Circulation

ORIGINAL RESEARCH ARTICLE

Vigorous Exercise in Patients With Congenital Long QT Syndrome: Results of the Prospective, Observational, Multinational LIVE-LQTS Study

Rachel Lampert, MD; Sharlene Day, MD; Barbara Ainsworth, PhD, MPH; Matthew Burg, PhD; Bradley S. Marino, MD; Lisa Salberg; Maria Teresa Tome Esteban, MD; Dominic J. Abrams, MD; Peter F. Aziz, MD; Cheryl Barth, BS; Elijah R. Behr, MD; Cheyanne Bell; Charles I. Berul, MD; Johan M. Bos, MD; David Bradley, MD; David S. Cannom, MD; Bryan C. Cannon, MD; Maryann Anandi Concannon, MSW; Marina Cerrone, MD; Richard J. Czosek, MD; Anne M. Dubin, MD; James Dziura, PhD; Christopher C. Erickson, MD; N.A. Mark Estes III, MD; Susan P. Etheridge, MD; Ilan Goldenberg, MD; Belinda Gray, MBBS, PhD; Carla Haglund-Turnquist; Kimberly Harmon, MD; Cynthia A. James, PhD; Christopher Johnsrude, MD; Prince Kannankeril, MD; Alice Lara, BSN; Ian H. Law, MD; Fangyong Li, MS; Mark S. Link, MD; Silvana M. Molossi, MD, PhD; Brian Olshansky, MD; Peter A. Noseworthy, MD; Elizabeth V. Saarel, MD; Shubhayan Sanatani, MD; Maully Shah, MBBS; Laura Simone, MS; Jonathan Skinner, MB ChB, MD; Gordon F. Tomaselli, MD; James Simon Ware, MD; Gregory Webster, MD; Wojciech Zareba, MD, PhD; Douglas P. Zipes, MD; Michael J. Ackerman, MD, PhD

BACKGROUND: Whether vigorous exercise increases risk of ventricular arrhythmias for individuals diagnosed and treated for congenital long QT syndrome (LQTS) remains unknown.

METHODS: The National Institutes of Health–funded LIVE-LQTS study (Lifestyle and Exercise in the Long QT Syndrome) prospectively enrolled individuals 8 to 60 years of age with phenotypic and/or genotypic LQTS from 37 sites in 5 countries from May 2015 to February 2019. Participants (or parents) answered physical activity and clinical events surveys every 6 months for 3 years with follow-up completed in February 2022. Vigorous exercise was defined as ≥6 metabolic equivalents for >60 hours per year. A blinded Clinical Events Committee adjudicated the composite end point of sudden death, sudden cardiac arrest, ventricular arrhythmia treated by an implantable cardioverter defibrillator, and likely arrhythmic syncope. A National Death Index search ascertained vital status for those with incomplete follow-up. A noninferiority hypothesis (boundary of 1.5) between vigorous exercisers and others was tested with multivariable Cox regression analysis.

RESULTS: Among the 1413 participants (13% <18 years of age, 35% 18–25 years of age, 67% female, 25% with implantable cardioverter defibrillators, 90% genotype positive, 49% with LQT1, 91% were treated with beta-blockers, left cardiac sympathetic denervation, and/or implantable cardioverter defibrillator), 52% participated in vigorous exercise (55% of these competitively). Thirty-seven individuals experienced the composite end point (including one sudden cardiac arrest and one sudden death in the nonvigorous group, one sudden cardiac arrest in the vigorous group) with overall event rates at 3 years of 2.6% in the vigorous and 2.7% in the nonvigorous exercise groups. The unadjusted hazard ratio for experience of events for the vigorous group compared with the nonvigorous group was 0.97 (90% CI, 0.57–1.67), with an adjusted hazard ratio of 1.17 (90% CI, 0.67–2.04). The upper 95% one-sided confidence level extended beyond the 1.5 boundary. Neither vigorous or nonvigorous exercise was found to be superior in any group or subgroup.

CONCLUSIONS: Among individuals diagnosed with phenotypic and/or genotypic LQTS who were risk assessed and treated in experienced centers, LQTS-associated cardiac event rates were low and similar between those exercising vigorously and those not exercising vigorously. Consistent with the low event rate, CIs are wide, and noninferiority was not demonstrated.

Correspondence to: Rachel Lampert, MD, Cardiology, Section of Cardiology, Dana 3, Yale University School of Medicine, 333 Cedar St, New Haven, CT 06520. Email rachel.lampert@yale.edu

This manuscript was sent to Arthur A.M. Wilde, Guest Editor, for review by expert referees, editorial decision, and final disposition.
Supplemental Material, the podcast, and transcript are available with this article at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.123.067590.
Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.
For Sources of Funding and Disclosures, see page 528.

Circulation is available at www.ahajournals.org/journal/circ

These data further inform shared decision-making discussions between patient and physician about exercise and competitive sports participation.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02549664.

Key Words: arrhythmias, cardiac ■ exercise ■ long QT syndrome

ORIGINAL RESEARCH ARTICLE

Clinical Perspective

What Is New?

- This is the first prospective study to investigate whether vigorous exercise increases risk of arrhythmic events in individuals with congenital long QT syndrome.
- In this study, long QT syndrome–triggered cardiac events were low in both those exercising vigorously and those exercising nonvigorously, and there was no statistical difference in event rate. CIs were wide, and noninferiority not demonstrated.
- Findings were similar in vigorous-competitive athletes 14 to 22 years of age.

What Are the Clinical Implications?

- These findings will further inform shared decision-making discussions between patient and physician about exercise and competitive sports participation.

Nonstandard Abbreviations and Acronyms

HR	hazard ratio
ICD	implantable cardioverter defibrillator
LIVE-HCM	Lifestyle and Exercise in Hypertrophic Cardiomyopathy
LIVE-LQTS	Lifestyle and Exercise in the Long QT Syndrome
LQTS	long QT syndrome
SCA	sudden cardiac arrest
SCD	sudden cardiac death

Exercise has well-established physical and mental health benefits and is an integral part of life for millions of people worldwide. However, for individuals with congenital long QT syndrome (LQTS), vigorous exercise has historically been restricted[1] and athletes with LQTS were disqualified from competitive sports because of concerns that physical activity may increase the risk of LQTS-triggered sudden cardiac death (SCD). LQTS is the most commonly detected genetic electrical abnormality, with a prevalence of manifest, genotype-positive LQTS in 1 in 2500 in a European population,[2] and is due to pathogenic variants in genes encoding ion channel α subunits critical for repolarization or for other channel-interacting proteins.[3] These result in amplification of both spatial and transmural dispersion of repolarization, which can create the substrate for polymorphic ventricular tachycardia (torsades de pointes) and ventricular fibrillation.[4] Previous studies suggesting that exercise is a common trigger of sudden cardiac arrest (SCA) and SCD, particularly in the most common genetic subtype of LQTS, type 1 LQTS (LQT1),[5] generated the concept that restriction from vigorous activity might improve survival in these patients. The extent to which LQTS contributes to SCD in athletes cannot be determined definitively because LQTS cannot be diagnosed on autopsy. However, in one series, 12% of athletes who survived SCA were diagnosed with LQTS,[6] and in another,[7] 3% of adults without findings on autopsy who underwent postmortem genetic testing had pathogenic variants potentially associated with LQTS.

However, in all of these studies describing potential roles of exercise in triggering arrhythmic events, the individuals were diagnosed with LQTS after the event and thus were not previously treated. A number of effective therapies decrease mortality in LQTS, including beta-blockers and other gene-specific medications, implantable cardioverter defibrillators (ICDs), and left cardiac sympathetic denervation.[3,8–10] Previous single-center retrospective series have described athletes with LQTS returning to sports after appropriate treatment without life-threatening arrhythmic events.[11–15] However, whether vigorous exercise influences the likelihood of arrhythmias has not been examined systematically or prospectively. The most recent American Heart Association/American College of Cardiology "Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities" statement, published in 2015, no longer recommends restriction from vigorous competitive sports for those with LQTS, but in the absence of comparative, prospective data, this recommendation has remained conservative (ie, "may be considered"; class 2B).[16] Furthermore, despite the relaxation of the blanket recommendation for restriction in 2015, extensive restrictions and continued disqualifications remain common.[17] Recent recommendations from the European Society of Cardiology remain more restrictive, recommending avoidance of vigorous exercise for most

individuals with LQTS.[18] The prospective, multinational, National Institutes of Health–funded LIVE-LQTS study (Lifestyle and Exercise in the Long QT Syndrome) was designed to provide data to inform patient-provider decisions, with its primary objective to determine whether engagement in vigorous exercise, including competitive sports, is associated with increased risk for life-threatening ventricular arrhythmias in individuals with known and treated LQTS.

METHODS

Study Design

LIVE-LQTS was an investigator-initiated (R.L., S.D., and M.J.A.) prospective observational study. The Yale human investigation committee and institutional review boards of participating sites approved this study. All patients provided signed informed consent. Methods of a parallel study focused on patients with hypertrophic cardiomyopathy (LIVE-HCM [Lifestyle and Exercise in Hypertrophic Cardiomyopathy]) have also been described previously.[19]

Patients and Recruitment

Individuals 8 to 60 years of age with a diagnosis of electrocardiographically manifest LQTS (defined as resting QTc ≥470 ms in male or 480 ms in female participants) or electrocardiographically concealed LQTS (genotype positive but without resting QTc prolongation) were eligible to participate. Those with conditions precluding vigorous exercise were excluded, as were those with QT prolongation attributable to syndromic conditions. Individuals with language or cognitive barriers with resulting inability to complete online or phone questionnaires were also excluded.

Patients were enrolled between May 2015 and February 2019 either through participating high-volume LQTS centers (n=37) in the United States, United Kingdom, Canada, Australia, and New Zealand or through contacting the central site (Yale) directly (self-enrolled; 28% of participants). Information was disseminated to patients by the advocacy organization Sudden Arrhythmic Death Syndromes Foundation, by other patient group internet sites and mailing lists, and through mailings to physicians. For site-enrolled patients, diagnosis of LQTS and eligibility and QT measurement were confirmed by the site. For self-enrolled patients, consent and medical release forms were obtained. Diagnosis and eligibility were then confirmed by chart review and interpretation of ECGs with manual QT measurement by the tangent method with the Bazett correction by the Mayo Clinic Electrophysiology/Electrocardiography Core Laboratory. Derivation of the final cohort of 1413 participants is shown in Figure 1.

Study Procedures

Study procedures were conducted similarly to the LIVE-HCM study.[19] Patients who consented to participate were contacted by the central study team and sent a link to online questionnaires to be completed in a REDcap database. The study team obtained records from sites and through medical release forms from physicians. Demographic, clinical, and genetic data were abstracted and entered into the REDcap database. Participants received a link every 6 months to a REDcap-based survey on occurrence of outcome events. If outcome events were reported, study coordinators contacted participants for details and obtained records. For patients who did not complete the planned 36 months of outcome surveys, records were obtained from sites or physicians to assess for events. Vital status at 3 years from study enrollment was confirmed for all patients through sites or national death registries. Follow-up was completed in February 2022.

Baseline Assessments

Exercise level, the primary independent variable, was based on the Minnesota Leisure Time Activity Questionnaire.[20] This instrument has been validated against both direct[21,22] (treadmill

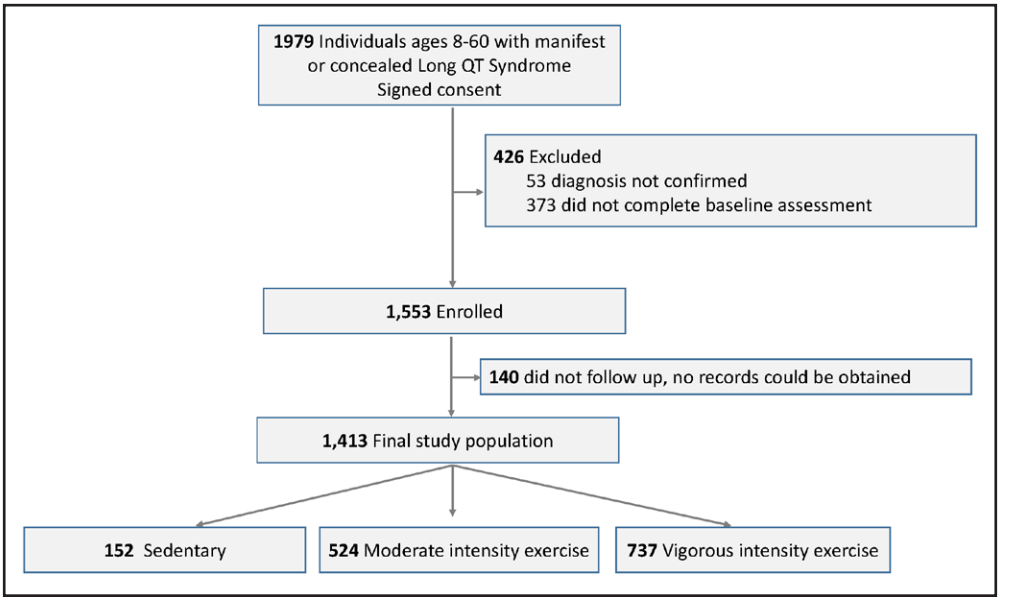

Figure 1. CONSORT (Consolidated Standards for Reporting Trials) diagram.

exercise performance and accelerometry) and indirect (frequent detailed activity records)[22] measures and has high test-retest reliability.[22,23] Participants identified physical activities performed in the past year, indicating the average time per event that they performed each activity, the number of times per month, and the number of months per year. Activities were associated with their metabolic equivalent intensity level, which measures the oxygen cost of physical activity in milliliters per kilogram per minute divided by the oxygen cost at rest (3.5 mL·kg^{-1}·min^{-1}). Metabolic equivalent values were assigned as previously defined in the 2011 Compendium of Physical Activities.[24] Vigorous activity was categorized by participation in at least 1 activity at metabolic equivalents ≥6.0 for ≥60 hours per year.[25] Participants engaged in activities at metabolic equivalents ≥4 and <6 for ≥60 hours per year but not meeting criteria for vigorous were categorized as moderately active, and those who did not meet either of these criteria were categorized as sedentary. Those in the moderate and sedentary groups were combined and categorized as nonvigorous for the primary analysis. Patients were also asked about current participation in organized, competitive-level athletics. Those meeting criteria for vigorous exercise who performed at least one of these activities competitively were categorized as the vigorous-competitive subgroup. For those 14 to 22 years of age, exercise participation was classified as vigorous-competitive only if competition was performed at the varsity, junior varsity (interscholastic), or traveling team level; as "other vigorous" if competition was performed at other levels or the exercise was noncompetitive; and as nonvigorous if moderate or sedentary.

Outcomes

A clinical events committee blinded to the patient's exercise category reviewed and adjudicated all outcome events. The primary prespecified composite end point included death, resuscitated SCA, syncope adjudicated to be definitely or likely arrhythmic, and appropriate ICD shocks, with or without syncope. All ICD shock events were reviewed by 2 electrophysiologists. If the study team was unable to obtain electrograms from the event, reports of electrograms from the clinical record were reviewed. Standard definitions were used to classify deaths as SCD, nonsudden cardiac death, or noncardiac death.[26]

Statistical Analysis

Sample Size and Power

The log-rank noninferiority module of PASS (Kaysville, UT) was used to determine sample size. The original sample size was estimated at 2036 participants on the basis of a 21-month recruitment period, total study time of 57 months, an event rate of 12.8% over 3 years (≈4.3% per year),[27–29] 10% dropout, and 90% power at the 0.05 one-sided significance level to declare noninferiority of vigorous or moderate compared with sedentary at the upper boundary for a hazard ratio (HR) of 1.5. These estimates were based on expected proportions of exercise intensity based on published data in the general population: 50% sedentary, 25% moderate, and 25% vigorous.[30] However, the ratio of individuals performing vigorous compared with sedentary and moderate activity was higher than these estimates. Therefore, before analysis, we revised the comparison to compare the vigorous group with the moderate and sedentary groups combined, defined for this analysis as nonvigorous. Our achieved sample size (737 vigorous and 676 nonvigorous) provides 91% power at the one-sided 0.05 significance level to declare noninferiority of vigorous to nonvigorous at the 1.5 HR boundary based on the estimated 3-year event rate of 12.8%.

Selection of the Noninferiority Boundary

For studies comparing interventions, it is customary to use data comparing the standard intervention with placebo, but data on the risk of vigorous or nonvigorous exercise are not available. We had a dual rationale for using an HR of 1.5 as the upper bound. First, the consensus of our steering committee and investigators was that 1.5 represented a clinically relevant margin. Second, 1.5 has been suggested as appropriate in trials in which no data are available on standard placebo differences.[31] This margin is similar to ranges reported in the literature for large trials.

Analysis of Primary and Secondary Outcomes

The primary outcome variable is a composite end point of time to first of SCD, SCA, appropriate ICD shock (for ventricular arrhythmia), or syncope deemed arrhythmic by the Clinical Events Committee. Time was calculated from date of enrollment to date of either the first event or last survey or clinical follow-up (censor). Kaplan-Meier plots were constructed to show event-free survival. The noninferiority hypothesis was that those participants who reported vigorous activity at enrollment were no more likely to have an event than those who reported nonvigorous activity (ie, not inferior within the specified margin based on an HR of 1.5). Event likelihood was compared between groups with Cox regression including activity level (vigorous versus nonvigorous activity) and prespecified covariates for age, sex, race, recruitment method (site or self), and presence of an ICD. Linear contrasts were estimated to compare the hazards of the vigorous group with those of the nonvigorous group. Noninferiority was concluded when the upper boundary of the 90% one-sided Wald CI was <1.5. Pairwise noninferiority comparisons of vigorous with moderate and sedentary groups were also performed per the original analysis plan.

Post hoc sensitivity analyses were performed including events that had been reported on surveys by patients but for which confirmation or details could not be obtained. Prespecified exploratory analyses were performed in subgroups of clinical interest, including a genotype-specific subset analysis of LQT1 and LQT2 and the subset of younger individuals 14 to 22 years of age, in whom high-level competition is common. For this group, 3 subgroups were defined: vigorous-competitive, including those competing in sports defined as vigorous on varsity, junior varsity, or traveling teams and thus clearly meeting previous definitions of competitive[1]; other vigorous, including lower-level competition and noncompetitive vigorous exercise; and nonvigorous as described previously. Because only 5 events were reported in this subset, only unadjusted analysis was performed. Sensitivity analyses were performed with masters athletes (those >35 years of age)[32] and genotype-negative/unknown participants removed.

Data sharing is not yet available.

RESULTS

Patient Population

Demographic, clinical, and genotype data are shown for vigorous and nonvigorous groups (Table 1) and with

Table 1. Baseline Demographic, Genetic, and Clinical Data

	Total (N=1413)	Nonvigorous (n=676)	Vigorous (n=737)	*P* value	Vigorous-competitive (n=409)	Vigorous-noncompetitive (n=328)	*P* value
Age, mean±SD, y	28.3±14.6	30.6±14.7	26.2±14.3	<0.001	21.0±12.2	32.8±14.0	<0.001
Age, n (%)				<0.001			<0.001
8–13 y	298 (21.1)	117 (17.3)	181 (24.6)		142 (34.7)	39 (11.9)	
14–22 y	333 (23.6)	127 (18.8)	206 (28.0)		151 (36.9)	55 (16.8)	
23–35 y	303 (21.4)	172 (25.4)	131 (17.8)		48 (11.7)	83 (25.3)	
36–49 y	363 (25.7)	189 (28.0)	174 (23.6)		55 (13.5)	119 (36.3)	
50–60 y	116 (8.2)	71 (10.5)	45 (6.1)		13 (3.2)	32 (9.8)	
BMI, mean±SD, kg/m^2	24.1±6.2	25.1±7.0	23.3±5.2	<0.001	22.3±4.8	24.4±5.5	<0.001
Sex, n (%)				<0.001			<0.001
Male	472 (33.4)	175 (25.9)	297 (40.3)		187 (45.7)	110 (33.5)	
Female	941 (66.6)	501 (74.1)	440 (59.7)		222 (54.3)	218 (66.5)	
Race, n (%)				0.89			0.17
White	1314 (93.9)	624 (93.6)	690 (94.3)		378 (92.9)	312 (96.0)	
Black or African American	0027 (01.9)	15 (02.2)	012 (01.6)		9 (2.2)	3 (0.9)	
American Indian/Alaska Native	0007 (00.5)	04 (00.6)	003 (00.4)		3 (0.7)	0 (0.0)	
Asian, Native Hawaiian, or Other Pacific Islander	0024 (01.7)	12 (1.8)	012 (1.6)		6 (1.5)	6 (1.8)	
Multiracial	0027 (01.9)	12 (1.8)	015 (2.0)		11 (2.7)	4 (1.2)	
Hispanic or Latino ethnicity, n (%)				0.04			0.98
Yes	67 (4.8)	40 (6.0)	27 (3.7)		15 (3.7)	12 (3.7)	
No	1338 (95.2)	631 (94.0)	707 (96.3)		391 (96.3)	316 (96.3)	
Enrollment origin, n (%)				0.71			<0.001
Self	401 (28.4)	195 (28.9)	206 (28.0)		90 (22.0)	116 (35.4)	
Site	1012 (71.6)	481 (71.2)	531 (72.1)		319 (78.0)	212 (64.6)	
Genotype, n (%)*				0.65			0.25
LQT1	636 (45.0)	307 (45.4)	329 (43.4)		198 (48.4)	131 (39.9)	
LQT2	425 (30.1)	207 (30.6)	218 (29.6)		113 (27.6)	105 (32.0)	
LQT3	85 (6.0)	35 (5.2)	50 (6.8)		24 (5.9)	26 (7.9)	
LQT1 plus other	41 (2.9)	22 (3.3)	19 (2.6)		10 (2.4)	9 (2.7)	
Other genes or combinations	66 (4.7)	34 (5.0)	32 (4.4)		18 (4.4)	14 (4.3)	
Negative	83 (5.9)	34 (5.0)	49 (6.7)		22 (5.4)	27 (8.2)	
Untested/unknown	77 (5.4)	37 (5.5)	40 (5.4)		24 (5.8)	16 (4.9)	
Resting QTc, mean±SD, ms	491.7±44.1	491.3±46.2	492.2±42.2	0.72	486.7±35.3	498.7±48.5	<0.001
Resting QTc, n (%)				0.10			0.23
Rest QTc within normal range	458 (32.4)	238 (35.2)	220 (29.9)		92 (28.0)	128 (31.3)	
Rest QTc increased (>470 ms in male participants/480 ms in female participants)	841 (59.5)	386 (57.1)	455 (61.7)		213 (64.9)	242 (59.2)	
Resting QTc ≥500 ms	461 (35.5)	229 (36.7)	232 (34.4)	0.38	113 (30.5)	110 (39.0)	0.02
Resting QTc ≥550 ms	115 (8.9)	64 (10.3)	51(7.6)	0.09	15 (4.1)	36 (11.8)	0.0001
Previous symptoms, n (%)				0.05			<0.001
Arrest/VT/VF	159 (11.3)	84 (12.4)	75 (10.2)		29 (7.1)	46 (14.0)	
Syncope	478 (33.8)	243 (35.9)	235 (31.9)		119 (29.1)	116 (35.4)	
None	776 (54.9)	349 (51.6)	427 (57.9)		261 (63.8)	166 (50.6)	
Arrest during exercise†	16 (11.4)	5 (6.8)	11 (16.7)	0.07	7 (25.9)	4 (10.3)	0.09
Syncope during exercise‡	175 (36.6)	84 (34.6)	91 (38.7)	0.62	43 (36.1)	48 (41.4)	0.44
Mode diagnosis, n (%)				0.24			0.04
Symptoms	374 (26.5)	179 (26.5)	195 (26.5)		92 (22.5)	103 (31.4)	

(*Continued*)

Table 1. Continued

	Total (N=1413)	Nonvigorous (n=676)	Vigorous (n=737)	*P* value	Vigorous-competitive (n=409)	Vigorous-noncompetitive (n=328)	*P* value
Family screening	810 (57.3)	393 (58.1)	417 (56.6)		241 (58.9)	176 (53.7)	
Electrocardiographic screening	6 (0.4)	1 (0.1)	5 (0.7)		2 (0.5)	3 (0.9)	
Incidental/other	155 (11.0)	77 (11.4)	78 (10.6)		45 (11.0)	33 (10.1)	
≥2 of the above	67 (4.7)	25 (3.7)	42 (5.7)		29 (7.1)	13 (4.0)	
Family history of LQT, n (%)	1219 (87.0)	584 (87.3)	635 (86.7)	0.07	352 (86.7)	283 (86.8)	0.99
Family history of SCD or resuscitated cardiac arrest, n (%)	718 (51.4)	369 (55.4)	349 (47.8)	0.03	185 (45.6	164 (50.6)	0.46
Beta-blocker, n (%)	1191 (84.3)	568 (84.0)	623 (84.5)	0.79	361 (88.3)	262 (79.9)	0.002
Nadolol or propranolol (% of those on beta-blocker), n (%)	927 (77.8)	432 (76.1)	495 (79.5)	0.20	299 (82.8)	196 (74.8)	<0.001
Mexiletine, n (%)	25 (1.8)	13 (1.9)	12 (1.6)	0.67	8 (2.0)	4 (1.2)	0.43
LCSD, n (%)	73 (5.2)	31 (4.6)	42 (5.7)	0.35	28 (06.8)	14 (04.3)	0.14
ICD present, n (%)	360 (25.5)	200 (29.6)	160 (21.7)	0.0007	61 (14.9)	99 (30.2)	<0.001
Any of above 3 vs none, n (%)	1285 (90.9)	618 (91.4)	667 (90.5)	0.55	377 (92.2)	290 (88.4)	0.08
Either beta-blocker or LCSD, n (%)	1214 (85.9)	580 (85.8)	634(86.0)	0.90	367 (89.7)	267 (81.4)	0.001
ICD indication, n (%)				0.71			0.96
Secondary prevention (arrest/VT/VF)	110 (31.8)	62 (32.3)	48 (31.1)		17 (28.8)	31 (32.7)	
Syncope	135 (39.0)	70 (36.5)	65 (42.2)		26 (44.1)	39 (41.1)	
Primary prevention	101 (29.2)	60 (31.3)	41 (26.6)		16 (27.1)	25 (26.3)	
First therapy zone rate cutoff, bpm (mean, standard deviation)	207.4 (15.4)	206.5 (15.8)	208.5 (14.9)	0.25	210.3 (15.2)	207.4 (14.8)	0.26
Pacemaker	20 (1.4)	8 (1.2)	12 (1.6)	0.002	4 (1.0)	8 (2.4)	<0.001

BMI indicates body mass index; ICD, implantable cardioverter defibrillator; LCSD, left cardiac sympathetic denervation; LQT, long QT; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Details for "other genes or combinations" appear in Table S8.

*Variants of uncertain significance were not considered positive.

†Denominator is number of patients who had a history of arrest.

‡Denominator is number of patients who had a history of syncope.

the nonvigorous divided into moderate and sedentary groups (Table S1). Among the 1413 participants, 67% were female, the mean age was 28±5 years. One hundred and fifty two were categorized as sedentary (11%), 524 (37%) participated in moderate-intensity exercise, and 737 (52%) participated in vigorous-intensity exercise. Among those engaging in vigorous exercise, 409 of 737 (55%) participated in at least 1 organized competitive sport (vigorous-competitive), and 328 (45%) were noncompetitive vigorous exercisers. Those engaging in vigorous exercise were on average younger, had lower body mass index, and were less likely to be female, to have an ICD, or to have experienced previous symptoms (syncope or SCA). Among those with ICDs, rate cutoff for therapy did not differ: 207±16 bpm versus 209±15 bpm (*P*=0.25). The presence of electrocardiographically manifest LQTS, defined as a resting QTc of ≥470 ms for male and 480 ms for female participants, was overall 60% and did not differ between exercise groups, nor did the presence of more severe QT prolongation (36% >500 ms and 9% >550 ms). Prescription of beta-blocking medications also did not differ in 84% overall; prescription of nonselective beta-blockers was also similar at 78% of those prescribed beta-blockers. Genotype distribution was similar. Self-enrolled participants made up 28% of both exercise groups. Characteristics of self- versus site-enrolled patients are shown in Table S2. Mean follow-up time was 37±12 months and did not differ between groups. Overall, 19% of participants reported that a physician whom they had seen recommended no or light activity only, and an additional 39% reported that competition was recommended to be completely or partially restricted (total 58%).

Those who exercised vigorously in a competitive fashion compared with those exercising vigorously for recreation on average were younger, had lower body mass index, were less likely to be female, were less likely to have symptoms, and were less likely to be self-enrolled. There was no difference in presence of manifest LQTS. The competitive exercisers were less likely to have an ICD and more likely to be prescribed beta-blockers. The ICD rate cutoff was 210±15 bpm in competitive and 207±15 bpm in vigorous-noncompetitive exercisers (*P*=0.26). Among vigorous-competitive exercisers, 142 were 8 to 13 years of age and participating in leagues; 151 were 14 to 22 years of age, among whom 116 participated on varsity, junior varsity, or traveling teams; and 116 were 23 to 60 years of age and participating in

leagues or organized events. The most common sports were baseball, basketball, running, soccer, and volleyball (Table S3).

Outcomes

As shown in Table 2, only 37 individuals (2.6%) reached the composite end point of SCD, SCA, appropriate ICD therapy (with or without syncope), or arrhythmic syncope. Eighteen (2.7%) of those classified as nonvigorous exercisers and 19 (2.6%) of those classified as vigorous exercisers experienced the composite end point, with corresponding rates of 8.6 events per 1000 patient-years in the nonvigorous group and 8.3 per 1000 person-years in the vigorous group. Events in sedentary, moderate, and vigorous exercisers are shown in Table S4 Event-free survival is shown in Figure 2 for the comparison of vigorous with nonvigorous exercisers and Figure S1 for the 3 exercise categories separately. There were no statistically significant differences in freedom from composite end points between the vigorous and nonvigorous groups.

Two participants experienced resuscitated SCA, and one participant died suddenly. One SCA occurred in a 17-year-old male individual in the nonvigorous group (LQT1, QTc 480 ms, prescribed propranolol), which occurred when he jumped off a bridge into the water for recreation. Another SCA occurred in a 17-year-old female participant in whom genetic testing not performed who was prescribed nadolol, had a QTc 481 ms, exercised vigorously, and competed in cheerleading; the SCA occurred while she was getting out of a pool after swimming recreationally. It is notable that both were described as noncompliant with beta-blocker therapy. The only SCD occurred in a 31-year-old woman who had been diagnosed initially with LQT1 at the time of study enrollment but was diagnosed subsequently with concomitant arrhythmogenic bileaflet mitral valve prolapse syndrome.[33] The sudden death occurred in the setting of an ICD with therapies that were purposefully deactivated by the patient.

Other Variables and Association With Outcome

As described in Table 3, individuals experiencing the composite outcome were more likely to have a history of syncope or cardiac arrest, to have an ICD, to be of Black race, and to have a prolonged QTc and less likely to be prescribed a beta-blocker. Other variables did not differ.

Of the 27 individuals receiving appropriate ICD shocks, 25 had received the ICD for secondary prevention. Event rate did not differ between genotype-positive individuals and those negative or unknown/untested (Table 3; Table S5). Of the vigorous exercisers who were genotype-negative (n=49) or unknown or untested (n=40), just 3 and 1, respectively, had neither a personal

Table 2. End-Point Events

	Nonvigorous (n=676)	Vigorous (n=737)	Total (n=1413)	Vigorous-competitive (n=409)	Vigorous-noncompetitive (n=328)
Follow-up time composite, mo	37.2±12.3	37.2±12.6	37.2±12.5	37.2±13.0	37.2±12.1
Total combined arrhythmic end point					
n (%)	18 (2.7)	19 (2.6)	37 (2.6)	12 (2.9)	7 (2.1)
Rate per 1000 person-y (95% CI)	8.6 (5.4–13.6)	8.3 (5.3–13.1)	8.5 (6.1–11.7)	9.5 (5.4–16.7)	6.9 (3.3–14.4)
Individual end points					
SCD					
n (%)	1 (0.1)	0	1 (0.07)	0	0
Rate per 1000 person-y (95% CI)	0.5 (0.1–3.3)	0 (0–1.6)	0.2 (0–1.6)	0 (0–2.9)	0 (0–3.6)
SCA					
n (%)	1 (0.1)	1 (0.1)	2 (0.1)	1 (0.2)	0
Rate per 1000 person-y (95% CI)	0.5 (0.1–3.3)	0.4 (0.1–3.1)	0.4 (0.1–1.8)	0.8 (0.1–5.5)	0 (0–3.6)
Arrhythmic syncope (VT/VF), patients with an ICD					
n (%)	13 (1.9)	12(1.6)	26 (1.8)	8 (2.0)	4 (1.2)
Rate per 1000 person-y (95% CI)	6.2 (3.6–10.7)	5.3 (3.0–9.3)	5.7 (3.9–8.5)	6.3 (3.2–12.7)	3.9 (1.5–10.5)
Definite or likely arrhythmic syncope, patients without an ICD					
n (%)	4 (0.6)	3 (0.4)	7 (0.5)	2 (0.5)	1 (0.3)
Rate per 1000 person-y (95% CI)	1.9 (0.7–5.1)	1.3(0.4–4.1)	1.6 (0.8–3.4)	1.6 (0.4–6.4)	1.0 (0.1–7.0)
Appropriate ICD shock (no syncope)					
n (%)	1 (0.1)	7 (0.9)	8 (0.6)	4 (1.0)	3 (0.9)
Rate per 1000 person-y (95% CI)	0.5 (0.1–3.3)	3.0 (1.4–6.4)	1.2 (0.4–3.4)	3 (1.2–8.3)	2.9 (0.9–9.1)

ICD indicates implantable cardioverter defibrillator; SCA, sudden cardiac arrest; SCD, sudden cardiac death; VF, ventricular fibrillation; and VT, ventricular tachycardia.

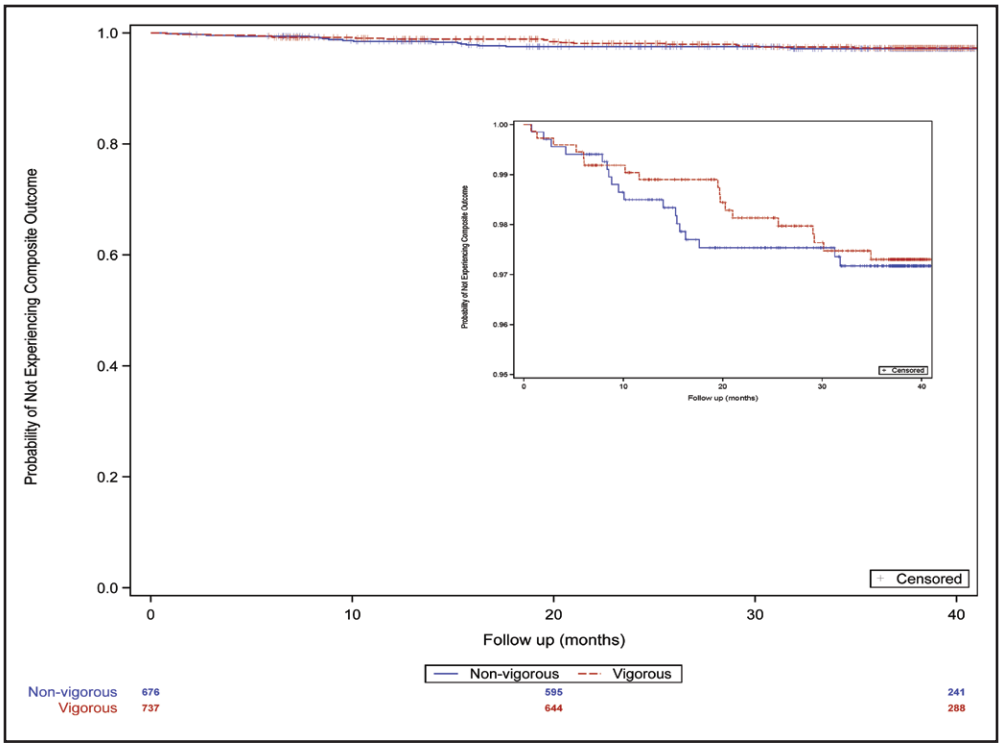

Figure 2. Kaplan-Meier survival curve for freedom from composite end point (death, sudden cardiac arrest, appropriate implantable cardioverter defibrillator shock, or arrhythmic syncope) by exercise group.
There was no statistically significant difference in freedom from composite end points between the those exercising vigorously and those exercising nonvigorously. Inset shows a magnified *y* axis.

history of arrest or syncope nor a family history of sudden death or LQTS. Among those receiving shocks, the rate cutoff did not differ between the vigorous and nonvigorous groups (mean±SD, 212.7±10.9 bpm versus 212.1±19.7 bpm). Event rate did not differ between participants enrolled by sites and those who self-enrolled (Table 3; Table S2).

Primary Analysis

In multivariable Cox regression analysis of the primary prespecified composite end point, for individuals engaging in vigorous exercise, the unadjusted HR for experience of events compared with those in the nonvigorous group was 0.97; the adjusted HR was 1.17. The upper 95% one-sided confidence level for the adjusted HR was 2.04 (ie, 90% 2-sided upper confidence level), not below the prespecified boundary of 1.5 for noninferiority (Figure 3).

Prespecified Exploratory Analyses and Sensitivity Analyses

As shown in Figure 3, in subgroups based on genotype, LQT1 and LQT2, HRs for events in vigorous versus nonvigorous exercisers were similar to that for the overall group and also similar for those with and without symptoms before enrollment and those with and without manifest LQTS (ie, resting QTc ≥470 ms for male and 480 ms for female participants). In sensitivity analyses removing masters athletes, HRs were similar with wider CIs (unadjusted HR, 1.07 [90% one-sided CI, 0.57–2.00]; adjusted HR, 1.42 [90% one-sided CI, 0.74–2.71]). In sensitivity analysis removing participants who were genotype negative or unknown, HRs were also similar with wider CIs (unadjusted HR, 0.83 [CI, 0.45–1.51]; adjusted HR, 1.08 [CI, 0.59–2.02]).

In neither the primary analysis nor any of the subanalyses was either nonvigorous or vigorous exercise demonstrated to be superior. In all groups and subgroups, CIs were wide and included effect sizes that could demonstrate superiority in either direction. Sensitivity analyses including events for which confirming data were not available and excluding the patient later diagnosed with arrhythmogenic bileaflet mitral valve prolapse syndrome showed similar findings. In prespecified pairwise comparison of vigorous, moderate, and sedentary exercisers, no group was noninferior or superior to another.

Prespecified Exploratory Analysis in the Young

There were 333 individuals 14 to 22 years of age, of whom 116 participated on varsity/junior varsity/traveling teams (vigorous competitive), 90 engaged in other vigorous exercise, and 127 engaged in moderate activity or were sedentary (nonvigorous) Demographic and clinical

Table 3. Baseline Demographic, Genetic, and Clinical Data: Subjects With Events Versus Subjects Without Events

	Total (n=1413)	Subjects without events (n=1376)	Subjects with events (n=37)	*P* value
Exercise group				0.92
Vigorous	737 (52.2)	718 (52.2)	19 (51.4)	
Nonvigorous	676 (47.8)	658 (47.8)	18 (48.6)	
Age, mean (SD), y	28.3 (14.6)	28.4 (14.6)	26.0 (14.5)	0.33
Age, n (%)				0.51
8–13 y	298 (21.1)	287 (20.9)	11 (29.7)	
14–22 y	333 (23.6)	326 (23.7)	7 (18.9)	
23–35 y	303 (21.4)	293 (21.3)	10 (27.0)	
36–49 y	363 (25.7)	356 (25.9)	7 (18.9)	
50–60 y	116 (8.2)	114 (8.3)	2 (5.4)	
BMI, mean (SD), kg/m^2	24.1 (6.2)	24.2 (6.2)	22.6 (5.7)	0.12
Sex, n (%)				0.12
Male	472 (33.4)	464 (33.7)	8 (21.6)	
Female	941 (66.6)	912 (66.3)	29 (78.4)	
Race, n (%)				0.04
White	1314 (93.0)	1282 (93.2)	32 (86.5)	
Black or African American	27 (1.9)	24 (1.7)	3 (8.1)	
American Indian/Alaska Native	7 (0.5)	7 (0.5)	0 (0.0)	
Asian, Native Hawaiian, or Other Pacific Islander	24 (1.7)	24 (1.7)	0 (0.0)	
Multiracial	27 (1.9)	25 (1.8)	2 (5.4)	
Hispanic or Latino ethnicity, n (%)				0.55
Yes	67 (4.8)	66 (4.8)	1 (2.7)	
No	1338 (95.2)	1302 (95.2)	36 (97.3)	
Genotype, n (%)*				0.02
LQT1	636 (45.1)	627 (45.6)	9 (24.3)	
LQT2	425 (30.1)	414 (30.1)	11 (29.7)	
LQT3	85 (6.0)	81 (5.9)	4(10.8)	
LQT1 plus other	41(2.9)	37 (2.7)	4 (10.8)	
Other channels or combinations	66 (4.7)	64 (4.7)	2 (5.4)	
Negative/variants of uncertain significance	83 (5.9)	79 (5.7)	4 (10.8)	
Unknown/untested	77 (5.4)	74 (5.4)	3 (8.1)	
QTc				
Resting QTc, mean (SD), ms	491.7 (44.1)	490.4 (42.8)	541.2 (62.9)	<0.001
Resting QTc, n (%)				
Rest QTc within normal	458 (32.4)	455 (33.1)	3 (8.1)	0.006
Rest QTc increased (≥470 ms for male/480 ms for female participants)	841 (59.5)	811 (58.9)	30 (81.1)	0.02
Resting QTc ≥500 ms	461 (35.5)	437 (34.5)	24 (72.7)	<0.001
Resting QTc ≥550 ms	115 (8.9)	103 (8.1)	12 (36.4)	<0.001
Previous symptoms				<0.0001
Arrest/VT/VF	159 (11.3)	145 (10.5)	14 (37.8)	
Syncope	478 (33.8)	458 (33.3)	20 (54.1)	
None	776 (54.9)	773 (56.2)	3 (8.1)	
Arrest during exercise†	16 (11.4)	15 (11.7)	1 (8.3)	0.72
Syncope during exercise‡	175 (36.6)	166 (36.2)	9 (45.0)	0.07

(*Continued*)

Table 3. Continued

	Total (n=1413)	Subjects without events (n=1376)	Subjects with events (n=37)	*P* value
Mode diagnosis, n (%)				<0.0001
Symptoms	374 (26.5)	345 (25.1)	29 (78.4)	
Family screening	810 (57.3)	805 (58.5)	5 (13.5)	
Electrocardiographic screening	6 (0.4)	6 (0.4)	0 (0.0)	
Incidental/other	155 (11.0)	155 (11.3)	0 (0.0)	
2 or more of the above	67 (4.7)	64 (4.7)	3 (8.1)	
Family history of LQT, n (%)	1219 (87.0)	1195(87.5)	24 (66.7)	0.0006
Family history of SCD or resuscitated cardiac arrest, n (%)	718 (51.4)	707 (52.0)	11 (30.6)	0.06
Beta-blocker, n (%)	1191 (84.3)	1164 (84.6)	27 (73.0)	0.05
Nadolol or propranolol, n (% of those on beta-blocker)	927 (65.6)	902 (65.6)	25 (67.6)	0.80
Mexiletine, n (%)	25 (1.8)	21 (1.5)	4 (10.8)	0.003
LCSD, n (%)	73 (5.2)	69 (5.0)	4 (10.8)	0.12
ICD present, n (%)	361 (25.5)	332 (24.1)	29 (78.4)	<0.0001
Any of above 3 vs none, n (%)	1285 (90.9)	1251 (90.9)	34 (91.9)	0.84
Either beta-blocker or LCSD, n (%)	1214 (85.9)	1186 (86.2)	28 (75.7)	0.07
ICD indication, n (%)				0.03
Secondary prevention (arrest/VT/VF)	95 (27.5)	83 (26.1)	12 (42.9)	
Syncope	135 (39.0)	121 (38.1)	14 (50.0)	
Primary prevention	101 (29.2)	99 (31.1)	2 (7.1)	
Zone 1 cutoff	207.4 (15.4)	206.9 (15.3)	211.9 (15.9)	0.10
Pacemaker	20 (1.4)	20 (1.5)	0	<0.0001

BMI indicates body mass index; ICD, implantable cardioverter defibrillator; LCSD, left cardiac sympathetic denervation; LQT, long QT; SCD, sudden cardiac death; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*Variants of uncertain significance were not considered positive.

†Denominator is number of patients who had a history of arrest.

‡Denominator is number of patients who had a history of syncope.

characteristics are shown in Table S6. There were 2 individuals with outcome events in the vigorous-competitive group, both with appropriate ICD shocks (1.7%,); 2 in the other vigorous group (2.2%, both appropriate ICD shocks); and 3 with outcome events in the nonvigorous group (2.5%, 1 SCA [described previously], and 2 appropriate ICD shocks.) Corresponding event rates per 1000 person-years in this age group were 5.6, 7.4, and 7.8 for the vigorous-competitive, other vigorous, and nonvigorous groups, respectively (Table S7). The HR for those 14 to 22 years of age in this vigorous-competitive group compared with others combined was 0.74 (CI, 0.19-2.96; Figure 3).

DISCUSSION

In this prospective study of 1413 individuals with LQTS, the overall event rate was low, with only 2.6% of those exercising vigorously and 2.7% of those exercising nonvigorously experiencing a probable LQTS-triggered arrhythmic event during over 3 years of follow-up. A similarly low rate was seen in young vigorous-competitive athletes (varsity, junior varsity, or traveling team). There were only 2 cardiac arrests, just one in a participant who engaged in habitual vigorous exercise, but neither event occurred during vigorous exercise. Most of the other events were appropriate ICD shocks in individuals previously identified as at higher risk. The only death was in a woman with LQT1 who was identified subsequent to enrollment to have an additional condition (arrhythmogenic bileaflet mitral valve prolapse syndrome) that also predisposes to ventricular arrhythmias and occurred in the context of purposeful ICD deactivation. Characteristics known to be associated with arrhythmic events in LQTS (QTc duration, previous symptoms, and absence of beta-blocker) were associated with arrhythmia recurrence in this study.

In all groups and subgroups, although the HR point estimates were near unity, CIs were wide and noninferiority was not demonstrated at the prespecified noninferiority threshold. This most likely stemmed from the fact that the observed overall event rate (<1% per year) was markedly lower than the study design–estimated event rate of >4% per year that was based on historical data at the time of the original study design (circa 2014), with resultant limited statistical power. However, effect sizes that could demonstrate the superiority of either

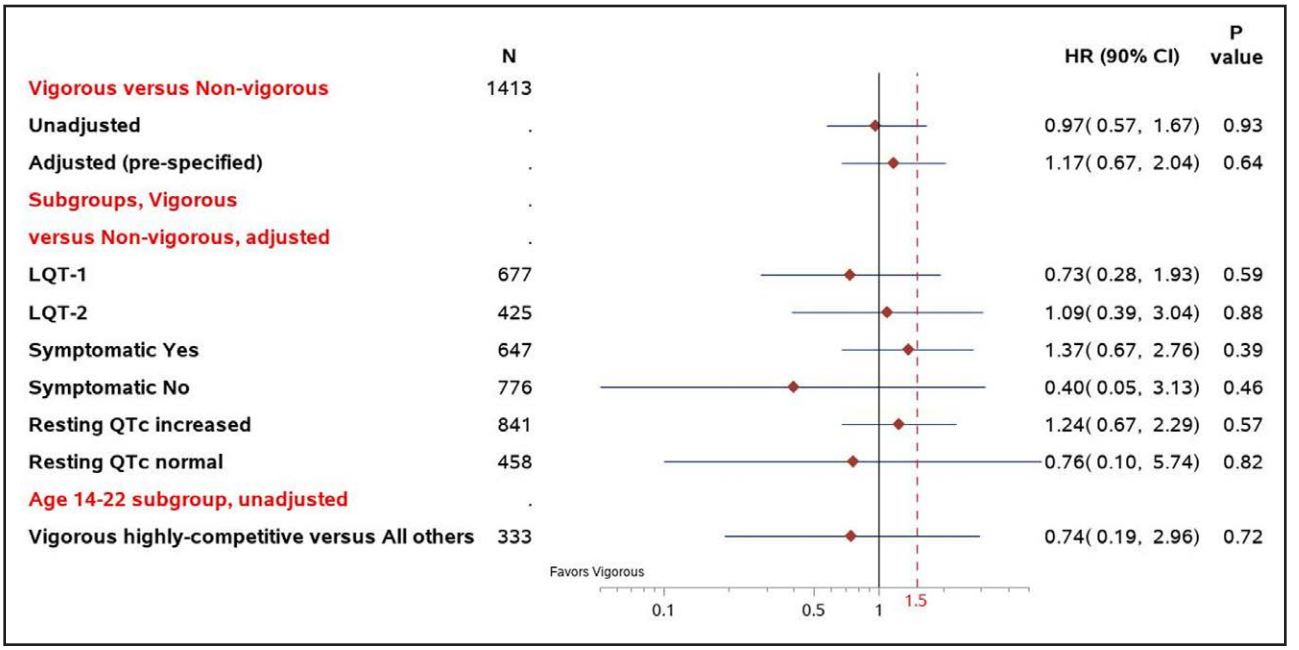

Figure 3. Forest plot for HR (one-sided 95% CI) comparing composite outcomes between exercise groups.
Hazard ratios (HRs) for primary, secondary, and post hoc analyses comparing the composite outcome (death, sudden cardiac arrest, appropriate implantable cardioverter defibrillator shock, arrhythmic syncope) between those exercising vigorously and those exercising nonvigorously. The 90% 2-sided CIs are presented. Upper limits of these intervals correspond to a one-sided 0.05 significance level used to evaluate noninferiority. Primary analysis is shown followed by post hoc analysis including clinical factors (QTc and presence of previous symptoms) and then post hoc analyses of subgroups known to differ in outcome rates: first, those with the 2 most common long QT (LQT) genotypes, LQT1 and LQT2; next, those with and without previous symptoms (syncope or cardiac arrest); and then those with and without prolonged resting QTc (≥470 ms for male participants or 480 ms for female participants). Finally, the subgroup of individuals from 14 to 22 years of age participating in vigorous-competitive exercise (varsity/junior varsity/traveling team) is compared with others in this age group.

vigorous or nonvigorous exercise fall within the CIs for all groups, with similar findings in pairwise comparisons between vigorous, moderate, and sedentary groups. Similarly, vigorous and nonvigorous exercisers differed in some characteristics associated with occurrence of events. Subgroup analyses showed similar HRs, the CIs were similarly wide. In addition, age, sex, and genotype show complex interactions in LQTS. Thus, although limited power and wide CIs preclude definitive conclusions, these data do not support what has been the widespread practice of universal restriction of vigorous-intensity exercise in patients with LQTS or the absence of restriction. This study further supports the importance of other previously demonstrated risk factors.

Retrospective single-center series have suggested that athletes with LQTS can continue to compete without reporting life-threatening events.[11–15] In response to these retrospective case series, the most recent (2015) American Heart Association/American College of Cardiology "Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities" statement no longer recommended universal restriction.[16] However, in the absence of prospective, comparative data, this recommendation remained conservative, describing sports participation for individuals with LQTS as something that "may be considered" (Class 2B). Restriction from sports and vigorous exercise remains common, with 58% of our participants reporting at least 1 physician recommending some form of exercise restriction, including 19% restricted to no or light exercise only. Similarly, in a recent series of 76 elite athletes (including 20 with LQTS) who were participating in either Division I university sports or professional sports, three-quarters were disqualified initially.[17] European Society of Cardiology guidelines are even more restrictive, recommending against competitive exercise for individuals with LQTS who have had an arrest or syncope, with or without an ICD, and recommending restriction in those with prolonged QT[18] in the absence of prospective data in treated individuals at the time those guidelines were written.

In the present study, the rate of events in the 116 vigorous-competitive young athletes clearly meeting previous definitions of competitive athlete[1] was similarly low, 5.6 per 1000 patient-years. These data, in combination with the previous retrospective studies of patients with LQTS and other genetic heart conditions, including elite athletes, do not support the practice of defaulting toward restriction from vigorous and competitive exercise for individuals diagnosed with cardiac diseases based on prudence.[1] Only clinical data in those exercising can define safety, and only prospective, comparative data can determine the relative risk of exercise.

Historically, decision-making about return to sports for athletes with a diagnosis of inherited arrhythmia syndromes and other genetic heart diseases has been done by physicians in a paternalistic fashion based on the premise that only those whose risk is no greater than the general population should be allowed to participate.[1] These data support a movement away from such an approach toward shared decision-making about return to play.[34] Risk of a disease-associated life-threatening arrhythmia is not zero, and some events may occur during exertion. However, overall, comparative data between those who exercise vigorously and those who do not show similarly low rates of events, both in this study of patients with LQTS and described in a recent parallel study in hypertrophic cardiomyopathy.[19]

The overall rate of arrhythmic events in this study, 2.6%, is lower than reported previously[27–29] in both those exercising vigorously and those exercising nonvigorously. A critical characteristic of this study population is the very high proportion of participants receiving appropriate therapeutic interventions as recommended by professional society consensus statements.[35] The importance of adrenergic blockade cannot be overemphasized. Although the large majority were prescribed beta-blockers, shown to improve survival in LQTS[36] with three-quarters of these receiving the specific nonselective beta-blockers shown to be most effective,[8] the absence of beta-blockade was associated with arrhythmia occurrence. This impact may be even higher because overall adherence was not assessed. Although the 2 SCA events occurred in individuals prescribed the preferred beta-blockers, both were described as nonadherent at the time of arrest. ICDs are effective as secondary prevention for those surviving SCA or those with symptoms despite beta-blockers and rarely as primary prevention in those with markers of highest risk.[10] A small number had undergone left cardiac sympathetic denervation. More than 90% of participants were receiving at least one of these well-established, guideline-directed medical therapies.[35] Those experiencing events in this study were, as expected, in the high-risk group of patients with LQTS who have had previous symptoms. Our data suggest that appropriate treatment may mitigate the triggering effects of exercise described in series of individuals presenting with syncope or arrest before diagnosis.[5] Thus, these data can be extrapolated only to individuals correctly diagnosed, risk-stratified, and maintained on guideline-directed medical therapy. Similarly, participants receiving shocks were programmed with high rate cutoffs, shown in previous studies to reduce shocks in athletes without compromising safety,[37] and appropriate programming may have decreased the event rate. Whether the very low LQTS-triggered event rates in both vigorous and nonvigorous exercisers seen in this study can be extrapolated to patients managed outside of specialized centers cannot be determined.

Individuals genotype positive but with resting QTc in the normal range (electrocardiographically concealed LQTS) were included given the continued uncertainty about sports participation for this group. The risk of arrhythmic events is lower in these individuals than in those with manifest LQTS but higher than in unaffected relatives.[9] In the 2015 American Heart Association/American College of Cardiology eligibility document,[16] sports participation for these individuals remains a Class 2A recommendation.

About one-quarter of participants were self-enrolled. Although these patients were modestly less likely to receive guideline-directed medical therapy (Table S2), most were prescribed beta-blockers. Because these patients were equally represented in the exercise groups, these patients had similar event rates (Table S2), and enrollment type was controlled for in the a priori model, the inclusion of these participants is unlikely to have created a bias in the results. Similarly, genotype-negative and genotype-unknown participants made up 11% of the population overall. Exercise training can induce significant QT prolongation that normalizes with detraining,[38] and repeat ECG after detraining was not part of the study. It is possible that some participants with a negative genetic test may not have had genotype-negative LQTS but an acquired training effect on the QTc. However, the large majority of these participants had clinical history consistent with LQTS. These participants were similarly represented in the exercise groups and were equally likely to have an event, and sensitivity analysis excluding them showed similar findings, suggesting that misdiagnosis was unlikely to bias the results.

Limitations

The primary limitation of this study was the lower-than-expected LQTS-associated cardiac event rate, which precludes conclusion of noninferiority of vigorous exercise. This is likely because of the very high proportion of participants appropriately treated, as noted above. The observed event rate, <1% per year in all exercise groups, is in keeping with the very low event rate published in 2017 from the most recent large single-center series of evaluated, risk-stratified, and treated patients at the Mayo Clinic.[39] Although neither vigorous nor nonvigorous exercise was seen to be superior, the low event rate with subsequent decreased power makes β error possible. However, effect sizes that could demonstrate the superiority of either vigorous exercise or nonvigorous exercise falls within the CIs for all groups, not supporting superiority of either approach. In addition, LIVE participants may not be representative of all patients with LQTS. Recruitment materials were aimed at individuals engaging in any level of physical activity, "whether you like to walk, run or read a book." However, the percentage of those engaged in vigorous exercise

was higher than expected based on data on exercise practices in Americans in general.[30,40] It is likely that individuals interested in exercise were more interested in study participation. However, this overrepresentation of individuals engaged in vigorous exercise allowed robust comparisons and exploratory subgroup analyses. The possibility of survival bias (which could go in either direction) cannot be excluded. However, it is reassuring that findings were similar in the younger group. Age at cardiac arrest was not obtained, and whether exercise carries different risk for those individuals surviving an arrest in infancy, a very high-risk group,[41] cannot be determined. To what extent the highest risk remains for those surviving through childhood is not determined.

Most participants in this study were White. Racial and ethnic differences in genetic variants in SCD decedents have been described.[7] Although one genetic analysis found that among healthy individuals more Black than White participants carried variants in 4 LQTS-causing potassium channel genes,[42] pathogenicity is not described, and the only systematic study of the prevalence of LQTS was performed in a White European population.[2] The prevalence of LQTS in Black or other populations is not known. Further studies of LQTS in populations of more diverse ancestry, both in terms of exercise and in general, are needed. Compliance with follow-up physical activity surveys was not adequate for time-dependent analysis.

Conclusions

Arrhythmic events were low in these appropriately treated individuals with LQTS in both those exercising vigorously and those exercising moderately or who were sedentary. Most events occurred in those participants whose previous assessment indicated evidence of heightened risk. Noninferiority was not demonstrated, and wide CIs included the possibility of superiority of either vigorous or nonvigorous exercise. These data can inform individualized shared decision-making conversations between patients and physicians on vigorous exercise participation in the context of overall expert assessment and management of LQTS.

ARTICLE INFORMATION

Received October 13, 2023; accepted May 31, 2024.

Affiliations

Yale School of Medicine, New Haven, CT (R.L., M.B., C. Barth, J.D., F.L, L.S.). University of Pennsylvania, Philadelphia (S.D.). University of Michigan Hospital, Ann Arbor (S.D., M.A.C.). School of Exercise and Health, Shanghai University of Sport, China (B.A.). College of Health Solutions/Arizona State University, Phoenix (B.A.). VA Hospital, West Haven, CT (M.B.). Cleveland Clinic, OH (B.S.M., P.F.A.). Lurie Children's Hospital, Chicago, IL (B.S.M., G.W.). Hypertrophic Cardiomyopathy Association, Denville, NJ (L.S.). Cardiology Section, Cardiovascular and Genomics Research Institute, St. George's, University of London, UK (M.T.T.E., E.R.B.). Cardiology Department, St. George's University Hospitals NHS Foundation Trust, London, UK (M.T.T.E., E.R.B.). Boston Children's Hospital, MA (D.J.A.). Departments of Cardiovascular Medicine, Pediatric and Adolescent Medicine, and Molecular Pharmacology and Experimental Therapeutics; Divisions of Heart Rhythm Services and Pediatric Cardiology, Windland Smith Rice Genetic Heart Rhythm Clinic, Mayo Clinic, Rochester, MN (C. Bell, J.M.B., B.C.C., C.H.-T., M.J.A.). Children's National Hospital, Washington, DC (C.I.B.). C.S. Mott Children's Hospital, Ann Arbor, MI (D.B.). Keck Medicine of USC, Los Angeles, CA (D.S.C.). Leon H. Charney Division of Cardiology, NYU Grossman Sch of Medicine, New York (M.C.). The Heart Institute, Cincinnati Children's Hospital Med Center, OH (R.J.C.). Stanford University School of Medicine, Palo Alto, CA (A.M.D.). University of Nebraska Medical Center, Children's Nebraska, Omaha (C.C.E.). Tufts Medical Center, Boston, MA (N.A.M.E., M.S.L.). UPMC, Pittsburgh, PA (N.A.M.E.). University of Utah, Salt Lake City (S.P.E.). Division of Cardiology, University of Rochester Medical Center, NY (I.G., W.Z.). Faculty of Medicine and Health, University of Sydney/Royal Prince Alfred Hospital, Australia (B.G.). Department of Family Medicine, University of Washington, Seattle (K.H.). Johns Hopkins University, Baltimore, MD (C.A.J.,G.F.T.). University of Louisville School of Medicine, KY (C.J.). Department of Pediatrics, Monroe Carell Jr Children's Hospital at Vanderbilt and Vanderbilt University, Nashville, TN (P.K.). Sudden Arrhythmia Death Syndrome Foundation, Salt Lake City, UT (A.L.). University of Iowa Carver College of Medicine, Iowa City (I.H.L., B.O.). UT Southwestern Medical Center, Dallas, TX (M.S.L.). Department of Pediatrics, Texas Children's Hospital, Baylor College of Medicine, Houston (S.M.M.). Department of Medicine/Cardiology, Mayo Clinic, Rochester, MN (P.A.N.). St. Lukes Medical Center/Primary Children's Hospital, Boise, ID (E.V.S.). Institution British Columbia Children's Hospital, University of British Columbia, Vancouver, Canada (S.S.). University of Pennsylvania School of Medicine, Children's Hospital of Philadelphia (M.S.). Cardiac Inherited Disease Group, Starship Children's Hospital, Auckland, New Zealand (J.S.). Albert Einstein College of Medine, Bronx, NY (G.F.T.). National Heart & Lung Inst & MRC London Institute of Medical Sciences, Imperial College London, UK (J.S.W.). Royal Brompton & Harefield Hospitals, Guy's and St. Thomas' NHS Foundation Trust, London, UK (J.S.W.). Indiana University School of Medine, Carmel, IN (D.P.Z.).

Sources of Funding

This study was funded by National Heart Lung and Blood Institute 1R01HL125918. The funding source had no role in the design and conduct of study, collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Disclosures

Dr Lampert reports honoraria and research support from Medtronic, Abbott-St. Jude, and Boston Scientific, as well as serving on the Advisory Board for Medtronic. Dr Day received consulting and grant funding from Lexicon Pharmaceuticals, grant funding from Bristol Myers Squibb, and DMC from Cytokinetics. L. Salberg consulted for Biomarin. Dr Tome Esteban consulted for BMS and Cytokinetics. Dr Abrams served on the Scientific Advisory Board for Thryv Therapeutics and consulted for Rocket Pharmaceuticals. Dr Aziz served on the Medtronic Advisory Committee. Dr Behr consulted for Boston Scientific. Dr Berul received research funding from Medtronic. Dr Cerrone provided teaching and CME activities for Abbott and Medtronic. Dr Erickson received funding from Integer. Dr Estes reports consulting for Boston Scientific and Medtronic. Dr Ethridge reports funding from Spauling Research (ECG reading) and UpToDate. Dr James was a consultant for Pfizer and Lexeo Therapeutics and received research funding from Lexeo Therapeutics and StrideBio. Dr Law was a consultant for Medtronic and St. Jude and a speaker for Boston Scientific. Dr Olshansky, AstraZeneca DSMB (Data Safety Monitoring Board). Dr Noseworthy and Mayo Clinic have filed patents related to the application of artificial intelligence to the ECG for diagnosis and risk stratification and have licensed several A-ECG algorithms to Anumana. Dr Noseworthy and Mayo Clinic have a relationship with AliveCor related to the measurement of the QT interval on the Kardia device. Dr Shah was a consultant for Medtronic and Tenaya. Dr Ware received research support and/or consultancy fees from MyoKardia, Bristol Myers Squibb, Foresite Labs, Pfizer, and Health Lumen. Dr Ware is supported by Medical Research Council (UK), British Heart Foundation (RE/18/4/34215), and the NIHR Imperial College Biomedical Research Centre. Dr Ackerman has served as a consultant for Abbott, BioMarin Pharmaceuticals, Boston Scientific, Bristol Myers Squibb, Daiichi-Sankyo, Illumina, Invitae, Medtronic, Tenaya Therapeutics, and UpToDate. Dr Ackerman and Mayo Clinic are involved in an equity/royalty relationship with AliveCor, Anumana, ARMGO Pharma, Pfizer, and Thryv Therapeutics. The other authors report no conflicts.

Supplemental Material

Tables S1–S8
Figure S1

REFERENCES

1. Maron BJ, Zipes DP. 36th Bethesda Conference: eligibility recommendations for competitive athletes with cardiovascular abnormalities. *J Am Coll Cardiol*. 2005;45:1318–1321. doi: 10.1016/j.jacc.2005.02.006
2. Schwartz PJ, Stramba-Badiale M, Crotti L, Pedrazzini M, Besana A, Bosi G, Gabbarini F, Goulene K, Insolia R, Mannarino S, et al. Prevalence of the congenital long-QT syndrome. *Circulation*. 2009;120:1761–1767. doi: 10.1161/CIRCULATIONAHA.109.863209
3. Schwartz PJ, Ackerman MJ, Antzelevitch C, Bezzina CR, Borggrefe M, Cuneo BF, Wilde AAM. Inherited cardiac arrhythmias. *Nat Rev Dis Primers*. 2020;6:58. doi: 10.1038/s41572-020-0188-7
4. Antzelevitch C, Oliva A. Amplification of spatial dispersion of repolarization underlies sudden cardiac death associated with catecholaminergic polymorphic VT, long QT, short QT and Brugada syndromes. *J Intern Med*. 2006;259:48–58. doi: 10.1111/j.1365-2796.2005.01587.x
5. Schwartz PJ, Priori SG, Spazzolini C, Moss AJ, Michael Vincent G, Napolitano C, Denjoy I, Guicheney P, Breithardt G, Keating MT, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation*. 2001;103:89–95.
6. Peterson DF, Siebert DM, Kucera KL, Thomas LC, Maleszewski JJ, Lopez-Anderson M, Suchsland MZ, Harmon KG, Drezner JA. Etiology of sudden cardiac arrest and death in US competitive athletes: a 2-year prospective surveillance study. *Clin J Sport Med*. 2020;30:305–314. doi: 10.1097/JSM.0000000000000598
7. Guo L, Torii S, Fernandez R, Braumann RE, Fuller DT, Paek K-H, Gadhoke NV, Maloney KA, Harris K, Mayhew CM, et al. Genetic variants associated with unexplained sudden cardiac death in adult White and African American individuals. *JAMA Cardiol*. 2021;6:1013–1022. doi: 10.1001/jamacardio.2021.1573
8. Chockalingam P, Crotti L, Girardengo G, Johnson JN, Harris KM, van der Heijden JF, Hauer RN, Beckmann BM, Spazzolini C, Rordorf R, et al. Not all beta-blockers are equal in the management of long QT syndrome types 1 and 2: Higher recurrence of events under metoprolol. *J Am Coll Cardiol*. 2012;60:2092–2099. doi: 10.1016/j.jacc.2012.07.046
9. Goldenberg I, Horr S, Moss AJ, Lopes CM, Barsheshet A, McNitt S, Zareba W, Andrews ML, Robinson JL, Locati EH, et al. Risk for life-threatening cardiac events in patients with genotype-confirmed long-QT syndrome and normal-range corrected QT intervals. *J Am Coll Cardiol*. 2011;57:51–59. doi: 10.1016/j.jacc.2010.07.038
10. Wang M, Peterson DR, Rosero S, McNitt S, Rich DQ, Seplaki CL, Polonsky B, Goldenberg I, Zareba W. Effectiveness of implantable cardioverter-defibrillators to reduce mortality in patients with long QT syndrome. *J Am Coll Cardiol*. 2021;78:2076–2088. doi: 10.1016/j.jacc.2021.09.017
11. Johnson JN, Ackerman MJ. Competitive sports participation in athletes with congenital long QT syndrome. *JAMA*. 2012;308:764. doi: 10.1001/jama.2012.9334
12. Aziz PF, Sweeten T, Vogel RL, Bonney WJ, Henderson J, Patel KR, Shah MJ. Sports participation in genotype positive children with long QT syndrome. *JACC Electrophysiol*. 2015;1:62–70. doi: 10.1016/j.jacep.2015.03.006
13. Chambers KD, Beausejour Ladouceur V, Alexander ME, Hylind RJ, Bevilacqua L, Mah DY, Bezzerides V, Triedman JK, Walsh EP, Abrams DJ. Cardiac events during competitive, recreational, and daily activities in children and adolescents with long QT syndrome. *J Am Heart Assoc*. 2017;21:e005445. doi: 10.1161/JAHA.116.005445
14. Tobert KE, Bos JM, Garmany R, Ackerman MJ. Return-to-play for athletes with long QT syndrome or genetic heart diseases predisposing to sudden death. *J Am Coll Cardiol*. 2021;78:594–604. doi: 10.1016/j.jacc.2021.04.026
15. Tobert KE, Bos JM, Cannon BC, Ackerman MJ. Outcomes of athletes with genetic heart diseases and implantable cardioverter-defibrillators who chose to return to play. *Mayo Clin Proc*. 2022;97:2028–2039. doi: 10.1016/j.mayocp.2022.03.024
16. Ackerman MJ, Zipes DP, Kovacs RJ, Maron BJ. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 10: The Cardiac Channelopathies: a scientific statement from the American Heart Association and American College of Cardiology. *J Am Coll Cardiol*. 2015;66:2424–2428. doi: 10.1016/j.jacc.2015.09.042
17. Martinez KA, Bos JM, Baggish AL, Phelan DM, Tobert KE, Newman DB, Scherer E, Petek BJ, Ackerman MJ, Martinez MW. Return-to-play for elite athletes with genetic heart diseases predisposing to sudden cardiac death. *J Am Coll Cardiol*. 2023;82:661–670. doi: 10.1016/j.jacc.2023.05.059
18. Heidbuchel H, Arbelo E, D'Ascenzi F, Borjesson M, Boveda S, Castelletti S, Miljoen H, Mont L, Niebauer J, Papadakis M, et al. Recommendations for participation in leisure-time physical activity and competitive sports of patients with arrhythmias and potentially arrhythmogenic conditions, part 2: ventricular arrhythmias, channelopathies, and implantable defibrillators. *Europace*. 2021;23:147–148. doi: 10.1093/europace/euaa106
19. Lampert R, Ackerman MJ, Marino BS, Burg M, Ainsworth B, Salberg L, Tome Esteban MT, Ho CY, Abraham R, Balaji S, et al. Vigorous exercise in patients with hypertrophic cardiomyopathy. *JAMA Cardiol*. 2023;8:595–605. doi: 10.1001/jamacardio.2023.1042
20. Taylor HL, Jacobs DR Jr, Schucker B, Knudsen J, Leon AS, Debacker G. A questionnaire for the assessment of leisure time physical activities. *J Chronic Dis*. 1978;31:741–755. doi: 10.1016/0021-9681(78)90058-9
21. Leon AS, Jacobs DR Jr, DeBacker G, Taylor HL. Relationship of physical characteristics and life habits to treadmill exercise capacity. *Am J Epidemiol*. 1981;113:653–660. doi: 10.1093/oxfordjournals.aje.a113144
22. Richardson MT, Leon AS, Jacobs DR, Ainsworth BE, Serfass R. Comprehensive evaluation of the Minnesota Leisure Time Physical Activity Questionnaire. *J Clin Epidemiol*. 1994;47:271–281. doi: 10.1016/0895-4356(94)90008-6
23. Folsom AR, Jacobs DR Jr, Caspersen CJ, Gomez-Marin O, Knudsen J. Test-retest reliability of the Minnesota Leisure Time Physical Activity Questionnaire. *J Chronic Dis*. 1986;39:505–511. doi: 10.1016/0021-9681(86)90195-5
24. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR Jr, Tudor-Locke C, Greer JL, Vezina J, Whitt-Glover MC, Leon AS. 2011 Compendium of physical activities: a second update of codes and met values. *Med Sci Sports Exer*. 2011;43:1575–1581. doi: 10.1249/MSS.0b013e31821ece12
25. Physical Activity Guidelines Advisory Committee. *2018 Physical Activity Guidelines Advisory Committee Scientific Report*. US Department of Health and Human Services; 2018
26. Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, Fonarow GC, Jacobs JP, Jaff MR, Lichtman JH, et al. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *J Am Coll Cardiol*. 2015;66:403–469. doi: 10.1016/j.jacc.2014.12.018
27. Horner JM, Kinoshita M, Webster TL, Haglund CM, Friedman PA, Ackerman MJ. Implantable cardioverter defibrillator therapy for congenital long QT syndrome: a single-center experience. *Heart Rhythm*. 2010;7:1616–1622. doi: 10.1016/j.hrthm.2010.08.023
28. Schwartz PJ, Spazzolini C, Priori SG, Crotti L, Vicentini A, Landolina M, Gasparini M, Wilde AA, Knops RE, Denjoy I, et al. Who are the long-QT syndrome patients who receive an implantable cardioverter-defibrillator and what happens to them? Data from the European Long-QT Syndrome Implantable Cardioverter-Defibrillator (LQTS ICD) registry. *Circulation*. 2010;122:1272–1282. doi: 10.1161/CIRCULATIONAHA.110.950147
29. Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol*. 2008;51:2291–2300. doi: 10.1016/j.jacc.2008.02.068
30. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A; American College of Sports Medicine. Physical activity and public health updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007;116:1081–1093. doi: 10.1161/CIRCULATIONAHA.107.185649
31. Lange S, Freitag G. Choice of delta: requirements and reality: results of a systematic review. *Biom J*. 2005;47:12–27. doi: 10.1002/bimj.200410085
32. Churchill TW, Baggish AL. Cardiovascular care of masters athletes. *J Cardiovasc Transl Res*. 2020;13:313–321. doi: 10.1007/s12265-020-09987-2
33. Sriram CS, Syed FF, Ferguson ME, Johnson JN, Enriquez-Sarano M, Cetta F, Cannon BC, Asirvatham SJ, Ackerman MJ. Malignant bileaflet mitral valve prolapse syndrome in patients with otherwise idiopathic out-of-hospital cardiac arrest. *J Am Coll Cardiol*. 2013;62:222–230. doi: 10.1016/j.jacc.2013.02.060
34. Baggish AL, Ackerman MJ, Lampert R. Competitive sport participation among athletes with heart disease: a call for a paradigm shift in decision making. *Circulation*. 2017;136:1569–1571. doi: 10.1161/CIRCULATIONAHA.117.029639
35. Priori DL, Wilde AA, Horie M, Cho Y, Behr ER, Blom N, Brugada J, Chiang C, Huikuri H, Kannankeril P, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Heart Rhythm*. 2013;10:1932–1963. doi: 10.1016/j.hrthm.2013.05.014
36. Moss AJ, Zareba W, Hall WJ, Schwartz PJ, Crampton RS, Benhorin J, Vincent GM, Locati EH, Priori SG, Napolitano C, et al. Effectiveness and

limitations of beta-blocker therapy in congenital long-QT syndrome. *Circulation*. 2000;101:616–623. doi: 10.1161/01.cir.101.6.616
37. Olshansky B, Atteya G, Cannom D, Heidbuchel H, Saarel E, Anfinsen O-G, Cheng A, Gold MR, Müssigbrodt A, Patton KK, et al. Competitive athletes with implantable cardioverter defibrillators: how to program? Data from the Implantable Cardioverter-Defibrillator Sports Registry. *Heart Rhythm*. 2019;16:581–587. doi: 10.1016/j.hrthm.2018.10.032
38. Dagradi F, Spazzolini C, Castelletti S, Pedrazzini M, Kotta MC, Crotti L, Schwartz PJ. Exercise training-induced repolarization abnormalities masquerading as congenital long QT syndrome. *Circulation*. 2020;142:2405–2415. doi: 10.1161/CIRCULATIONAHA.120.048916
39. Rohatgi RK, Sugrue A, Bos JM, Cannon BC, Asirvatham SJ, Moir C, Owen HJ, Bos KM, Kruisselbrink T, Ackerman MJ. Contemporary outcomes in patients with long QT syndrome. *J Am Coll Cardiol*. 2017;70:453–462. doi: 10.1016/j.jacc.2017.05.046
40. Elgaddal N, Kramarow EA, Reuben C. Physical activity among adults aged 18 and over: United States, 2020. *NCHS Data Brief*. 2022:1–8.
41. Spazzolini C, Mullally J, Moss A, Schwartz P, McNitt S, Ouellet G, Fugate T, Goldenberg I, Jons C, Zareba W, et al. Clinical implications for patients with long QT syndrome who experience a cardiac event during infancy. *J Am Coll Cardiol*. 2009;54:832–837.
42. Ackerman MJ, Tester DJ, Jones GS, Will ML, Burrow CR, Curran ME. Ethnic differences in cardiac potassium channel variants: implications for genetic susceptibility to sudden cardiac death and genetic testing for congenital long QT syndrome. *Mayo Clin Proc*. 2003;78:1479–1487. doi: 10.4065/78.12.1479