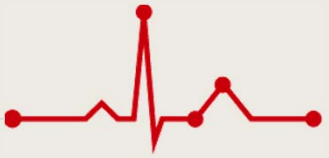
KHRS 2021 The 13th Annual Scientific Session of the Korean Heart Rhythm Society

Update on Long QT Syndrome



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COI Disclosure

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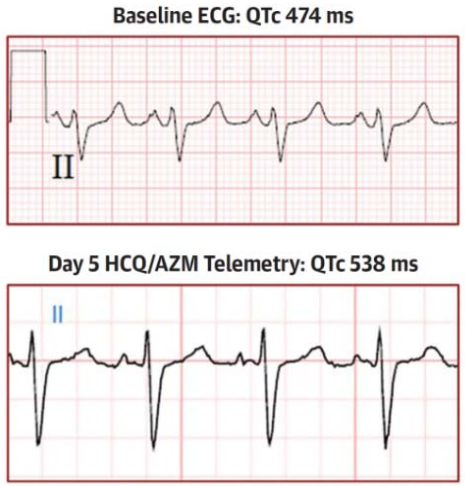
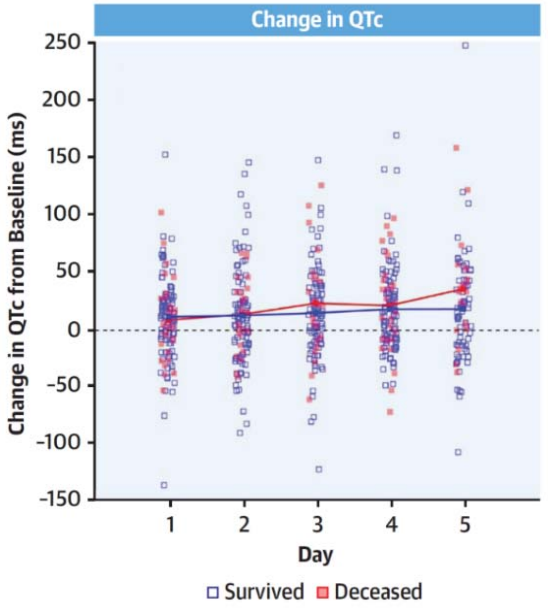
The author has no financial conflicts of interest to disclose concerning the presentation

Hydroxychloroquine/Azithromycin and QT Prolongation in COVID-19 Patients

O'Connell, JACC EP 2021;7:16–25

- Among 415 patients who received concomitant HCQ/AZM, the QTc increased from 443±25 ms to 473±40 ms (87 [21%] patients had a QTc ≥500 ms).
- Factors associated with QTc prolongation ≥500 ms were age (p <0.001), BMI <30 kg/m2 (p =0.005), HF (p <0.001), elevated creatinine (p=0.005), and peak troponin (p <0.001).
- Hospitalized patients with COVID-19 treated with HCQ/AZM had a significant and progressive increase in QTc during combination drug therapy.





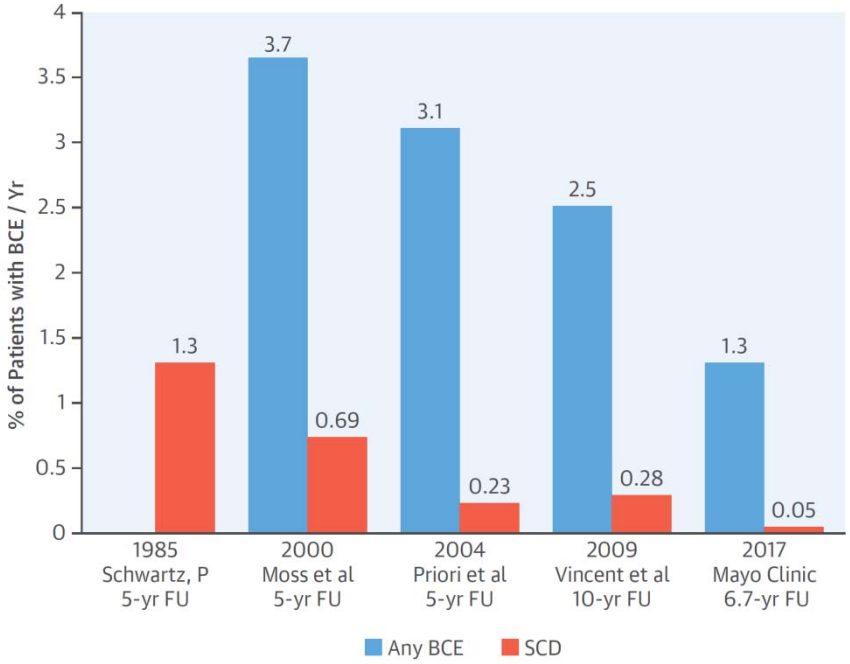
Considerations for Drug Interactions on QTc Interval in Exploratory COVID-19 Treatment

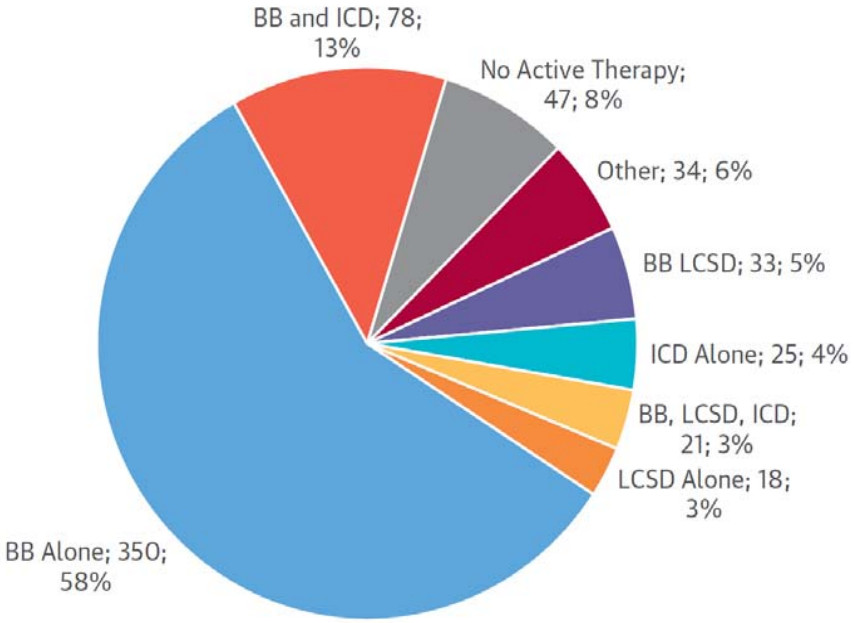
Roden, Harrington (AHA), Poppas (ACC) and Russo (HR), Heart Rhythm 2020;17:e231-e232

- ECG/QT interval monitoring
    1. Withhold the drugs in patients with baseline QT interval prolongation (e.g., QTc interval ≥500 ms) or with known congenital LQTS.
    2. Monitor cardiac rhythm and QT interval, and withdraw the drugs if QTc interval exceeds a preset threshold of 500 ms.
    3. In patients critically ill with COVID-19, frequent caregiver contact may need to be minimized, so optimal electrocardiographic interval and rhythm monitoring may not be possible.
- Correction of hypokalemia to a level of >4 mEq/l and hypomagnesemia to a level of >2 mg/dl
- Avoidance of other QTc interval–prolonging agents whenever feasible

Contemporary Outcomes in Patients With LQTS

Rohatgi, JACC 2017;70:453–62



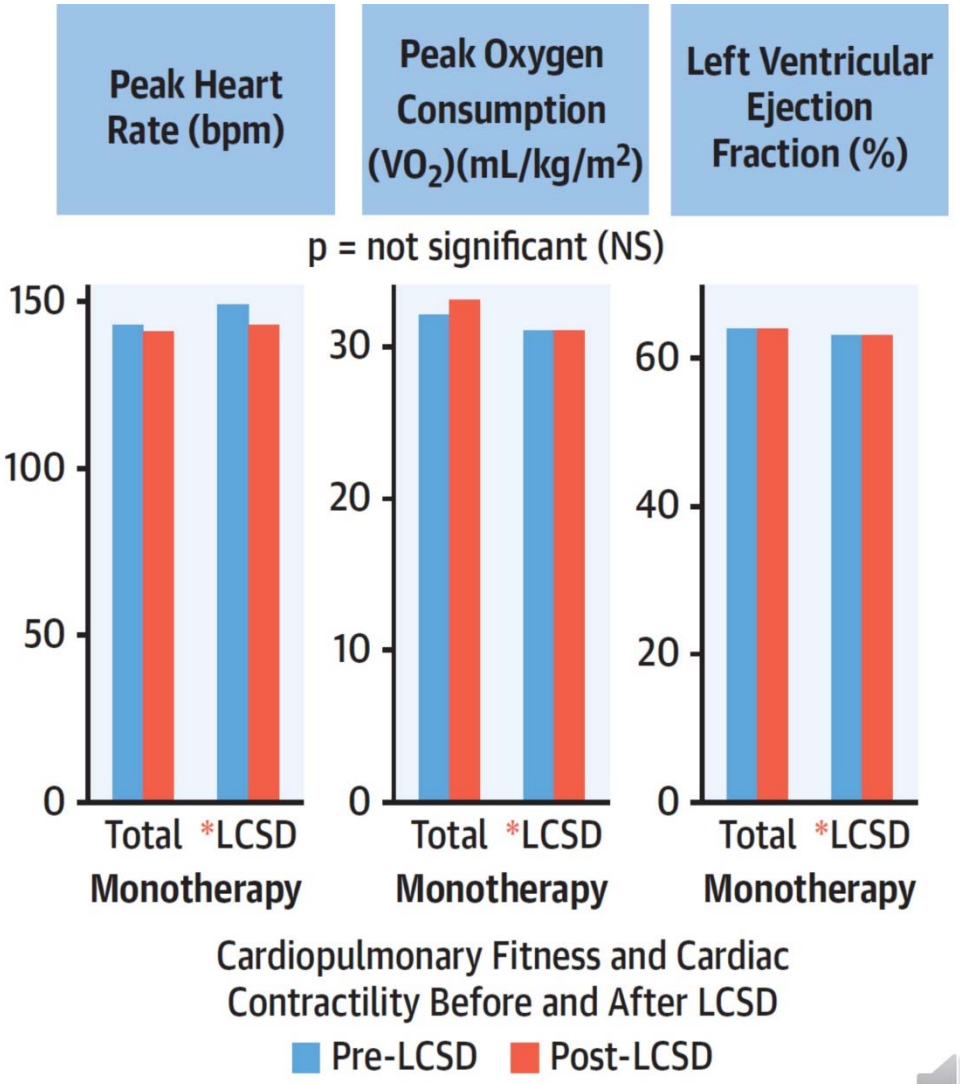


- 606 patients with LQTS (LQT1 in 47%, LQT2 in34%, and LQT3 in 9%) who were evaluated in Mayo Clinic's Genetic Heart Rhythm Clinic from January 1999 to December 2015.
- Over a median follow-up of 6.7 years, 556 (92%) patients have not experienced an LQTS-triggered BCE. Only 8 of 440 (2%) previously asymptomatic patients have experienced a single BCE.

The Effect of LCSD on Exercise in Patients With LQTS

Andersen, JACC EP 2019;5:1084–90

- Patients with LQTS and LCSD (2006 to 2017) who had both pre- and post-LCSD exercise stress tests (N =55; 39 females; age at LCSD 22±12 years; follow-up 5.1±2.5 years; 36 patients with LQT1; 15 patients with LQT2).
- There was no difference in peak HR, peak VO_2, peak QTc, or respiratory exchange ratio pre- and post-LCSD.
- LCSD provides increased protection from an LQTS-triggered event without negatively affecting peak HR, cardiopulmonary fitness, or cardiac contractility.



Channelopathies as Causes of Sudden Cardiac Death

Card Electrophysiol Clin 9 (2017) 537–549
http://dx.doi.org/10.1016/j.ccep.2017.07.005

Peter J. Schwartz, MD[a,*], Michael J. Ackerman, MD, PhD[b,c,d], Arthur A.M. Wilde, MD, PhD[e,f]

KEYWORDS

• Brugada syndrome • Catecholaminergic polymorphic ventricular tachycardia • Genetic testing • Ion channels • Long QT syndrome • Ryanodine receptor • Left cardiac sympathetic denervation

KEY POINTS

- All patients with channelopathies should undergo genetic screening because the identification of the disease-causing mutation allows diagnosis or exclusion of the disease in the entire family.
- For patients with long QT syndrome and catecholaminergic polymorphic ventricular tachycardia, left cardiac sympathetic denervation should be considered before the implantable cardiovert-defibrillator (ICD) for quality of life.
- Risk stratification for asymptomatic patients with the Brugada syndrome remains ill-defined and, even with a spontaneous type 1 pattern, the low risk suggests careful judgment before implanting an ICD.

Arrhythmogenic Foods –A Growing Medical Problem

Woosley, Trends in Cardiovascular Med 2020;30:310-2

- Grapefruit juice or energy drinks (ED) could have direct arrhythmogenic actions, especially in patients with congenital LQTS.
- Of the 11 cases related to a serious event after ingestion of ED, 5 reported acute heavy ED consumption, 4 reported co-ingestions with alcohol or other drugs, and 2 were found to have a channelopathy (Goldfarb, Am J Cardiol 2014;113:168-72).

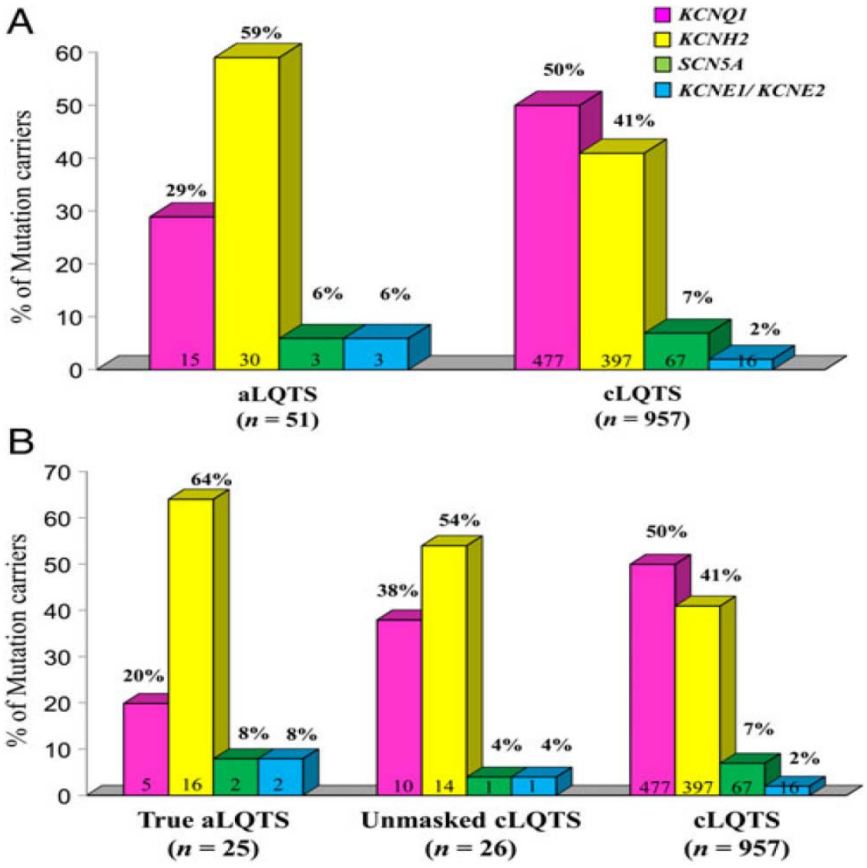
Published cases of adverse cardiovascular events after ingestion of energy drinks

Case	Year (Reference)	Presentation	Age (yrs)/Sex	ED and Co-Ingestions	Caffeine Consumed (mg)	Cardiac Investigations	Cardiac Abnormalities Identified*	Outcome
1	2011[6]	AF	16 M	Red Bull	Unknown	ECG TTE	None	Conversion to SR
2	2011[6]	AF	14 M	Red Bull; vodka	Unknown	ECG TTE	None	Conversion to SR
3	2012[7]	AF	13 M	—	85	ECG TTE	None	Conversion to SR
4	2007[8]	AF	58 M	—	575	ECG TTE Cath	EF 45% ≥ 65%	Conversion to SR
5	2008[9]	SVT	23 F	GNC Speed Shot	250	ECG	None	Conversion to SR
6	2012[10]	Prolonged QT	13 F	—	160	ECG EST Gen	LQTS1 (KCNQ1)	QT interval ↓
7	2012[11]	TdP	22 F	—	480	ECG TTE Cath Gen	LQTS1 (KCNQ1)	Aborted SD
8	2001[12]	VF	25 F	Race Energy Blast	570	ECG Autopsy	MVP	SD
9	2009[13]	VF	28 M	—	640	ECG TTE Cath	EF ↓ ≥ nl	Aborted SD
10	2013 (case 1)	VF	19 M	Monster; marijuana	160	ECG TTE Cath EPS†	None	Aborted SD
11	2012[14]	VF	24 M	Red Bull; vodka	80	ECG	Brugada type 1	Aborted SD
12	2013 (case 2)	Cardiac arrest†	57 M	NOS	1,300	ECG TTE Cath	LVH with RWMA	Aborted SD
13	2012[15]	VT/SVT	24 M	—	—	ECG TTE Cath MRI	EF ↓ ≥ nl	Conversion to SR
14	2012[16]	ST elevation	17 M	Red Bull, Monster	560–800	ECG TTE Nuc	EF ↓ ≥ nl	Resolution
15	2012[17]	ST elevation	24 M	XL; MDMA	1,600	ECG	None	SD
16	2011[18]	ST elevation	19 M	Red Bull	160–240	ECG TTE Cath	None	Resolution
17	2012[19]	ST elevation	24 M	—; vodka	—	ECG TTE Cath	Acute thrombosis	Emergent CABG

The Genetics Underlying Acquired LQTS

Itoh, European Heart J 2016;37:1456-64

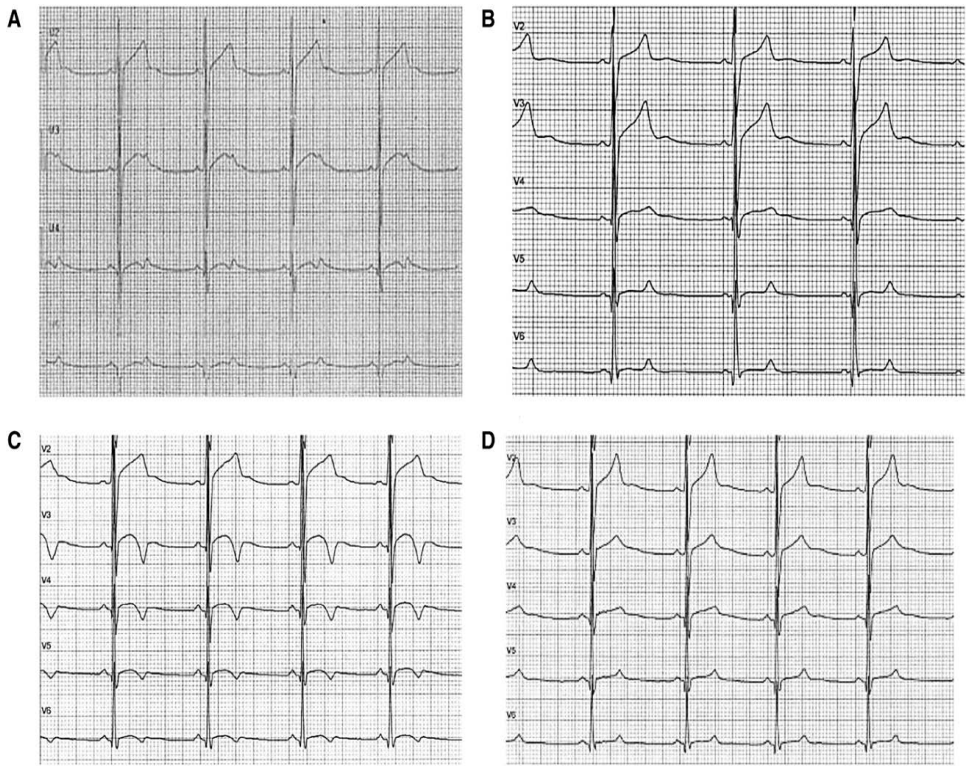
- Screened for the five major LQTS genes among 188 acquired LQTS probands from Japan (n=147), France (n=20), and Italy (n=21).
- In 53 (28%) acquired LQTS subjects, 47 disease-causing mutations were identified.
- A third of acquired LQTS patients carry congenital LQTS mutations, those on KCNH2 being more common.



Exercise-Induced Repolarization Abnormalities → another acquired LQTS?

Dargradi, Circulation 2020;142:2405–15

- Some young athlete manifest QT interval prolongation and repolarization abnormalities strongly suggests that they are affected by LQTS.
- Among those who are genotype (-), >40% normalize their ECG after detraining, but the abnormalities tend to recur with resumption of training.
- These genotype (-) subjects should be managed as if they had drug-induced LQTS.
- It would seem reasonable to allow them to practice their sport, but at an intensity that does not trigger reappearance of repolarization abnormalities.

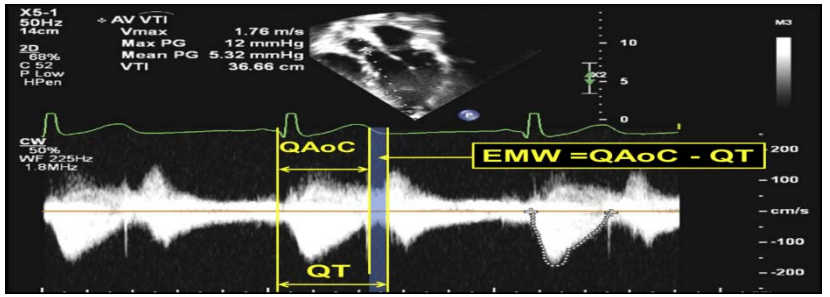


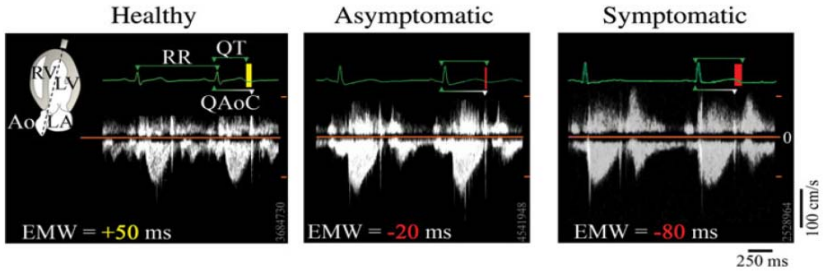
A. Preparticipation screening B. 3-month detraining
C. Soccer training again, D. 7-months detraining

Echocardiography-Guided LQTS Risk Stratification

Sugrue, JACC 2020;76:2834–43

- 651 LQTS patients with and 50 healthy controls.
- Electromechanical window (EMW) is a difference between electrical (QT) and mechanical (QAoC) systole.
- A negative EMW was found among nearly all patients with LQTS compared to controls, with more profound EMW negativity in symptomatic patients with LQTS.
- EMW outperformed QTc in predicting symptomatic patients (area under the curve: 0.78 vs. 0.70; p =0.01).

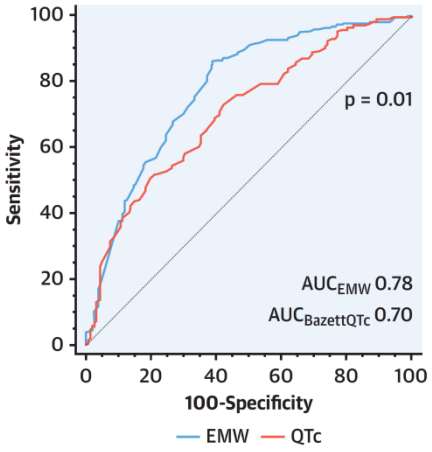




EMW is more negative in LQTS patients than controls

Patients with a history of LQTS-associated life-threatening cardiac events have a more negative EMW

The EMW outperforms the QTc as a predictor of symptomatic status



Recommendations Competitive and Leisure Sports

Ventricular Arrhythmias, Channelopathies, and Implantable Defibrillators

Heidbuchel, Corrado, Europace 2021;23:147–8

- All LQTS athletes should avoid QT prolonging drugs and electrolyte imbalance.
- All LQTS athletes with prior symptoms or prolonged QTc should be on therapy with β-blockers at target dose.
- Athletes with LQTS and prior CA or arrhythmic syncope should not be allowed to practice competitive sports (with or without ICD).
- Athletes with a QTc >500 ms, a de novo disease-causing mutation (especially if LQT1), or genetically confirmed LQTS with a QTc ≥470 ms in men or ≥480 ms in women should not practice more than light- to moderate intensity recreational sports, even when on β-blockers.
- Recommendations to sports participation require open discussion with the athlete and their entourage, finding a balance between life protection and quality of life during shared decision-making.
- It is reasonable to allow individual sports at low to moderate intensity for asymptomatic athletes with an LQT1 mutation but QTc <470/480 ms and who are on prophylactic β-blocker therapy, but team sports and high-intensity sports are discouraged.
- It is reasonable to allow all types of sports participation for asymptomatic athletes with an LQT2 or LQT3 mutation but QTc <470/480 ms, and who are on prophylactic β-blocker therapy.
- For asymptomatic athletes with other LQTS mutations and QTc <470/480 ms, cardiogenetics consult and shared decision-making are required.

Proposal for More Liberal Eligibility Decision-Making in Athletes With LQTS

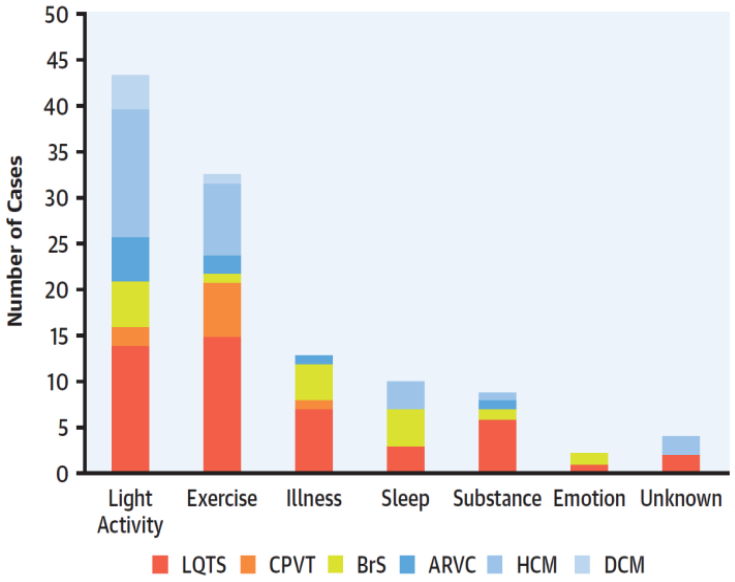
Panhuyzen-Goedkoop and Wilde, Neth Heart J 2018;26:146–53

1. In asymptomatic phenotype (+) LQTS with QT interval ≥500ms sports participation is restricted, and β-blockers are recommended.
2. In symptomatic phenotype (+) LQTS sports participation should be restricted and only low intensity sports, can be considered. β-blockers are recommended. ICD implantation is recommended in patients with previous SCA and in patients with syncope and/or VT while receiving β-blockers.
3. When there are no VA events recorded with the ICD during at least 3-month follow-up and the QTc is <500ms recorded on repeated ECGs the physician may consider return-to-play in sports provided the athlete does not participate in swimming and diving (LQT1).
4. Genotype (+) phenotype (-) LQTS individuals are allowed to participate in all sports.
5. All patients should avoid QT prolonging drugs (www. crediblemeds.org), dehydration and/or excessive sweating, electrolyte disturbances, hyperthermia, and exercise during fever. In patients with LQT1 swimming and diving should be discouraged.

A Paradigm Shift in the Care of Athletes With Cardiac Disorders?

Drezner, Br J Sports Med 2013;47:4-5

- Children and adolescents with inherited arrhythmia syndrome frequently exceed the vigorous (7 METS) and very vigorous (10 MET) activity levels that are recommended by guidelines during routine daily and school activities (Gow, Circ AE 2013;6:939-45).
- The rate of appropriate shocks during sports was low and of the total shocks received, less than one-quarter occurred during sports. ICD shocks during sports were not associated with serious adverse sequelae (Saarel, Circ AE 2018;11:e006305).
- For the majority of athletes who elected return-to play, their return was uneventful (Turkowski, Circulation 2018;137:1086–8).
- Only 30% of resuscitated SCA cases due to cardiac inheritable disease occurred while exercising (Rucinski, JACC 2020;75:2698–707).



Activity at the time of resuscitated SCA among 115 survivors with a cardiac inheritable disease

Gene Therapy for LQTS

- Lumacaftor + Ivacaftor shortened QTc significantly in two patients with LQT2. In the wash-out period a rebound in QTc was observed (Schwartz, European Heart J 2019;40:1832–6).
- KCNQ1 antibodies activate IKs channels, accelerate ventricular repolarization, and suppress arrhythmias in an in vitro cellular model of LQT2 (Maguy, JACC 2020;75:2140-52).
- Dual-component suppression-and-replacement *KCNQ1* gene therapy approach for LQT1 rescued the prolonged APD in induced pluripotent stem cell cardiomyocytes derived from 4 patients with LQT1. Capable of providing complete rescue of *KCNQ1* function. Suppression-and-replacement *KCNQ1* gene therapy is applicable to all patients with LQT1 because it targets the whole *KCNQ1* gene rather than specific variants (Dotzler, Circulation 2021;143:1411–25).
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