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Vigorous Exercise in Patients With Hypertrophic Cardiomyopathy

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IMPORTANCE Whether vigorous intensity exercise is associated with an increase in risk of ventricular arrhythmias in individuals with hypertrophic cardiomyopathy (HCM) is unknown.

OBJECTIVE To determine whether engagement in vigorous exercise is associated with increased risk for ventricular arrhythmias and/or mortality in individuals with HCM. The a priori hypothesis was that participants engaging in vigorous activity were not more likely to have an arrhythmic event or die than those who reported nonvigorous activity.

DESIGN, SETTING, AND PARTICIPANTS This was an investigator-initiated, prospective cohort study. Participants were enrolled from May 18, 2015, to April 25, 2019, with completion in February 28, 2022. Participants were categorized according to self-reported levels of physical activity: sedentary, moderate, or vigorous-intensity exercise. This was a multicenter, observational registry with recruitment at 42 high-volume HCM centers in the US and internationally; patients could also self-enroll through the central site. Individuals aged 8 to 60 years diagnosed with HCM or genotype positive without left ventricular hypertrophy (phenotype negative) without conditions precluding exercise were enrolled.

EXPOSURES Amount and intensity of physical activity.

MAIN OUTCOMES AND MEASURES The primary prespecified composite end point included death, resuscitated sudden cardiac arrest, arrhythmic syncope, and appropriate shock from an implantable cardioverter defibrillator. All outcome events were adjudicated by an events committee blinded to the patient's exercise category.

RESULTS Among the 1660 total participants (mean [SD] age, 39 [15] years; 996 male [60%]), 252 (15%) were classified as sedentary, and 709 (43%) participated in moderate exercise. Among the 699 individuals (42%) who participated in vigorous-intensity exercise, 259 (37%) participated competitively. A total of 77 individuals (4.6%) reached the composite end point. These individuals included 44 (4.6%) of those classified as nonvigorous and 33 (4.7%) of those classified as vigorous, with corresponding rates of 15.3 and 15.9 per 1000 person-years, respectively. In multivariate Cox regression analysis of the primary composite end point, individuals engaging in vigorous exercise did not experience a higher rate of events compared with the nonvigorous group with an adjusted hazard ratio of 1.01. The upper 95% 1-sided confidence level was 1.48, which was below the prespecified boundary of 1.5 for noninferiority.

CONCLUSIONS AND RELEVANCE Results of this cohort study suggest that among individuals with HCM or those who are genotype positive/phenotype negative and are treated in experienced centers, those exercising vigorously did not experience a higher rate of death or life-threatening arrhythmias than those exercising moderately or those who were sedentary. These data may inform discussion between the patient and their expert clinician around exercise participation.

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Multimedia

Supplemental content

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Group Information: A list of additional members of the LIVE Consortium appears in Supplement 2.

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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 hypertrophic cardiomyopathy (HCM), the possibility that physical activity may heighten the risk of sudden cardiac death (SCD) has led to exercise restriction and disqualification from competitive sports. HCM is defined by unexplained left ventricular hypertrophy (LVH) and has a worldwide prevalence of approximately 1 in 500 individuals.[1] It is the most common genetic cardiomyopathy and is inherited as a mendelian trait in approximately 50% of patients, predominantly due to pathogenic variants in genes that encode sarcomeric proteins. In others, it is expressed as a complex trait with contributions from both polygenic and acquired factors. Some patients with HCM may experience symptoms of heart failure and atrial and/or ventricular arrhythmias, whereas others have normal longevity and good quality of life.[2] As HCM is a well-recognized cause of SCD in previously undiagnosed young individuals, including athletes,[3] there has been intense debate over the last 4 decades over medical recommendations around participation at any level of physical activity for individuals diagnosed with HCM, including recreational exercise and competitive sports. US and European consensus guidelines dating back to 1985[4] have recommended against vigorous recreational physical activity and ineligibility for sports participation for all patients with HCM—a conservative approach in light of the lack of any outcomes data. However, restriction from exercise has adverse consequences. Individuals with HCM exercise less than the general population and report a higher prevalence of obesity, heightened anxiety, and reduced emotional well-being.[5,6]

Recommendations are evolving, with the most recent American Heart Association/American College of Cardiology (AHA/ACC) 2020 guidelines[7] now recognizing the benefits of mild-moderate–intensity recreational exercise in patients with HCM. This new class I recommendation was supported by evidence from the Randomized Exploratory Study of Exercise Training in Hypertrophic Cardiomyopathy (RESET-HCM) clinical trial, in which adult patients who followed prescriptions of moderate-intensity exercise showed significant improvements in exercise capacity and physical functioning.[8] Although the study was underpowered for safety, there were no major adverse events and no increase in nonfatal arrhythmias in the exercise-trained group compared with the usual-activity group. The 2020 ACC/AHA HCM guidelines[7] and the 2019 European guideline[9] also introduced a new recommendation that participation in vigorous recreational exercise and competitive sports participation could be considered using a framework of shared decision-making[10] for all[7] or some[9] patients with HCM. However, the ACC/AHA recommendation remains a class IIB recommendation due to limited data on whether vigorous physical activity increases the risk of ventricular arrhythmic events in patients with HCM. There remains uncertainty even for those who carry a genetic variant without left ventricular hypertrophy (LVH) (ie, genotype positive/phenotype negative), particularly in light of postmortem studies that have identified pathogenic genetic variants in 5% to 10% of individuals who experience SCD without structural abnormalities at autopsy.[11,12] The guidelines prioritize these knowledge gaps as a major unmet need. The prospective, multinational, National Institute of Health–funded Lifestyle and Exercise in Hypertrophic Cardiomyopathy (LIVE-HCM) study was designed to provide data to inform patient-clinician 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 and/or mortality in individuals with HCM.

Key Points

Question Is vigorous exercise associated with an increased risk of mortality or ventricular arrhythmia in individuals with hypertrophic cardiomyopathy (HCM)?

Findings In this cohort study including 1660 participants, individuals exercising vigorously did not have an associated higher mortality or a higher incidence of ventricular arrhythmias.

Meaning In this study, these data do not support universal restriction of vigorous exercise for individuals with HCM.

Methods

Study Design

This was an investigator-initiated, prospective, observational cohort study. This study was approved by the Yale Human Investigation Committee and by the institutional review boards of participating sites. All patients provided signed informed consent. A list of study sites and investigators is listed in the eAppendix in Supplement 1. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Patients and Recruitment

Individuals aged 8 to 60 years with a diagnosis of overt HCM (phenotype positive), or genotype positive/phenotype negative status, were eligible to participate. Individuals were excluded if they had conditions precluding vigorous exercise (advanced HCM-related symptoms, ie, New York Heart Association class III or IV, or non-HCM-related conditions), as were those with LVH due to syndromic conditions or infiltrative disease. Individuals unable to complete online or phone questionnaires due to language or cognitive barriers were also excluded.

Patients were enrolled either through 42 participating high-volume HCM centers, in the US, UK, Canada, Australia, and New Zealand, or through contacting the central site (Yale) directly (self-enrolled), between May 18, 2015, and April 25, 2019. Information was disseminated to patients by the advocacy organization Hypertrophic Cardiomyopathy Association, other patient group internet sites and mailing lists, and via mailings to physicians. Participants self-identified with the following race and ethnicity categories: Black, Hispanic or Latino, White, and other, which included unspecified race and ethnicity. For site-enrolled patients, diagnosis of HCM and eligibility were confirmed by the site. For self-enrolled patients, af-

ter consent and medical release forms were signed, diagnosis and eligibility were confirmed by chart review. Interpretation of echocardiogram images or cardiac magnetic resonance (CMR) images was performed by a core laboratory at the Mayo Clinic and at the University of Michigan, respectively.

Study Procedures

Patients who consented were contacted by the central study team and sent a link to online questionnaires via a REDcap database (Vanderbilt University). Records were obtained from sites and via medical release forms from physicians. Demographic, clinical, and genetic data were abstracted and entered into the REDcap database. Participants received a link to a brief survey querying the occurrence of outcome events every 6 months. If outcome events were reported, study coordinators contacted participants for details, and records were obtained. If patients did not complete the planned 36 months of outcome surveys, records were obtained from sites or physicians to assess for events. Vital status was confirmed for all patients via sites or national death registries. Follow-up was complete on February 28, 2022.

Baseline Assessments

The primary independent variable, exercise level, was based on the Minnesota Leisure Time Activity Questionnaire,[13] which has been validated against both direct[14,15] (treadmill exercise performance, accelerometry) and indirect (frequent detailed activity records)[15] criteria, and has high test-retest reliability.[15,16] Participants identified physical activities performed in the past year, indicating the months per year, times per month, and the average time per event they performed each activity. Activities were assigned a metabolic equivalent (MET) intensity level defined as the oxygen cost of physical activity in milliliter per kilogram minute divided by the oxygen cost at rest (3.5 mL/kg·min). MET values were obtained from the 2011 Compendium of Physical Activities.[17] Participation in at least 1 activity at MET intensity level of 6.0 or greater for 60 or more hours per year was categorized as vigorous.[18] This level of intensity is beyond what has been recommended for patients with HCM for exercise.[19] Participation in activities at MET intensity level of 4 or greater but less than 6 for 60 or more hours per year and not meeting the criteria for vigorous was categorized as moderate, and participation in activities not meeting either of these criteria was categorized as sedentary. Those in moderate and sedentary groups were categorized as nonvigorous for the primary analysis. Patients were also queried about current participation in competitive level athletics. A subset of those meeting criteria for vigorous exercise performed at least 1 activity competitively and were categorized as the vigorous-competitive subgroup.

Outcomes

All outcome events were reviewed and adjudicated by a clinical events committee blinded to the patient's exercise category. The primary prespecified composite end point included death, resuscitated sudden cardiac arrest (SCA), syncope adjudicated to be definitely or likely arrhythmic, and appropriate implantable cardioverter defibrillator (ICD) shocks, with or without syncope. All ICD shock events were reviewed by 2 electrophysiologists (I.H.L. and E.V.S. for pediatric patients; M.S.L. and B.O. for adult patients). If electrograms could not be obtained, reports of electrograms from the record were reviewed. Deaths were classified as arrhythmic SCD, nonsudden cardiac death, or noncardiac death using standard definitions.[20]

Statistical Analysis

Sample Size and Power

Sample size was determined using the log-rank noninferiority module of PASS, version 2012 (NCSS). Original sample size was estimated at 2250 participants based on a 21-month recruitment period, a total study time of 57 months, an event rate of 11.5% over 3 years,[21,22] a 10% dropout rate, and 90% power at the 1-sided significance level of .05 to declare noninferiority of vigorous and moderate to 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 patients with HCM and the general population: 25% vigorous, 25% moderate, and 50% sedentary.[5,23] However, the ratio of individuals performing vigorous compared with sedentary and moderate activity was higher than expected. Therefore, before analysis, we revised the comparison to compare the vigorous group to the moderate and sedentary groups combined, defined for this analysis as nonvigorous. Our achieved sample size provides 91% power at the 1-sided .05 significance level to declare noninferiority of vigorous to nonvigorous at the 1.5 HR boundary.

Selection of the Noninferiority Boundary

For studies comparing interventions, it is customary to use data comparing the standard intervention with placebo, but analogous data are not available for exercise risk. Our rationale for using an HR of 1.5 as the upper bound was 2-fold. First, consensus derived from clinical judgment among 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.[24] This margin is within the range reported in large trials in the literature.

Analysis of Primary Outcome

The primary outcome variable is a composite end point of time to first of either death, SCA, appropriate ICD shock (for ventricular arrhythmia), or arrhythmic syncope. Time was determined from date of enrollment to date of either first event, transplant (censored at time of transplant: 4 sedentary, 7 moderate, 3 vigorous), or of date of last survey or clinical follow-up. Kaplan-Meier plots were constructed showing event-free survival. Our noninferiority hypothesis was that participants reporting vigorous activity at enrollment were no more likely to have an event than those reporting nonvigorous activity (ie, not inferior within the specified margin based on an HR of 1.5). Event likelihood was compared between groups using Cox regression including activity level (vigorous vs nonvigorous activity) as well as covariates for age, sex, race, recruitment method (site or self), age at diagnosis, and presence of an ICD.

Linear contrasts were estimated to compare the hazards of the vigorous group with the moderate/sedentary group. A noninferiority boundary for the HR of 1.5 was used with noninferiority concluded when the upper boundary of the 95% 1-sided Wald CI was less than 1.5. Pairwise noninferiority comparisons of vigorous with moderate and sedentary groups are also provided per the original analysis plan. Post hoc sensitivity analyses were performed excluding first, genotype-positive/phenotype-negative individuals, and then participants with exertional dyspnea or chest pain (New York Heart Association [NYHA] class II). A similar analysis was performed to compare the vigorous-competitive subgroup with the nonvigorous group. Subsequent models included controlling for known clinical risk factors for SCD[7] which differed between groups (effect size >12%) including history of arrest in the entire overt HCM group, followed by septal thickness (excluding those with apical variant.) To determine whether apical-variant HCM or the presence of a pathogenic gene variant impacted any associations of exercise with the composite end point among those with overt HCM, interaction testing was performed. Data were analyzed using SAS software, version 9.4 (SAS Institute).

Results

Patient Population

Demographic, clinical, and genotype data are shown for vigorous and nonvigorous groups (**Table 1**) and with the nonvigorous group divided into moderate and sedentary groups (eTable 1 in the Supplement). Among the 1660 participants, 996 were male (60%), 664 were female (40%), mean (SD) age was 39 (15) years, and 398 participants (24%) self-enrolled. Participants identified with the following race and ethnicity categories: 58 Black (3.4%), 81 Hispanic or Latino (4.9%), 1487 White (89.6%), and 115 other (6.9%). Derivation of the final cohort of 1660 participants is shown in eFigure 1 in the Supplement. A total of 252 individuals (15%) were categorized as sedentary, 709 (43%) participated in moderate-intensity exercise, and 699 (42%) participated in vigorous-intensity exercise. Among those engaging in vigorous exercise, 259 of 699 individuals (37%) participated competitively, and 440 (63%) participated noncompetitively. A total of 1534 participants (92%) had overt HCM (ie, phenotype positive), among whom 398 (24%) reported exertional dyspnea (NYHA class II). Compared with the nonvigorous exercise group, those engaging in vigorous exercise were on average younger (mean [SD] age, 36.1 [15.3] years vs 40.5 [13.9] years), more likely to be male (467 of 699 [66.8%] vs 518 of 961 [53.9%]), more likely to be genotype positive/phenotype negative (positive, 330 of 699 [47.2%] vs 415 of 961 [43.2%]), and less likely to be NYHA class II (90 of 625 [14.4%] vs 271 of 909 [29.8%]) (Table 1). There was no significant difference in the rate of prior ICD implants. The prevalence of risk factors for SCD (ie, history of syncope or nonsustained ventricular tachycardia, family history of SCD, degree of hypertrophy, presence of late gadolinium enhancement on CMR) and presence of an HCM-associated pathogenic variant did not differ between groups. Median (IQR) follow-up was 38 (36-40) months, which did not differ between groups. Among the patients who were phenotype positive, 598 of 1534 (39%) reported that a physician whom they had seen recommended no or light activity only, and in an additional 660 of 1534 (43%), competition was recommended to be restricted (total, 1258 of 1534 [82%]). Analogous recommendations were reported by patients who were phenotype negative: no or light activity in 24 of 126 (19%) and restriction of competition in 33 of 1534 (26%; total, 57 of 126 [45%]).

Compared with vigorous noncompetitive athletes, the subgroup of vigorous competitive athletes was younger (mean [SD] age, 29.3 [15.8] years vs 40.0 [13.5] years), more likely to be genotype positive/phenotype negative (positive, 134 of 259 [51.7%] vs 196 of 440 [44.5%]), more likely to have apical HCM (42 of 259 [19.9%] vs 63 of 440 [15.2%]), and less likely to have an ICD (69 of 259 [32.7%] vs 185 of 440 [44.7%]). Traditional risk factors for SCD did not differ. Among the 259 vigorous competitive athletes, 47 (18%) were aged 8 to 13 years; 74 (29%) were aged 14 to 22 years, among whom 54 (21% of total vigorous competitive athletes) participated on varsity, junior varsity, or traveling teams; and 138 (53%) were aged 23 to 60 years, participating in leagues or organized events. The most common sports were baseball/softball, running/track, soccer, and basketball (eTable 2 in Supplement 1).

Outcomes

As shown in **Table 2**, 77 of 1660 individuals (4.6%) reached the composite end point of death, SCA, appropriate ICD therapy (with or without syncope), or arrhythmic syncope. Forty-four participants (4.6%) of those classified as nonvigorous and 33 (4.7%) classified as vigorous experienced the composite end point, with corresponding rates of 15.3 and 15.9 per 1000 person-years, respectively. Survival free of adverse events is shown in **Figure 1** and eFigure 2 in Supplement 1. Breakdown of adverse events by vigorous, moderate, and sedentary groups appears in eTable 3 in Supplement 1, and survival analyses are separated by the 3 groups in eFigure 2 in Supplement 1.

Characteristics of participants experiencing SCD (n = 8) or SCA (n = 6) are shown in **Table 3**. There were no events in individuals without overt HCM. Among the 7 individuals engaged in vigorous exercise who experienced SCA or SCD, 3 episodes of SCA occurred during exercise (2 recreational and 1 competitive) and 2 SCDs and 1 SCA occurred during activities of daily living. Activity at the time of 1 SCD was unknown. ICDs failed to convert a ventricular arrhythmia in 1 child in the sedentary group who experienced SCA while standing in line at school and failed to prevent SCD in 1 adult in the moderate group while hunting and 1 adult in the vigorous group while driving. Among the remaining 11 participants with SCA or SCD without an ICD, 4 had at least 1 risk factor for SCD.

Primary Analysis

In multivariate Cox regression analysis of the primary prespecified composite end point, individuals engaging in vigorous exercise did not experience a higher rate of events compared with those in the nonvigorous group, with an adjusted HR of 1.01. The upper 95% 1-sided confidence level (UCL) was 1.48, below the prespecified boundary of 1.5 for noninferiority (**Figure 2**).

Table 1. Baseline Demographic, Genetic, and Clinical Data

Characteristic	Nonvigorous (n = 961)	Vigorous (n = 699)	Cohen *d* or *h*	Vigorous noncompetitive (n = 440)	Vigorous competitive (n = 259)	Cohen *d* or *h*
Age, mean (SD), y	40.5 (13.9)	36.1 (15.3)	0.31	40.0 (13.5)	29.3 (15.8)	0.74
Age, No. (%)						
<18	101 (10.5)	121 (17.3)	−0.20	28 (6.4)	93 (35.9)	−0.77
18-25	67 (7.0)	82 (11.7)	−0.16	51 (11.6)	31 (12.0)	−0.01
>25	793 (82.5)	496 (71.0)	0.28	361 (82.0)	135 (52.1)	0.65
Sex, No. (%)						
Male	518 (53.9)	467 (66.8)	−0.26	298 (67.7)	169 (65.3)	0.05
Female	443 (46.1)	232 (33.2)	0.26	142 (32.3)	90 (34.7)	−0.05
Race, No. (%)						
Black	36 (3.7)	22 (3.1)	0.03	13 (3.0)	9 (3.5)	−0.03
Hispanic/Latino	49 (5.1)	32 (4.6)	0.02	17 (3.9)	15 (5.8)	−0.09
White	856 (89.1)	631 (90.3)	−0.04	393 (89.3)	238 (91.9)	−0.09
Other	69 (7.2)	46 (6.6)	0.02	34 (7.7)	12 (4.6)	0.13
Genotype, No. (%)						
Positive	415 (43.2)	330 (47.2)	−0.08	196 (44.5)	134 (51.7)	−0.14
Variant uncertain significance	74 (7.7)	64 (9.2)	−0.05	39 (8.9)	25 (9.7)	−0.03
Negative	153 (15.9)	120 (17.2)	−0.03	80 (18.2)	40 (15.4)	0.07
Unknown/not tested	319 (33.2)	185 (26.5)	0.15	125 (28.4)	60 (23.2)	0.12
Family history, No. (%)						
FH SCD/resuscitated arrest	378 (39.3)	281 (40.2)	−0.02	182 (41.4)	99 (38.2)	0.07
FH HCM	537 (55.9)	401 (57.4)	−0.03	250 (56.8)	151 (58.3)	−0.03
Phenotype negative, No. (%)	52 (5.4)	74 (10.6)	−0.19	26 (5.9)	48 (18.5)	−0.40
Overt HCM, No. (%)[a]	909 (94.6)	625 (89.4)	0.19	414 (94.5)	211(71.9)	0.40
Age at diagnosis, mean (SD), y	31.8 (15.6)	30.1 (15.8)	0.11	32.1 (15.3)	26.2 (16.2)	−0.38
Mode of diagnosis, No. (%)						
Symptoms	376 (41.4)	233 (37.3)	0.08	160 (38.6)	73 (34.6)	0.08
Family screening	223 (24.5)	165 (26.4)	−0.04	110 (26.6)	55 (26.1)	0.01
ECG screening	31 (3.4)	31 (5.0)	−0.08	25 (6.0)	6 (2.8)	0.16
Incidental/other	317 (34.9)	223 (35.7)	−0.02	139 (33.6)	84 (39.8)	−0.13
Apical morphology, No. (%)	79 (8.7)	105 (16.8)	−0.25	63 (15.2)	42 (19.9)	−0.12
History of cardiac arrest, No. (%)	31 (3.4)	36 (5.8)	−0.12	20 (4.8)	16 (7.6)	−0.12
Exertional symptoms, No. (%)	271 (29.8)	90 (14.4)	0.38	64 (15.5)	26 (12.3)	0.09
History of syncope, No. (%)	231 (25.4)	141 (22.6)	0.07	106 (25.6)	35 (16.6)	0.22
History of NSVT, No. (%)	247 (27.2)	147 (23.5)	0.09	109 (26.3)	38 (18.0)	0.20
Myectomy, No. (%)	200 (22.0)	88 (14.1)	0.21	70 (16.9)	18 (8.5)	0.26
ICD, No. (%)	397 (43.7)	254 (40.6)	0.06	185 (44.7)	69 (32.7)	0.25
Pacemaker, No. (%)	12 (1.3)	4 (0.6)	0.07	4 (1.0)	0	0.20
Secondary prevention ICD indication (% of those with ICD), No. (%)	47 (5.2)	45 (7.2)	0.08	29 (15.7)	16 (23.1)	−0.19
LV maximal wall thickness, mean, (SD), mm	21.5 (12.2)	20.0 (6.3)	0.15	19.9 (6.2)	20.2 (6.6)	−0.05
LVEF, mean (SD), %	66.2 (7.7)	66.1 (7.1)	0.01	65.9 (7.3)	66.7 (6.7)	−0.11
LVOT rest gradients, mean (SD), mm Hg	23.0 (25.9)	18.3 (22.3)	0.19	19.2 (23.4)	16.5 (19.9)	0.12
≥30 mm Hg, No. (%)	164 (22.6)	68 (14.1)	0.22	50 (15.4)	18 (11.5)	0.11
LVOT provoked gradients (Valsalva or exercise), mean (SD), mm Hg	51.1 (46.3)	39.6 (42.0)	0.26	39.8 (41.2)	39.2 (43.9)	0.02
≥30 mm Hg, No. (%)	279 (54.2)	135 (42.2)	0.24	94 (42.7)	41 (41.0)	0.03
Late gadolinium enhancement, No. (%)						
None	691 (76.0)	472 (75.5)	0.01	312 (75.4)	160 (75.8)	−0.01
Mild/moderate/patchy/<15%	161 (17.7)	110 (17.6)	0.00	69 (16.7)	41 (19.4)	−0.07
Extensive/>15%	57 (6.3)	43 (6.9)	−0.02	33 (8.0)	10 (4.7)	0.14

Abbreviations: ECG, electrocardiogram; EF, ejection fraction; FH, family history; ICD, implantable cardioverter defibrillator; LV, left ventricular; NSVT, nonsustained ventricular tachycardia; OT, outflow tract; SCD, sudden cardiac death.

[a] Variables below are presented for participants with overt HCM.

Table 2. End Point Events

End Point	Nonvigorous (n = 961)	Vigorous (n = 699)	Total (n = 1660)	Vigorous competitive (n = 259)	Vigorous noncompetitive (n = 440)
Total composite end point					
No.	44	33	77	10	23
Rate per 1000 person-year (95% CI)	15.3 (11.4-20.5)	15.9 (11.3-22.4)	15.6 (12.5-19.6)	13.1 (7.0-24.0)	17.6 (11.7-26.5)
Individual end points					
Death[a]					
No.	8	4	12	1	3
Rate per 1000 person-year (95% CI)	2.7 (1.4-5.5)	1.9 (0.7-5)	2.3 (1.2-4)	1.3 (0.2-9)	2.2 (0.7-7.0)
Cardiac arrest					
No.	2	4	6	3	1
Rate per 1000 person-year (95% CI)	0.7 (0.2-2.7)	1.9 (0.7-5.0)	1.1 (0.5-2.6)	3.9 (1.2-12)	0.7 (0.1-5.0)
Arrhythmic syncope, patients with ICD					
No.	19	15	34	2	13
Rate per 1000 person-year (95% CI)	6.6 (4.2-10.3)	7.1 (4.3-11.8)	6.8 (4.9-9.6)	2.6 (0.6-10.3)	9.8 (5.7-16.9)
Appropriate ICD shock (no syncope)					
No.	11	8	19	1	7
Rate per 1000 person-year (95% CI)	3.8 (1.9-7.6)	3.8 (1.9-7.6)	3.8 (2.4-6.0)	1.3 (0.2-9.1)	5.3 (2.5-11.0)
Definite or likely arrhythmic syncope, patients without ICD					
No.	8	7	15	3	4
Rate per 1000 person-year (95% CI)	2.7 (1.4-5.5)	3.3 (1.6-6.9)	3.0 (1.8-5.0)	3.9 (1.2-12.0)	3.0 (1.1-8.0)

Abbreviation: ICD, implantable cardioverter defibrillator.

[a] Includes 8 sudden cardiac deaths and 4 noncardiac deaths.

Secondary and Post Hoc Analyses

In a prespecified secondary analysis, those engaging in vigorous-competitive exercise also did not experience an increased arrhythmic risk compared with the nonvigorous group, with an HR of 0.71 and UCL of 1.32. (Figure 2). In prespecified pairwise subanalyses, moderate exercise was noninferior to a sedentary lifestyle. No subgroup was found superior to another.

Post hoc analyses were performed in subgroups with characteristics that differed by an effect size of greater than 12% between the vigorous and nonvigorous groups. First, patients who were genotype positive/phenotype negative were excluded. Among this subgroup of patients who were phenotype positive, similar point estimates for the HR for vigorous activity compared with the nonvigorous group were seen. Controlling for known risk factors for SCD which differed between groups (history of arrest, and septal thickness), did not impact the findings. Next, those with NYHA class II were excluded. In this subgroup of phenotype positive patients who were asymptomatic, findings were similar. In neither the primary nor any of the subanalyses was nonvigorous or vigorous exercise demonstrated to be superior (Figure 2). Among those with overt HCM, there was no interaction between either apical phenotype or the presence of a pathogenic variant and exercise in association with the composite end point.

Although all SCD and SCA events occurred in male participants (Table 3), the overall occurrence of outcome events did not differ between male (45 of 985 [4.6%]) and female (32 of 675 [4.8%) participants, nor was there a sex difference in outcomes within the exercise categories.

There were 203 individuals aged 14 to 22 years, among whom 56 individuals (28%) were competing in varsity sports/traveling teams, (42 with overt HCM), 50 engaging in other vigorous exercise, either recreationally or at lower levels of competition, and 97 engaging in moderate exercise or who were sedentary. Demographic and clinical characteristics are shown in eTable 4 in Supplement 1. There was 1 outcome event in the varsity/traveling team group, (resuscitated cardiac arrest, Table 3 and eTable 5 in Supplement 1), none in the other vigorous group, and 6 outcome events in the moderate/sedentary group (2 deaths, Table 3; 3 appropriate ICD shocks and 1 arrhythmic syncope, eTable 5 in Supplement 1) corresponding to event rates per 1000 person-years of 5.7 (95% CI, 0.8-40.8), 0, and 20.7 (95% CI, 9-46.2) for varsity/traveling, other-vigorous group, and moderate-sedentary group, respectively.

Discussion

In this prospective cohort study of 1660 individuals with HCM or those who are genotype positive/phenotype negative (8%), findings suggest that those engaged in vigorous exercise did not experience a heightened risk of death, cardiac arrest, appropriate ICD shocks, or arrhythmic syncope compared with individuals engaging in low- to moderate-

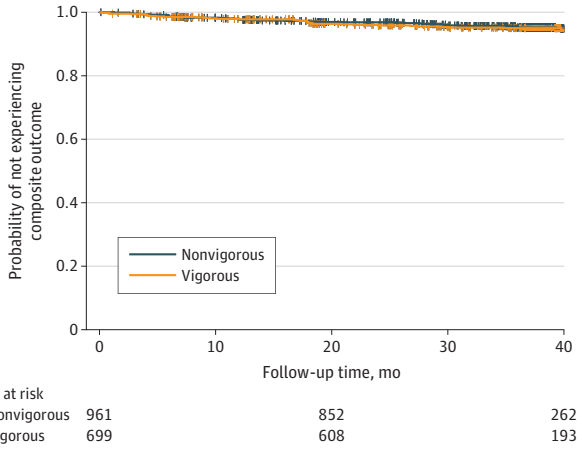
intensity physical activity. Individuals who were participating in high-intensity competitive sports were also not at heightened associated risk of death. Overall absolute event rates were low, with fewer than 5% reaching the composite outcome over 3 years of follow-up. Post hoc analysis limited to those with overt HCM showed a similar HR; however, noninferiority was not demonstrated based on the prespecified boundary. In neither the primary patient population nor any subgroup comparison was vigorous or nonvigorous exercise shown to be safer (ie, superior). Most life-threatening adverse events occurred during activities of daily living. Among the subgroup of 42 younger, highly competitive athletes with overt HCM, there was 1 adverse event (nonfatal), which did not occur during competitive exercise. In total, these findings do not support universal restriction of vigorous intensity exercise in patients with HCM.

These prospective data challenge long-held beliefs that vigorous and competitive exercise increase the likelihood of arrhythmia for individuals with HCM,[4,25] which has driven guideline recommendations for 4 decades. These conservative recommendations were based on early observational series showing that HCM was a common cause of SCD among athletes and that most events occurred during exercise.[3] Subsequent studies[26-28] of SCD in athletes have suggested that HCM is accountable for a smaller proportion of events and that few episodes of SCD occur during exercise. Recent series of athletes with HCM who continue to participate in sports have shown no adverse events,[29-31] with the exception of 1 report including 2 athletes with HCM who died during high-intensity exercise after returning to play.[32] In a prior study[33,34] of athletes with ICDs, including 77 with HCM, the athletes were equally likely to experience ventricular arrhythmias during non-sports-associated activity as during a sports-associated activity. A retrospective cross-sectional study[35] of individuals with HCM did not show increased ventricular arrhythmias in those with higher cumulative hours of exercise. These studies have been limited, however, by small sample size, older patient populations, their retrospective nature, and/or lack of a control group of less-active individuals.

The safety of highly competitive athletics, such as varsity high school and college competition for individuals with HCM, has been debated.[36] In this study, the 42 high school and varsity college athletes with overt HCM had a lower rate of adverse events than individuals of a similar age in the moderate/sedentary groups. This age group is too small for meaningful statistical analysis with or without controlling for potential confounding differences. However, it is reassuring that the overall event rate was low and that the single event was nonfatal and did not occur during competition. Despite these limitations, these data will inform shared decision-making as endorsed by recent guidelines.[7] Ongoing and future studies of highly competitive athletes will also be informative in guiding these decisions.

In the general population, exercise can increase the immediate risk of SCD, even in habitual exercisers, yet habitual exercise lowers the lifetime risk of SCD and mortality compared with those who do not exercise regularly; this is termed the *paradox of exercise*.[37] This is consistent with the role of the autonomic nervous system in arrhythmogenesis. Catecholamines are arrhythmogenic, whereas vagal tone, which increases with regular exercise, is protective against ventricular arrhythmia.[38] In the current study, 3 individuals had SCA during vigorous exercise. However, SCA and SCD occurred predominantly at other times, regardless of engagement in vigorous exercise. One national claims database analysis suggested an association of vigorous exercise with lower mortality in an older population of individuals with HCM, although detailed exercise and clinical data were not available.[39] The current study did not show graded improvement in mortality with increasing exercise as shown in the general population. However, there was no increase in mortality or total arrhythmic end points seen, and the relatively young age and short time frame may not have allowed for demonstration of the longer-term benefits of exercise.

Figure 1. Kaplan-Meier Survival Curve for Freedom From Composite End Point (Death, Cardiac Arrest, Appropriate Implantable Cardioverter Defibrillator Shock, or Arrhythmic Syncope) by Exercise Group



Vigorous and nonvigorous groups did not differ in freedom from composite end point.

Whether there is an optimal duration, frequency, and/or intensity of exercise for individuals with HCM cannot be determined from these data, as the purpose of the study was to provide information on risk for those wishing to exercise, and the study was not powered to show superiority in any exercise classification group. In the general population, most studies show a graded benefit with increasing intensity of exercise,[40,41] although some show a J-shaped curve with higher mortality at highest levels of intensity.[42] More than one-third of participants were instructed by physicians to perform no exercise at all or only light-intensity activities. These data do not support this overly conservative approach. However, future studies will be needed to determine what exercise volume and intensity will be most beneficial for patients with HCM.

The rationale for including the genotype-positive/phenotype-negative groups in the prespecified primary analysis group was lingering uncertainty about risk in these individu-

Table 3. Characteristics of Individuals Experiencing Sudden Cardiac Death (SCD) or Sudden Cardiac Arrest (SCA)[a]

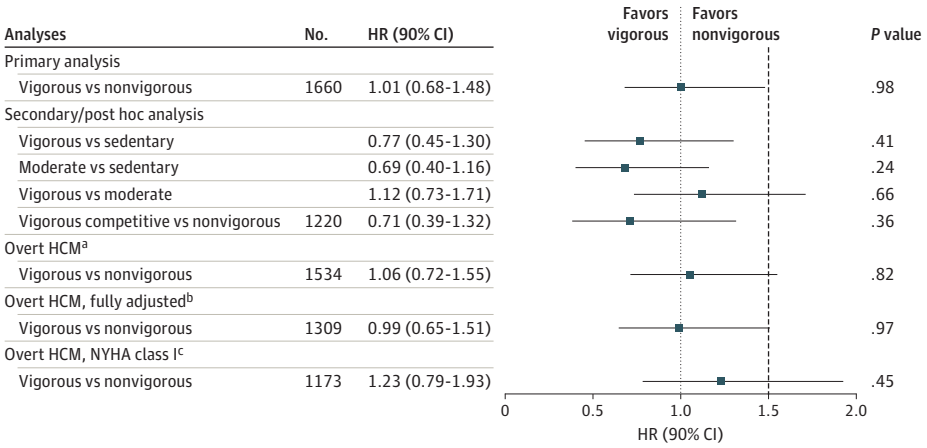
Exercise group	Event	Enrollment age, y	ICD[b]	Risk factors	Activity with event
Sedentary	SCA	12.6	Yes	None	Standing in line at school
Sedentary	SCD	15.5	No	None	Sleep
Sedentary	SCD	53.5	No	Syncope	Sleep
Moderate	SCA	8.9	No	None	Jogging/warmup for karate
Moderate	SCD	21.9	No	Syncope, NSVT	Sleep
Moderate	SCD	31.6	Yes	None	Hunting
Moderate	SCD	35.7	No	FH SCD, NSVT	Unknown
Vigorous	SCA	9.5	No	None	Sitting at assembly
Vigorous competitive	SCA	18.4	No	None	Running recreationally
Vigorous	SCD	23.9	No	FH SCD	Home alone
Vigorous competitive	SCA	35.4	No	None	Cycling recreationally
Vigorous	SCD	53.2	No	None	Unknown
Vigorous competitive	SCA	54.6	No	None	Sand volleyball, between games
Vigorous competitive	SCD	57.1	Yes	None	Driving car

Abbreviations: FH, family history; ICD, implantable cardioverter defibrillator; NSVT, nonsustained ventricular tachycardia.

[a] All participants experiencing these end points were male.

[b] Number of appropriate ICD therapies not associated with cardiac arrest appear in Table 2.

Figure 2. Forest Plot for Hazard Ratio (HR) (1-Sided 95% CI) Comparing Composite Outcomes Between Exercise Groups



HRs for primary, secondary, and post hoc analyses comparing the composite outcome (death, cardiac arrest, appropriate implantable cardioverter defibrillator [ICD] shock, arrhythmic syncope) between those exercising vigorously and those exercising nonvigorously. Presented are 90% 2-sided CIs. The upper limits of these intervals correspond to a 1-sided .05 significance level used to evaluate noninferiority. Primary analysis is shown followed by 2 secondary analyses: pairwise comparisons of the 3 groups and after excluding noncompetitive vigorous individuals to compare vigorous-competitive vs nonvigorous. Post hoc analyses are shown of subgroups.

[a] The first subgroup included those with overt hypertrophic cardiomyopathy (HCM), ie, phenotype-positive only, and controlled for prespecified covariates age, sex, race, recruitment method (site or self), age at diagnosis, and presence of an ICD.

[b] The next model added sudden cardiac death risk factors that differed by an effect size of at least 12% between the groups (history of sudden cardiac arrest and septal thickness).

[c] The final subgroup excluded those with exercise-related symptoms (ie, asymptomatic, phenotype-positive only).

als, which our data suggest significantly impacts patient care. Approximately one-half of genotype-positive/phenotype-negative participants reported receiving recommendations for some or complete exercise restriction. Although engaging in vigorous exercise and competitive sports is considered reasonable for genotype-positive/phenotype-negative individuals by US and European guidelines (class IIA), both documents acknowledge limited data in this group.[7] Recent molecular autopsy series[11,12] suggest a potentially nonzero risk of SCD for these individuals, with identification of pathogenic genetic variants for HCM in 5% to 10% of young individuals who experience SCD despite absence of hypertrophy or structural abnormalities. As it is unclear whether these genetic findings were the primary trigger for SCD, prospective outcome studies in genotype-positive/phenotype-negative individuals continue to be warranted. The absence of events in this group in the present study is reassuring and supportive of current guideline recommendations, but continued surveillance of these individuals is advisable.

As fewer patients exercising vigorously were symptomatic compared with those who exercised moderately or were sedentary, a post hoc analysis was performed in asymptomatic patients with overt HCM (71%), excluding those with exertional symptoms, which may have precluded more intense exercise. Even after removing symptomatic patients, the point estimate for vigorous exercise was similar, and neither exercise group was superior to the other. Although we cannot exclude the possibility that patients exercising vigorously were less severely affected, it is also possible that deconditioning due to exercise restriction may have increased symptomatic burden, as suggested by improvements in physical functioning and quality of life seen in the RESET trial.

Limitations

This study has some limitations. Participants in the LIVE-HCM study may not be representative of all patients with HCM. Although recruitment materials were aimed at individuals engaging in any level of physical activity, the percentage of those engaged in vigorous exercise was higher than expected based on prior surveys of patients with HCM[5] as well as data on exercise practices in US residents in general.[23,43] It is likely that individuals interested in exercise were more interested in study participation. However, the over-representation of individuals engaged in vigorous exercise allowed for robust comparisons and exploratory subgroup analyses.

Although almost one-quarter of participants were self-enrolled, most had received care at high-volume HCM centers with expertise in management and risk assessment of patients with HCM, as recommended by current guidelines.[7] Whether the data can be extrapolated to patients managed outside of these centers cannot be determined.

The percentage of participants with ICDs was higher than in most published HCM cohorts.[2] Although the reason for this is unclear, prior data on safety of sports for individuals with HCM and ICDs may have led to higher enrollment of participants with ICDs who were more active than the average patients with HCM.

Individuals exercising vigorously differed in some ways from those exercising less vigorously or those who were sedentary. However, most known risk factors for sudden death did not differ between the groups, and controlling for those that did had no impact on the study findings. The possibility of survival bias, which could go in either direction, cannot be excluded. However, although the subgroup of younger individuals (aged 14-22 years) was too small for meaningful analysis, it is reassuring that there were fewer events in the groups of competitive or other vigorous exercise than in those with moderate exercise or those who were sedentary.

Conclusions

Results of this cohort study suggest that among individuals with HCM or those who are genotype positive/phenotype negative and treated in experienced centers, those exercising vigorously did not experience a higher rate of death or life-threatening arrhythmias than those exercising moderately or those who were sedentary. These data may inform discussion between patients and physicians regarding vigorous exercise participation, in the context of overall expert assessment and management of HCM, using an individualized shared decision-making framework.

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Group Information: A list of additional members of the LIVE Consortium appears in Supplement 2.

Data Sharing Statement: See Supplement 3.

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