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Prognostic role of syncope in patients with Long QT Syndrome

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Mannheim

ADVANCES IN CARDIAC ARRHYTHMIAS
and
GREAT INNOVATIONS IN CARDIOLOGY
XXVII GIORNATE CARDIOLOGICHE TORINESI

Turin
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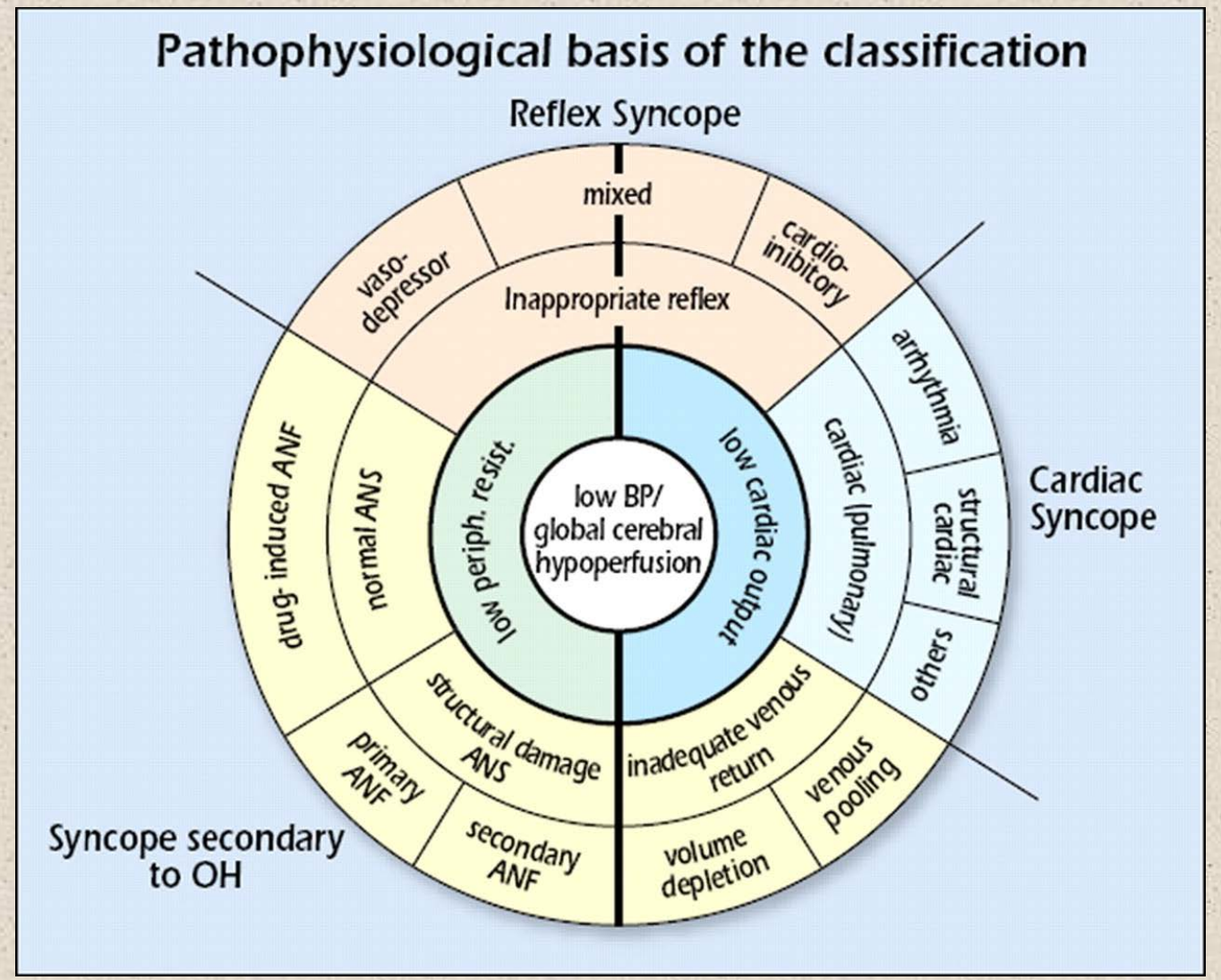
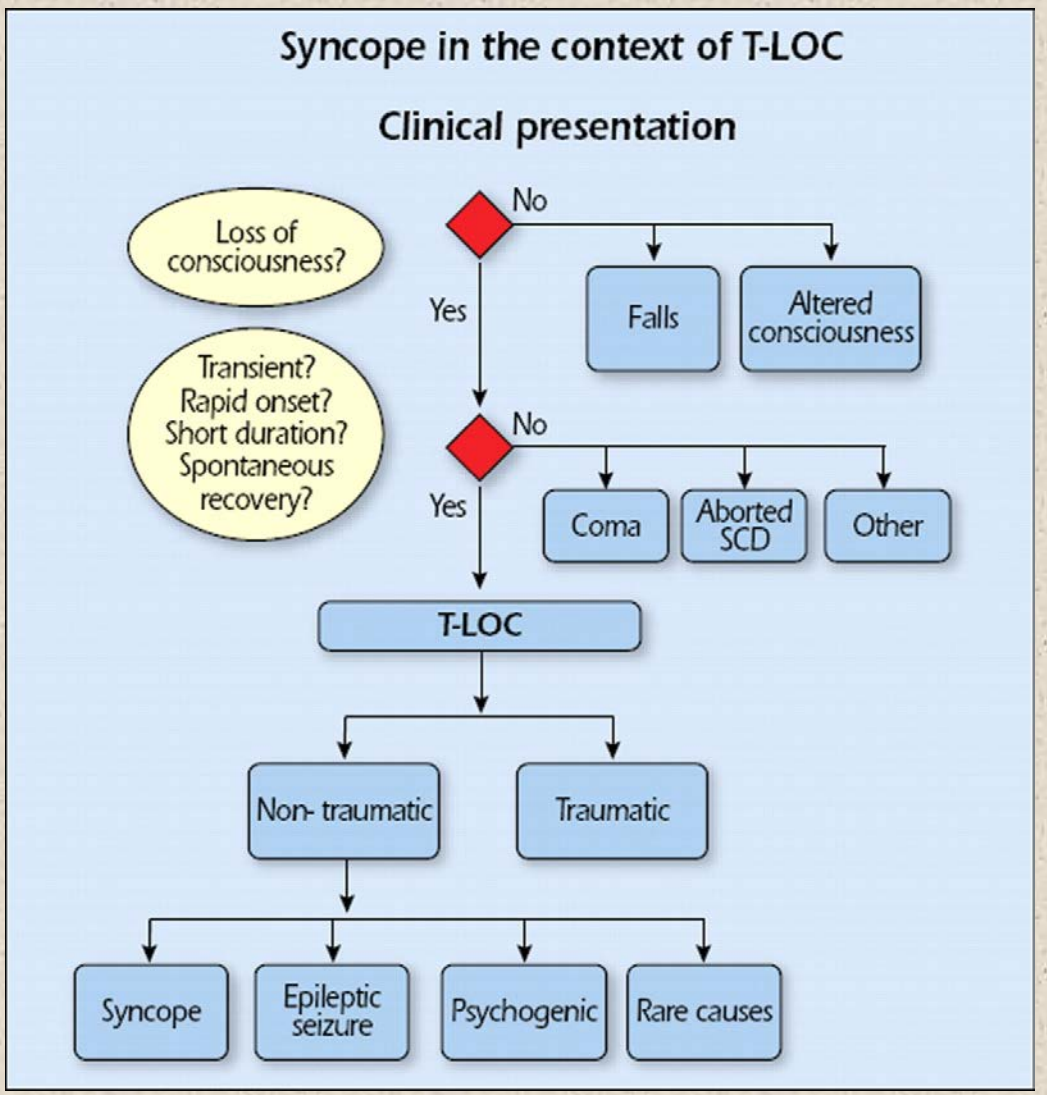
Prognostic role of syncope in patients with LQTS



Moya et al. Eur Heart J. 2009; 30: 2631-71

Prognostic role of syncope in patients with LQTS



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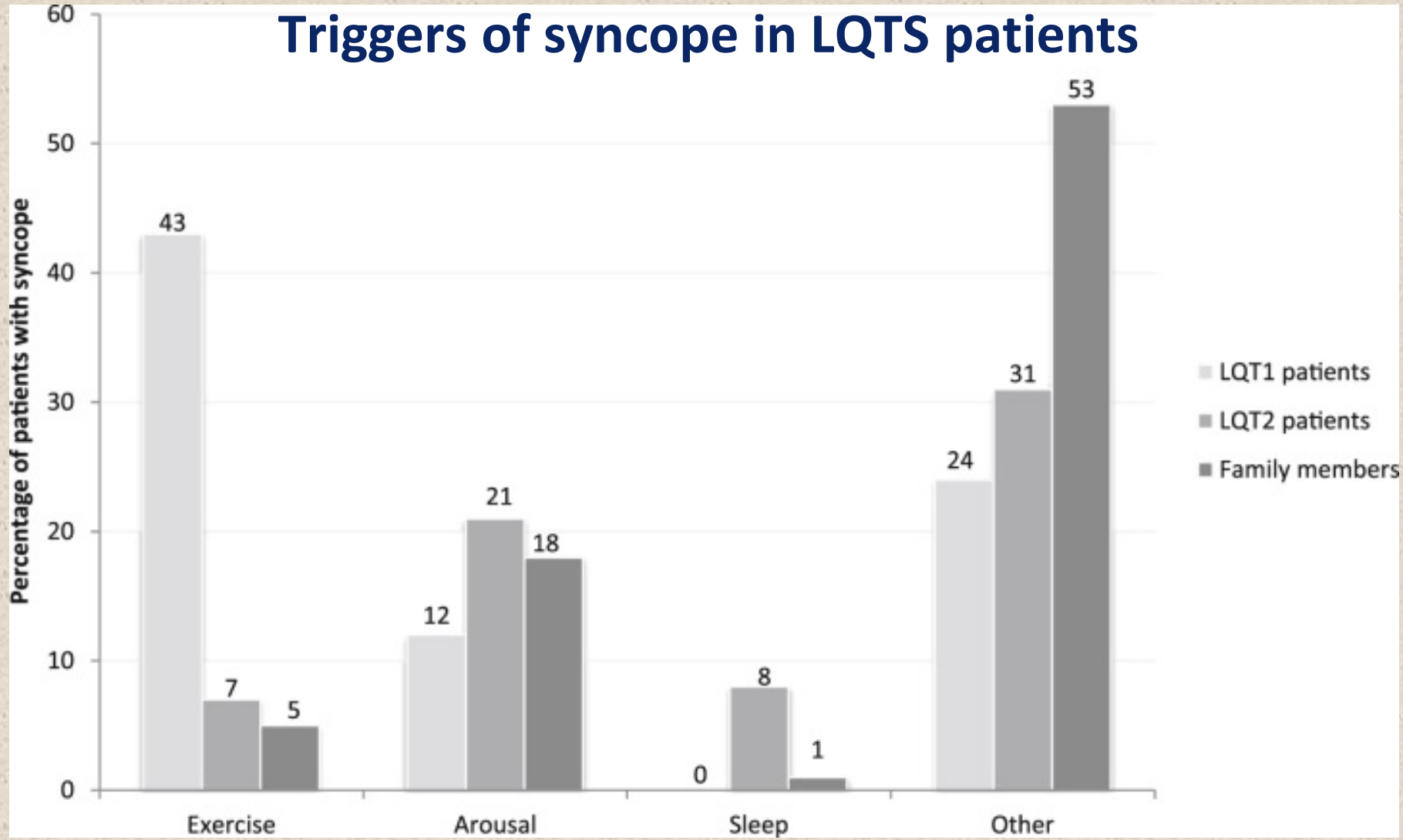

Olde Nordkamp et al. Am J Cardiol. 2014; 114: 1223-8

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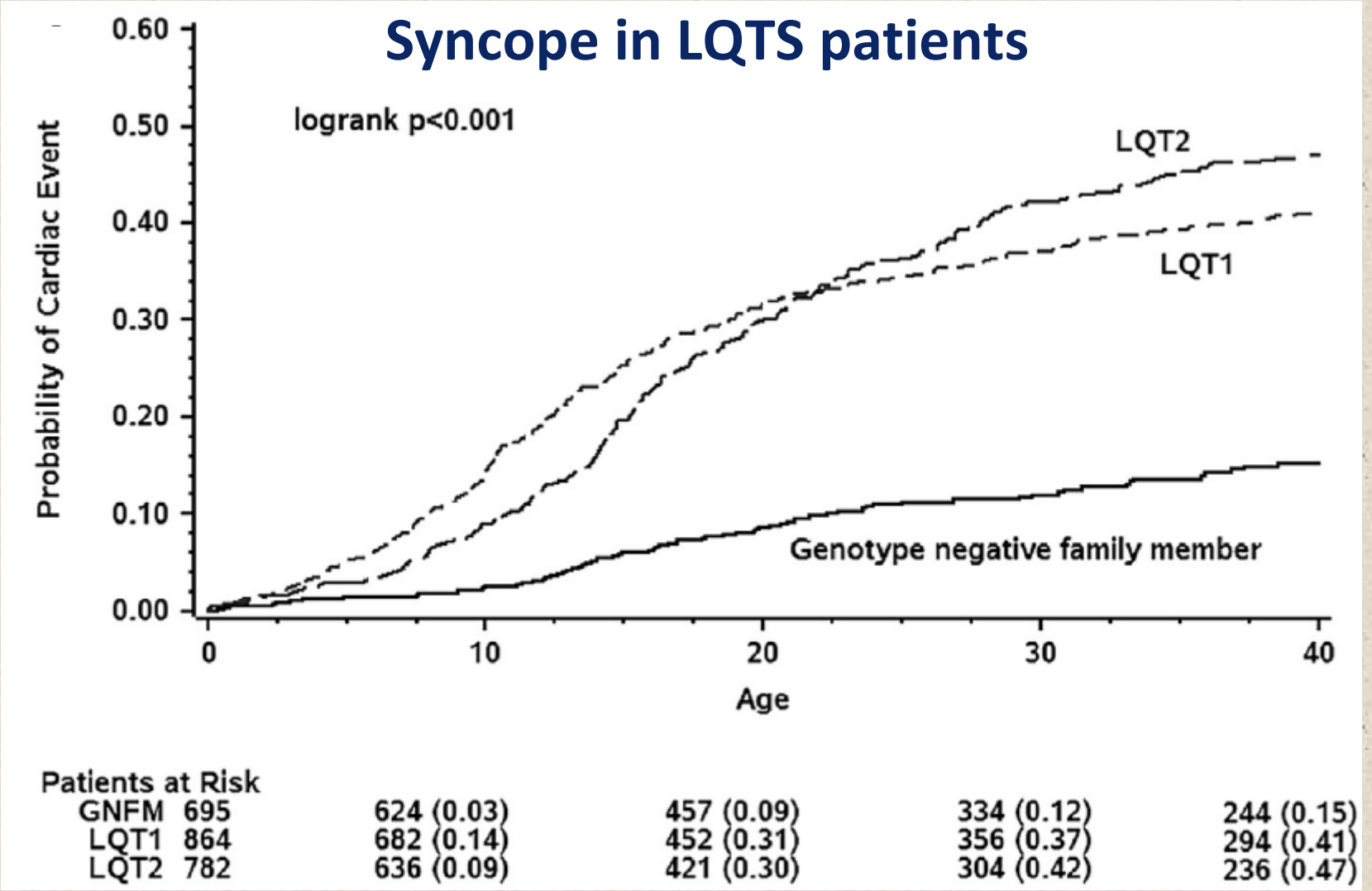

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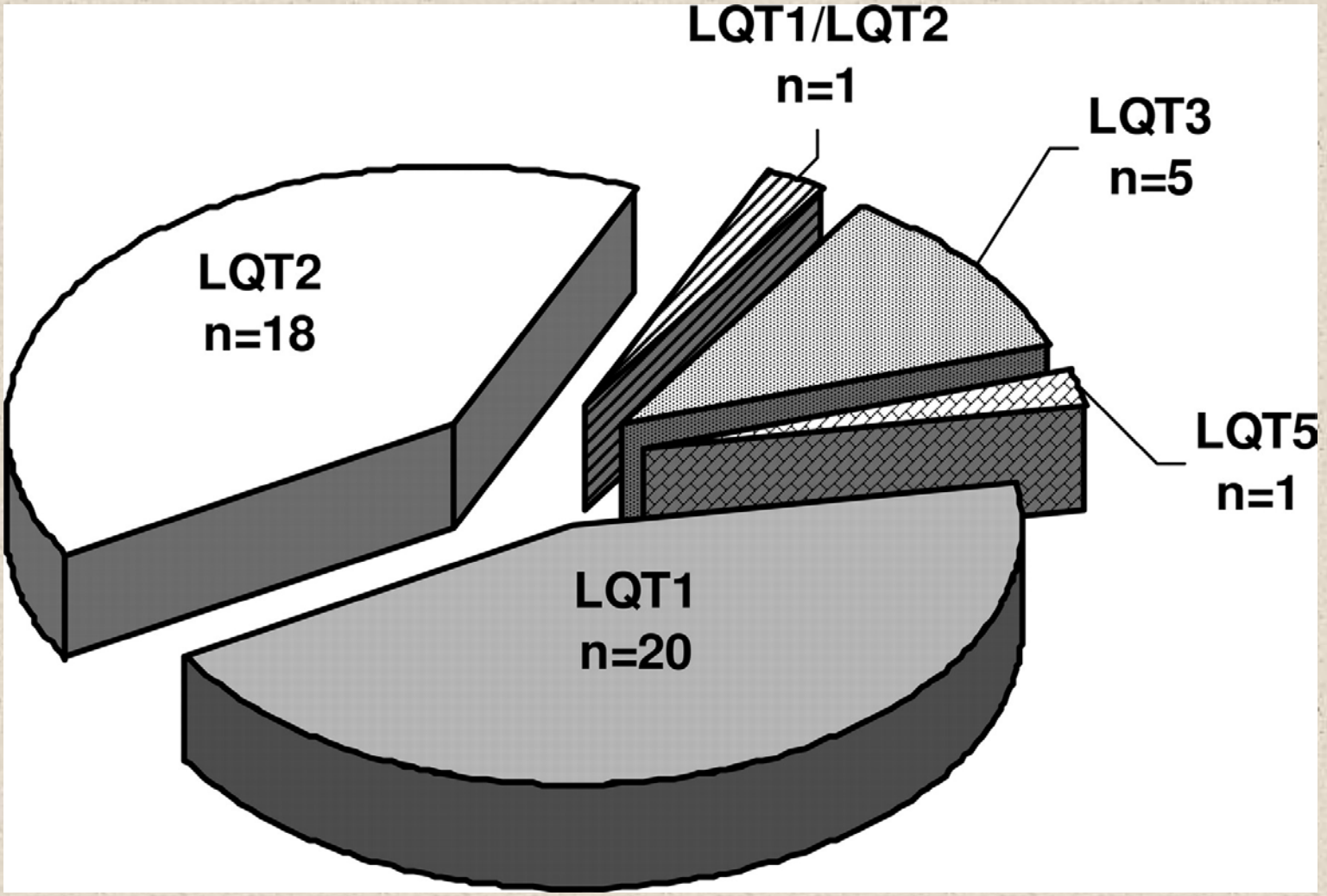
Prognostic role of syncope in patients with LQTS

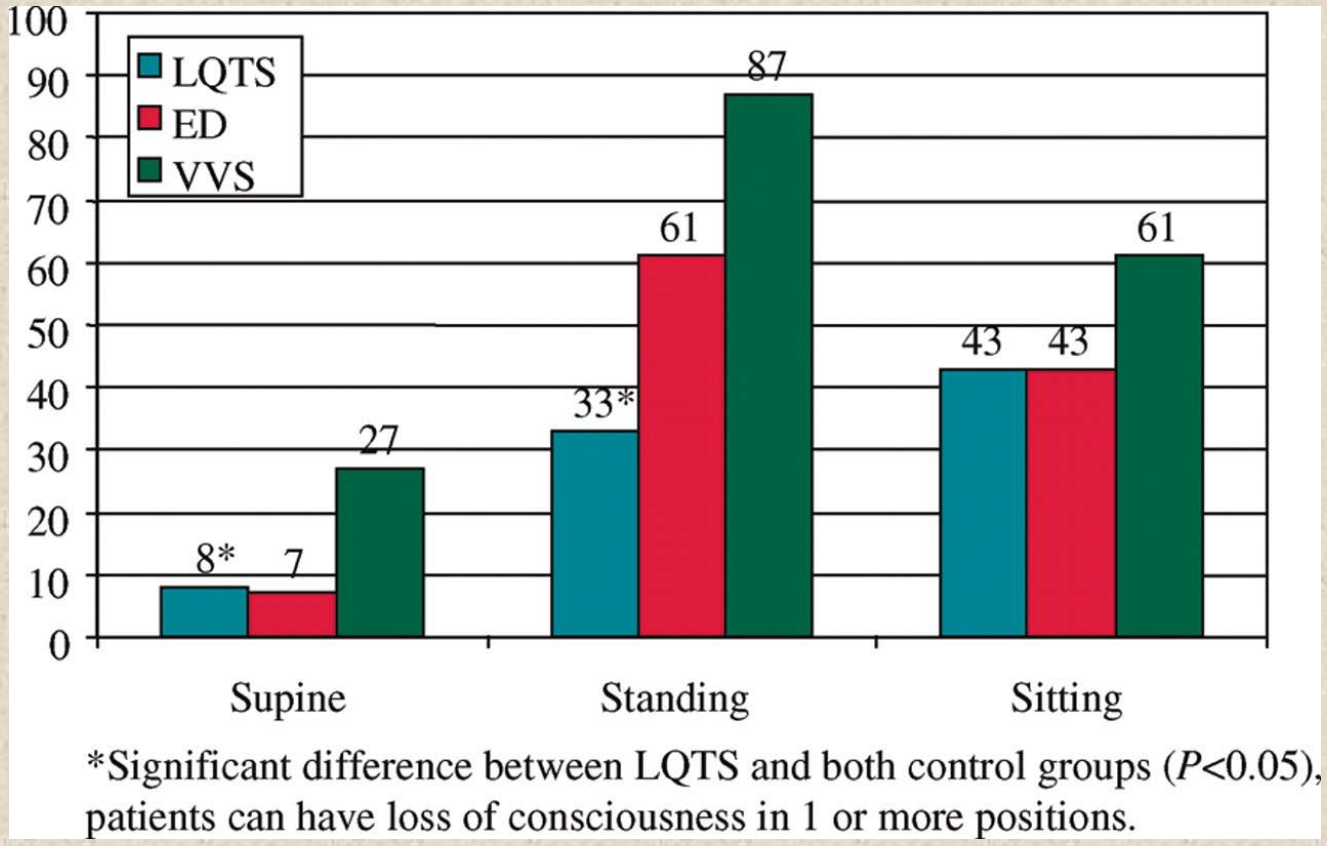
Distribution of LQTS genotypes



Taggart et al. Circulation 2007; 115: 2613-20

Prognostic role of syncope in patients with LQTS

Value of history-taking in syncope patients: in whom to suspect long QT syndrome?

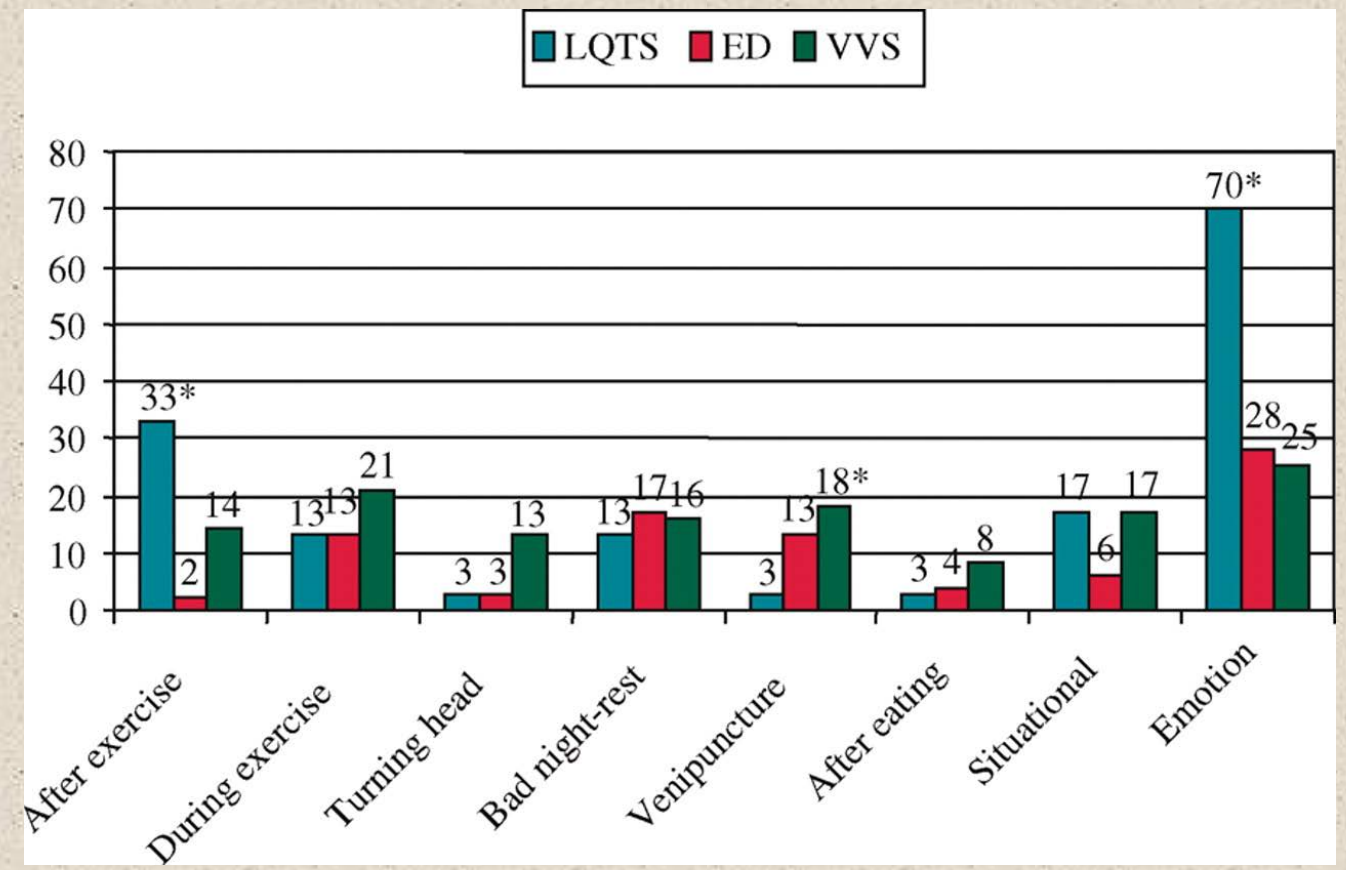


*Significant difference between LQTS and both control groups ($P<0.05$), patients can have loss of consciousness in 1 or more positions.

Colman et al. Europace 2009; 11: 937-43

Prognostic role of syncope in patients with LQTS

Value of history-taking in syncope patients: in whom to suspect long QT syndrome?



Colman et al. Europace 2009; 11: 937-43

Prognostic role of syncope in patients with LQTS

Table 2 Frequency of prodromal symptoms and family history in long QT syndrome (LQTS) patients, emergency department (ED) patients, and in patients with vasovagal syncope younger than 40 years

	LQTS ($n = 32$)[a]	ED ($n = 113$)[b]	Vasovagal ($n = 69$)[c]	*P*-value, ED vs. LQTS	*P*-value, VVS vs. LQTS	LR ED (95% CI)	LR VVS (95% CI)
Nausea	8 (29%)	50 (46%)	41 (60%)	0.10	**0.005**	0.6 (0.3–1.2)	**0.56 (0.38–0.81)**
Sweating	18 (67%)	65 (60%)	18 (71%)	0.50	0.71	1.1 (0.8–1.5)	1.06 (0.78–1.4)
Paleness	18 (67%)	53 (63%)	54 (83%)	0.74	0.08	1.1 (0.7–1.4)	1.25 (0.93–1.67)
Light-headedness	23 (82%)	79 (73%)	55 (80%)	0.33	0.78	1.1 (0.9–1.3)	0.97 (0.79–1.20)
Blurring of vision	14 (54%)	46 (44%)	37 (55%)	0.36	0.91	1.2 (0.8–1.9)	1.03 (0.68–1.56)
Wanting to lie down	14 (50%)	52 (48%)	45 (66%)	0.83	0.14	1.0 (0.7–1.6)	1.30 (0.88–1.99)
Palpitations	12 (44%)	22 (21%)	29 (43%)	**0.01**	0.92	**2.1 (1.2–3.7)**	0.97 (0.59–1.61)
Chest pain	4 (15%)	14 (13%)	13 (19%)	0.79	0.43	1.2 (0.4–3.2)	1.29 (0.46–3.61)
Shoulder pain	0	10 (9.3%)	4 (6%)	0.11	0.26	NA	NA
Funny smell/taste	2 (7.7%)	5 (4.7%)	5 (7.5%)	0.54	0.63	1.6 (0.3–8.0)	0.97 (0.20–4.69)
Abdominal discomfort	4 (16%)	10 (9.5%)	12 (18.0%)	0.35	0.54	1.7 (0.6–4.9)	1.14 (0.41–3.2)
Tingling around the mouth and/or fingers	5 (20%)	20 (19%)	18 (28%)	0.91	0.45	1.1 (0.4–2.5)	1.39 (0.58–3.33)
Family history of syncopal episodes–no. (%)	23 (72%)	10 (9%)	23 (33%)	**<0.001**	**<0.001**	**3.2 (1.9–5.6)**	**2.4 (1.3–4.2)**
Family history of sudden death–no. (%)	21 (66%)	12 (10%)	12 (17%)	**<0.001**	**<0.001**	**2.6 (1.6–4.2)**	**2.4 (1.5–3.9)**
Family history of cardiovascular disease–no. (%)	23 (72%)	31 (28%)	35 (51%)	**<0.001**	**0.04**	**2.6 (1.5–4.5)**	**1.8 (0.96–3.2)**

FAST, Fainting Assessment Trial; LR, likelihood ratio; VVS, vasovagal syncope. Values in bold face are statistically significant.
[a]In six patients data of at least one symptom are missing or patient does not know.
[b]In nine patients data of at least one symptom are missing or patient does not know.
[c]In four patients data of at least one symptom are missing or patient does not know.

Colman et al. Europace 2009; 11: 937-43

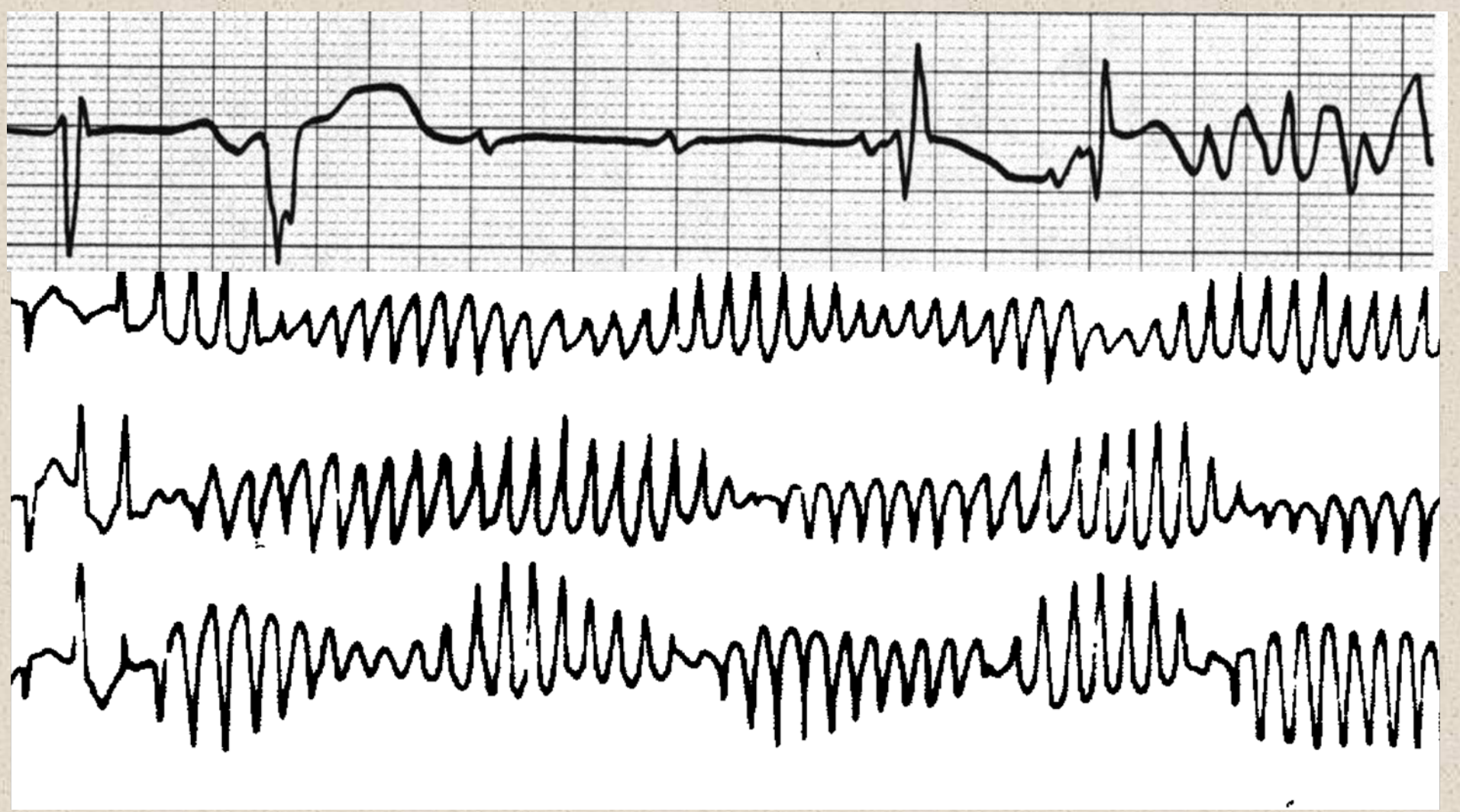
Prognostic role of syncope in patients with LQTS

Long QT syndrome patients may faint due to neurocardiogenic syncope

Conclusion Syncope in LQTS can be of neurocardiogenic origin and is not necessarily due to TdP. The reason for neurocardiogenic syncope in LQTS is unknown, but involvement of the autonomic nervous system outside the heart is possible.

Toft et al. Europace 2003; 5: 367-70

Prognostic role of syncope in patients with LQTS



Prognostic role of syncope in patients with LQTS

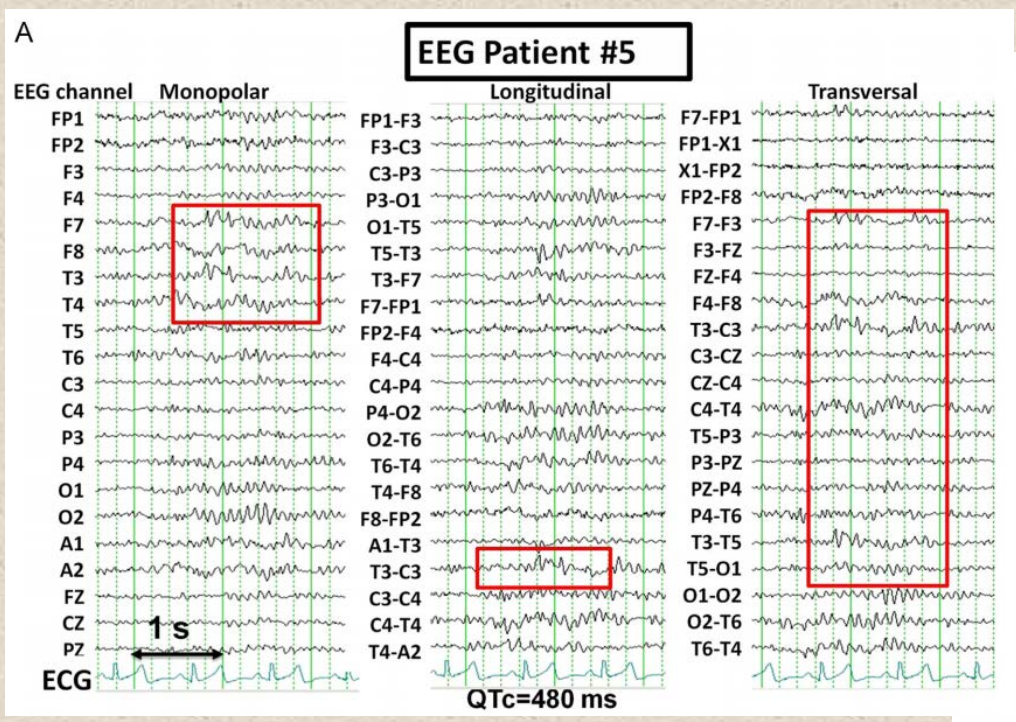
Abnormal electroencephalograms in patients with long QT syndrome

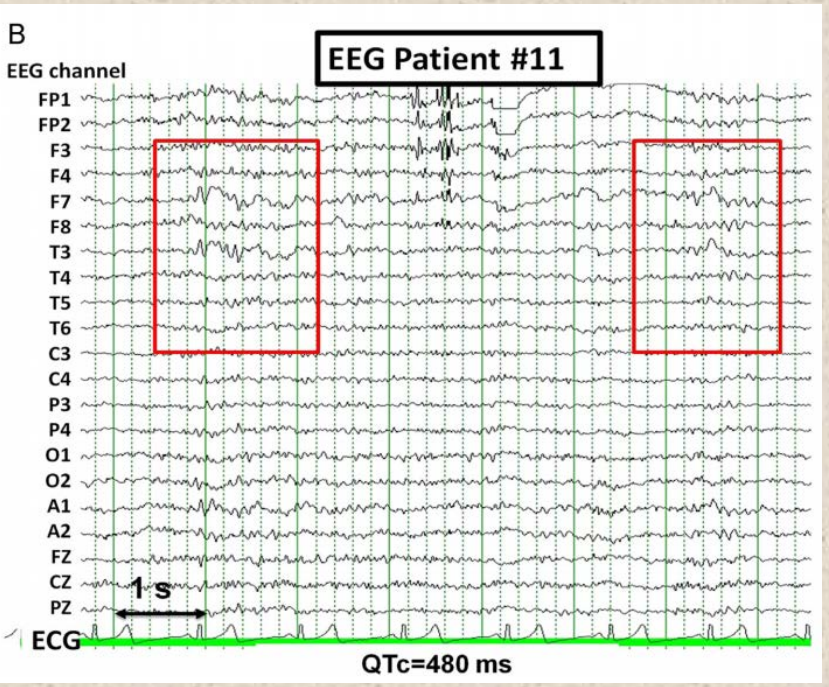
In this prospective pilot study, EEG abnormalities were found in 72% of individuals with genetically confirmed LQTS due to potassium channel mutations that was more frequent than in healthy controls. These results may indicate that ion channel dysfunction leading to cardiac arrhythmias may coexpress as abnormal findings in the EEG. These findings may be of importance in understanding the possible coexistence of cerebral and cardiac symptoms.

Haugaa et al. Heart Rhythm 2013; 10: 1877-83

Prognostic role of syncope in patients with LQTS

Abnormal electroencephalograms in patients with long QT syndrome





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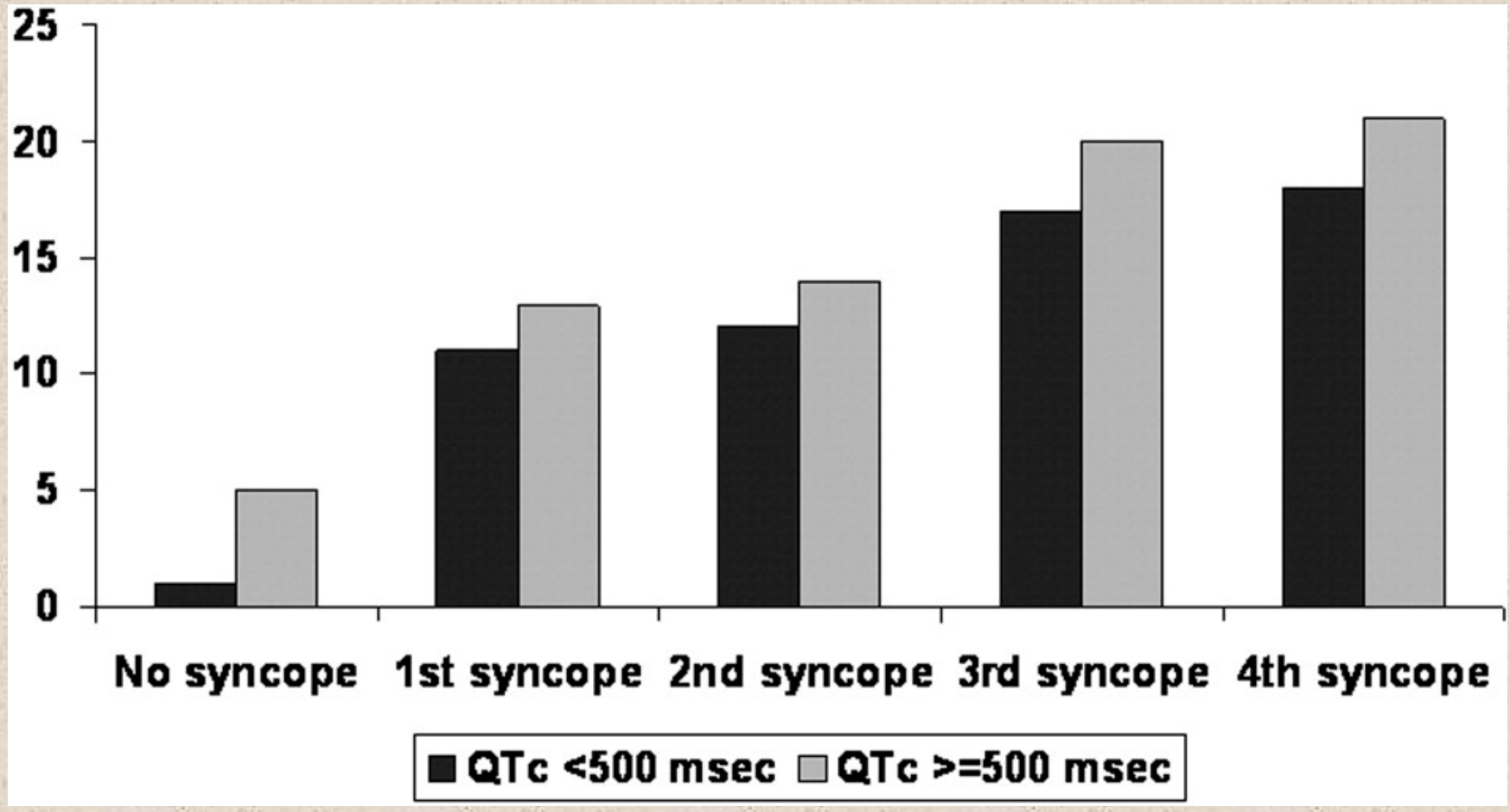
Prognostic role of syncope in patients with LQTS



Liu et al. J Am Coll Cardiol 2011; 57: 941-50.

Prognostic role of syncope in patients with LQTS

Recurrent Syncope as a Predictor of Sudden Death

Variable	Adjusted Risk		
	HR‡	95% CI	p Value
First syncope event vs. no events	6.54	3.96–10.80	<0.001
Second syncope event vs. no events	6.69	6.65–12.25	<0.001
Third syncope event vs. no events	12.51	7.03–22.28	<0.001
≥4 Syncope events vs. no events	14.65	8.02–26.76	<0.001

Liu et al. J Am Coll Cardiol 2011; 57: 941-50.

Prognostic role of syncope in patients with LQTS

Risk of fatal arrhythmic events in long QT syndrome patients after syncope

Table 3 Risk Factors for the First Syncope Event After the Start of Beta-Blocker Treatment in Long QT Syndrome Patients With Previous Episodes of Syncope

Parameter	HR	95% CI	p Value
Male subjects age 0 to 13 yrs vs. male subjects age 14 to 40 yrs	3.16	1.92–5.78	<0.001
Female subjects age 0 to 13 yrs vs. male subjects age 14 to 40 yrs	3.04	1.82–5.08	<0.001
Female subjects age 14 to 40 yrs vs. male subjects age 14 to 40 yrs	2.27	1.45–3.58	<0.001
QTc interval >500 ms	1.10	0.86–1.42	0.46

Jons et al. J Am Coll Cardiol 2010; 55:783-8

Prognostic role of syncope in patients with LQTS

Risk of fatal arrhythmic events in long QT syndrome patients after syncope

Table 2 Cox Model for Risk Factors Related to Severe Cardiac Events in Patients Presenting With the First Syncope Event and Repeated Syncope Events On and Off Beta-Blocker Therapy

Parameter	HR	95% CI	p Value
Syncopal episodes and beta-blocker therapy			
≥1 syncopal events on beta-blocker therapy*	3.59	2.25–5.74	<0.001
>1 syncopal event off beta-blocker therapy*	1.96	1.37–2.82	<0.001
QTc interval >500 ms	1.76	1.32–2.27	<0.001
Female subjects age 14 to 40 yrs†	1.86	1.40–2.49	<0.001
Time-dependent beta-blocker therapy	0.46	0.32–0.65	<0.001

*Relative to subjects with only 1 syncopal episode occurring while off beta-blocker therapy.
†Relative to male subjects age 14 to 40 years.
CI = confidence interval; HR = hazard ratio; QTc = corrected QT.

Jons et al. J Am Coll Cardiol 2010; 55:783-8

Prognostic role of syncope in patients with LQTS

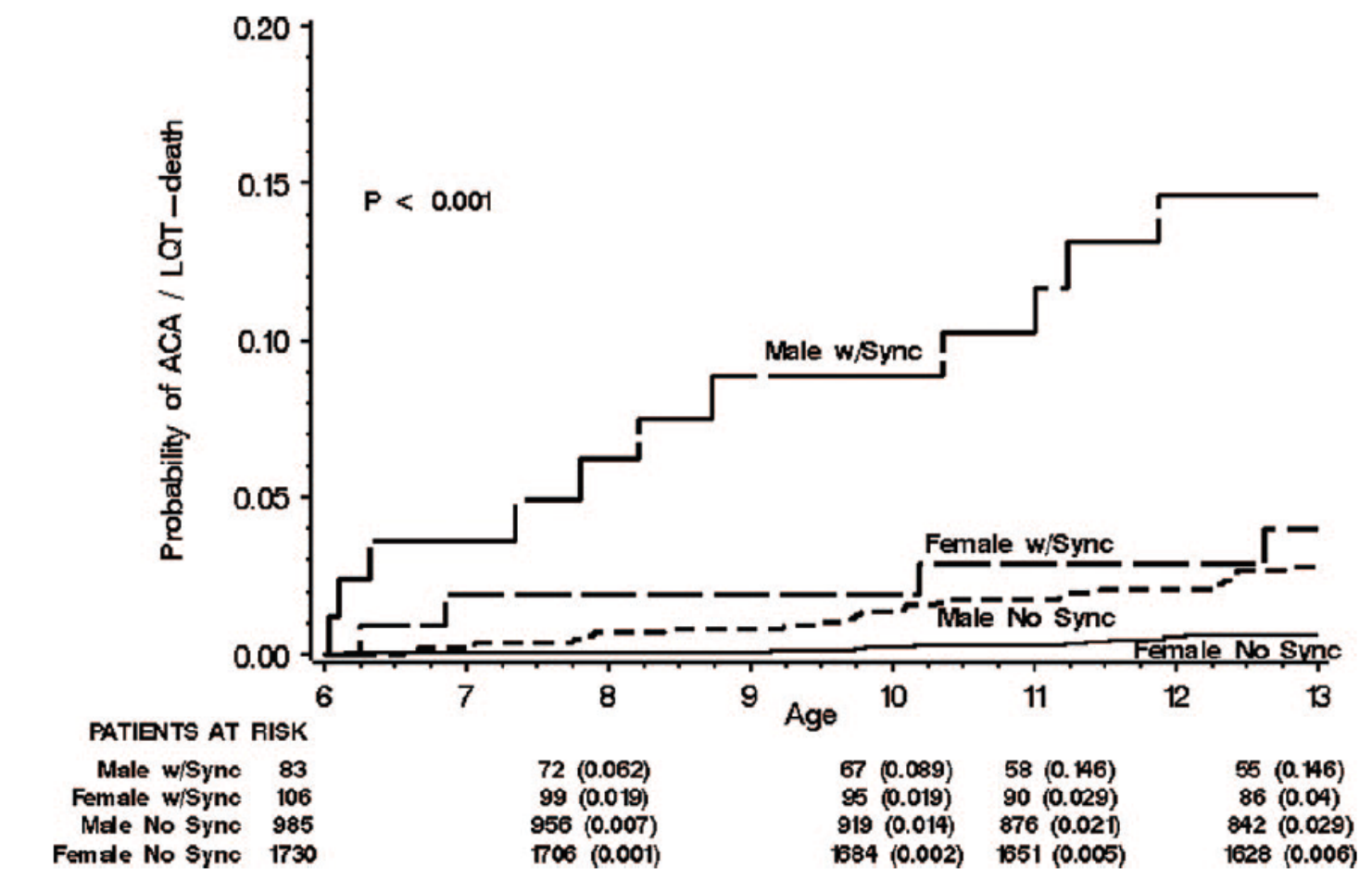
Factors for ACA or SCD During Childhood: Risk Factors for Boys and Girls

	Males		Females		
Risk Factor	HR (95% CI)	*P*	HR (95% CI)	*P*	*P* for Interaction†
QTc duration					0.055
QTc >500 vs ≤500 ms	2.72 (1.50–4.92)	0.001	0.95 (0.39–2.33)	0.91	
Prior syncope					0.01‡
Recent (<2 y) vs no syncope	6.16 (3.41–11.15)	<0.001	27.82 (9.72–79.60)	<0.001	
Remote (≤2 y) vs no syncope	2.67 (1.22–5.85)	0.01	12.04 (3.79–38.26)	<0.001	

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

Prognostic role of syncope in patients with LQTS

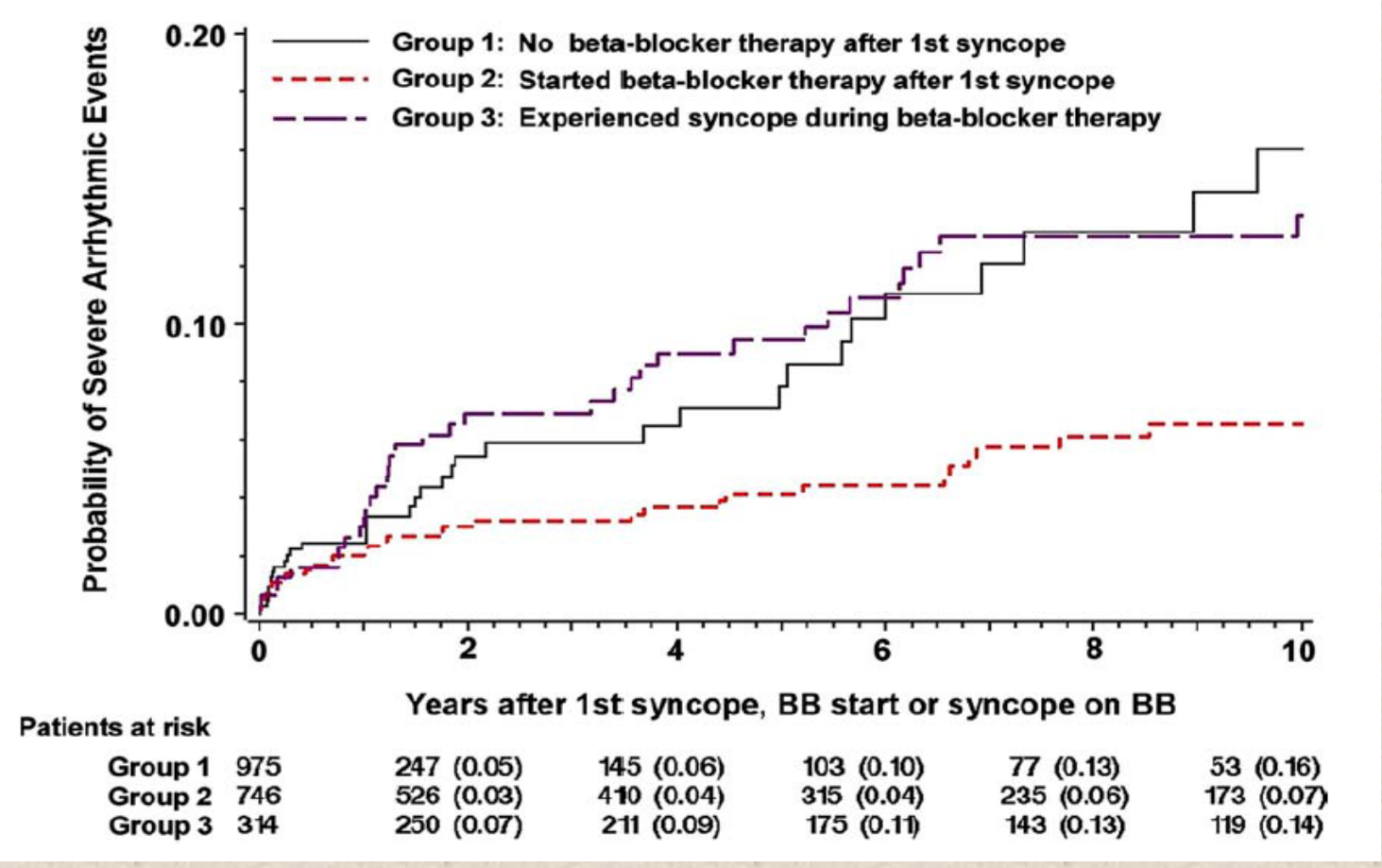
Sudden death after 6 years of age



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

Prognostic role of syncope in patients with LQTS

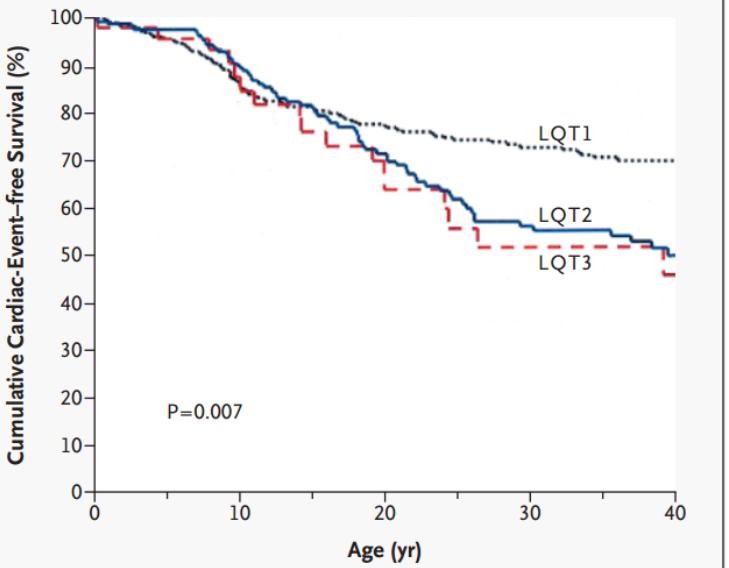
The Cumulative Risk of Severe Arrhythmic Events and Beta-Blocker Therapy



Jons et al. J Am Coll Cardiol 2010; 55: 783–8

Prognostic role of syncope in patients with LQTS

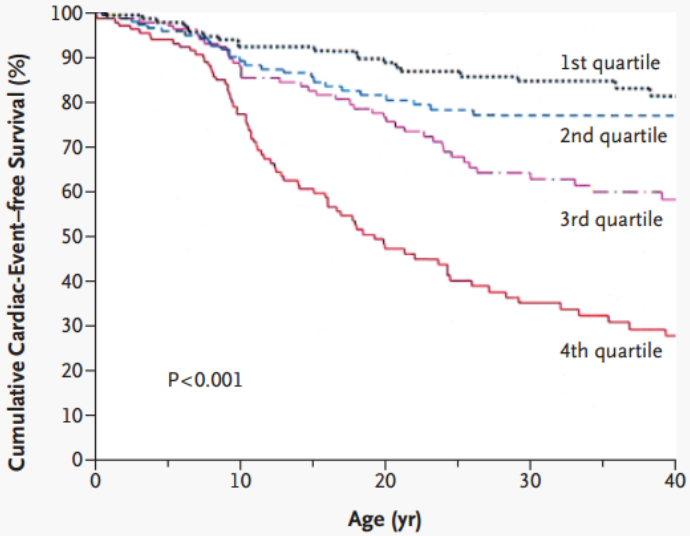
Risk Stratification in the Long-QT Syndrome



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

Figure 1. Kaplan–Meier Estimates of Survival Free of Cardiac Events among the 580 Patients with the Long-QT Syndrome in the Risk-Stratification Analysis, According to the Genetic Locus of the Mutation.

The difference among the groups was significant (P=0.007 by the log-rank test).



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

Figure 2. Kaplan–Meier Estimates of Cumulative Survival Free of Cardiac Events among the 580 Patients with the Long-QT Syndrome in the Risk-Stratification Analysis, According to the Quartile of the QT Interval Corrected for Heart Rate (QTc).

The four quartiles of QTc were as follows: first, 446 msec or less; second, 447 to 468 msec; third, 469 to 498 msec; and fourth, more than 498 msec. The difference among the quartiles was significant (P<0.001).

Prognostic role of syncope in patients with LQTS

Risk of death in the LQTS when a sibling has died

Table 2 Risk of aborted cardiac arrest or LQT-related death

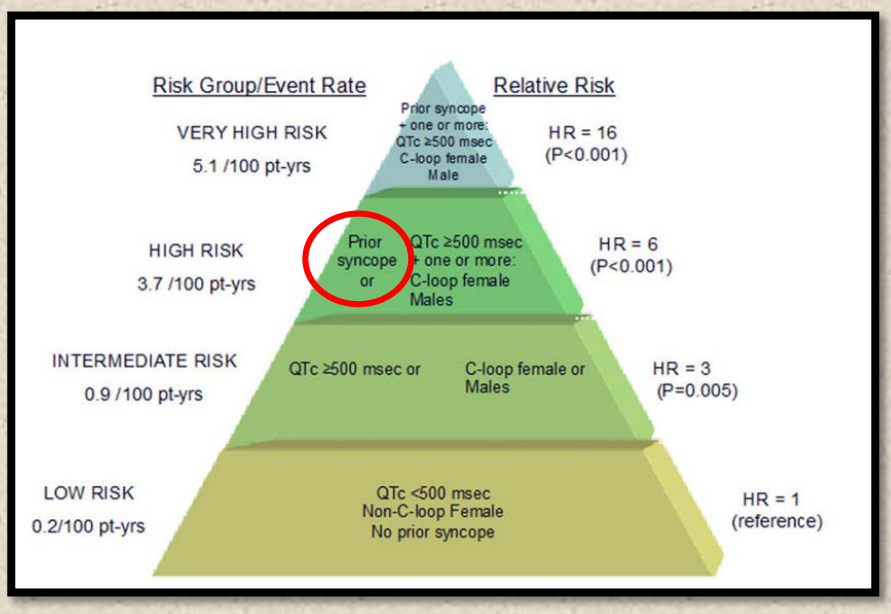
	Hazard ratio	95% confidence interval	*P* value
QTc ≥ 0.53 s : QTc < 0.53 s	2.54	1.91–3.37	<0.01
Syncope 0–2 years : no syncope	11.26	8.00–15.84	<0.01
Syncope >2 years : no syncope	3.26	2.21–4.81	<0.01
Beta-blocker	0.47	0.32–0.68	<0.01
ICD implantation	0.13	0.02–0.96	0.045
Death of sibling	1.14	0.72–1.79	0.58

Gender and gender × time covariates were also included in the models.
ICD = implantable cardioverter-defibrillator; LQT = long QT.

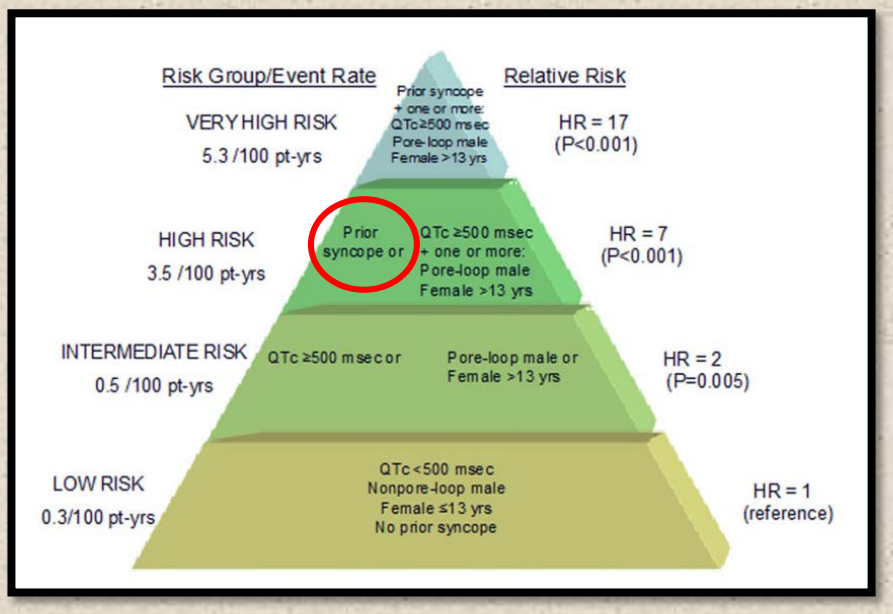
Kaufman et al. Heart Rhythm 2008; 5: 831-6

Prognostic role of syncope in patients with LQTS

Proposed risk stratification scheme for aborted cardiac arrest or sudden cardiac death in LQT1 and LQT2 patients



LQT1



LQT2

Barsheshet et al. Ann Noninvasive Electrocardiol. 2013; 18: 499-509.

Prognostic role of syncope in patients with LQTS

Risk stratification and management in LQTS (1)

Recommendations	Class[a]	Level[b]
The following lifestyle changes are recommended in all patients with a diagnosis of LQTS: (a) Avoidance of QT-prolonging drugs (http://www.crediblemeds.org). (b) Correction of electrolyte abnormalities (hypokalaemia, hypomagnesaemia, hypocalcaemia) that may occur during diarrhoea, vomiting or metabolic conditions. (c) Avoidance of genotype-specific triggers for arrhythmias (strenuous swimming, especially in LQTS1, and exposure to loud noises in LQTS2 patients).	I	B

Priori et al. Eur Heart J 2015: doi:10.1093/eurheartj/ehv316

Prognostic role of syncope in patients with LQTS

Risk stratification and management in LQTS (2)

Recommendations	Class[a]	Level[b]
Beta-blockers are recommended in patients with a clinical diagnosis of LQTS.	I	B
ICD implantation with the use of beta-blockers is recommended in LQTS patients with previous cardiac arrest.	I	B

Priori et al. Eur Heart J 2015: doi:10.1093/eurheartj/ehv316

Prognostic role of syncope in patients with LQTS

Risk stratification and management in LQTS (3)

Recommendations	Class[a]	Level[b]
Beta-blockers should be considered in carriers of a causative LQTS mutation and normal QT interval.	IIa	B
ICD implantation in addition to beta-blockers should be considered in LQTS patients who experienced syncope and/or VT while receiving an adequate dose of beta-blockers.	IIa	B

Priori et al. Eur Heart J 2015: doi:10.1093/eurheartj/ehv316

Prognostic role of syncope in patients with LQTS

Risk stratification and management in LQTS (4)

Recommendations	Class[a]	Level[b]
Left cardiac sympathetic denervation should be considered in patients with symptomatic LQTS when (a) Beta-blockers are either not effective, not tolerated or contraindicated; (b) ICD therapy is contraindicated or refused; (c) Patients on beta-blockers with an ICD experience multiple shocks.	IIa	C

Priori et al. Eur Heart J 2015: doi:10.1093/eurheartj/ehv316

Prognostic role of syncope in patients with LQTS

Risk stratification and management in LQTS (5)

Recommendations	Class[a]	Level[b]
Sodium channel blockers (mexiletine, flecainide or ranolazine) may be considered as add-on therapy to shorten the QT interval in LQTS3 patients with a QTc >500 ms.	IIb	C
Implant of an ICD may be considered in addition to beta-blocker therapy in asymptomatic carriers of a pathogenic mutation in *KCNH2* or *SCN5A* when QTc is >500 ms.	IIb	C

Priori et al. Eur Heart J 2015: doi:10.1093/eurheartj/ehv316

Prognostic role of syncope in patients with LQTS

Diagnosis of LQTS (1)

Recommendations	Class[a]	Level[b]
LQTS is diagnosed with either – QTc ≥480 ms in repeated 12-lead ECGs or – LQTS risk score >3	I	C

Priori et al. Eur Heart J 2015: doi:10.1093/eurheartj/ehv316

Prognostic role of syncope in patients with LQTS

Diagnosis of LQTS (2)

Recommendations	Class[a]	Level[b]
LQTS is diagnosed in the presence of a confirmed pathogenic LQTS mutation, irrespective of the QT duration.	I	C
ECG diagnosis of LQTS should be considered in the presence of a QTc ≥460 ms in repeated 12-lead ECGs in patients with an unexplained syncopal episode in the absence of secondary causes for QT prolongation.	IIa	C

Priori et al. Eur Heart J 2015: doi:10.1093/eurheartj/ehv316