. 2016; 67(9): 1053–1058.



To a Class I Indication for Mexiletine in LQT3!

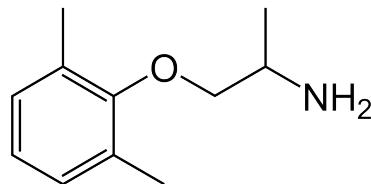


Mexiletine is indicated in LQT3 patients with a prolonged QT interval.⁹⁴⁸

I

C

Mexiletine



Zeppenfeld K et al.
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Eur Heart J. 2022 Aug 26;ehac262.



Left Cardiac Sympathetic Denervation

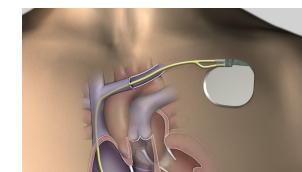


ICD contraindicated
or declined

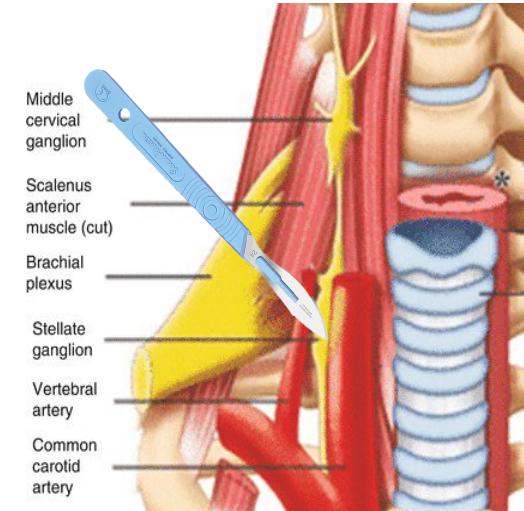
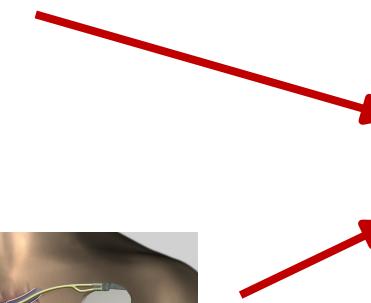
or



Beta-blockers and
Genotype-specific drugs



Multiple shocks



LCSD

Zeppenfeld K et al.
2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.
Eur Heart J. 2022 Aug 26;ehac262.

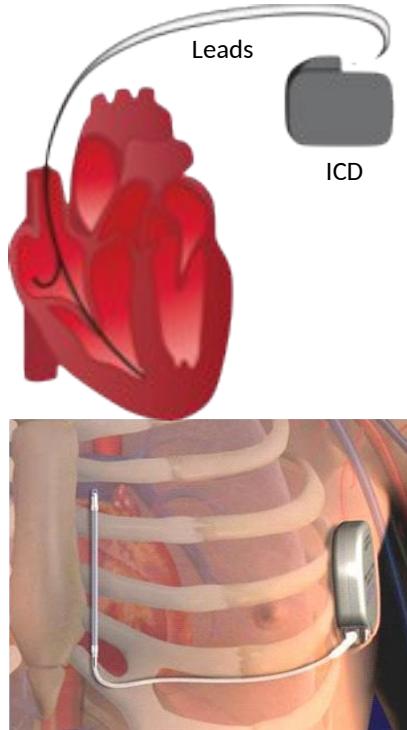
LCSD is indicated in patients with symptomatic^d LQTS when: (a) ICD therapy is contraindicated or declined; (b) patient is on beta-blockers and genotype-specific drugs with an ICD and experiences multiple shocks or syncope due to VA. [541,957–959](#)

I

C



Implantable Cardioverter Defibrillator



ICD implantation in addition to beta-blockers is recommended in LQTS patients with CA. 952,953,962,963	I	B
ICD implantation is recommended in patients with LQTS who are symptomatic ^d while receiving beta-blockers and genotype-specific therapies.	I	C
ICD implantation may be considered in asymptomatic LQTS patients with high-risk profile (according to the 1-2-3 LQTS Risk calculator) in addition to genotype-specific medical therapies (mexiletine in LQT3 patients). 82,940,947,948	IIb	B

NEW!

Zeppenfeld K et al.
2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.
Eur Heart J. 2022 Aug 26;ehac262.



Reduction in Mortality with ICD in Patients with LQTS

	No. of Deaths/Total N			Hazard Ratio (95% CI)	P Value
	All	No ICD	ICD		
All-cause mortality*	389/3,035	366/2,438	23/597	0.54 (0.34-0.86)	0.010
All-cause mortality censored at the age of 50 years	137/3,035	130/2,538	7/497	0.29 (0.14-0.61)	0.001
Sudden cardiac death	116/3,035	112/2,438	4/597	0.22 (0.09-0.55)	0.001

Wang M et al.
 Effectiveness of Implantable Cardioverter-Defibrillators to Reduce Mortality in Patients With Long QT Syndrome.
 J Am Coll Cardiol. 2021 Nov 23;78(21):2076-2088.



86% hazard reduction

Cardiac arrest



73% hazard reduction

Syncope on BB therapy



58% hazard reduction

Syncope while off BB with QTc ≥500 ms



THANK YOU FOR YOUR ATTENTION!

