OBJECTIVES The goal of this study was to explore the association between exercise duration versus exercise intensity and adverse outcome in patients with arrhythmogenic cardiomyopathy (AC).

BACKGROUND Vigorous exercise aggravates and accelerates AC, but there are no data assessing the harmful effects of exercise intensity and duration in these patients.

METHODS Exercise habits at time of diagnosis were recorded by standardized interviews in consecutive AC patients. Exercise $>$6 metabolic equivalents was defined as high intensity, and exercise duration was categorized as long if above median. Life-threatening ventricular arrhythmia (VA) was defined as aborted cardiac arrest, documented sustained ventricular tachycardia, ventricular fibrillation, or appropriate implantable cardioverter-defibrillator therapy.

RESULTS We included 173 AC patients (53% probands; 44% female; 41 ± 16 years of age). Median weekly exercise duration was 2.5 h (interquartile range: 2.0 to 5.5 h), and 91 patients (52%) reported high-intensity exercise. VA had occurred in 83 patients (48%) and was more prevalent in patients with high-intensity exercise than low-intensity exercise (74% vs. 20%, $p < 0.001$), and more prevalent in long-duration than short-duration exercise (65% vs. 31%, $p < 0.001$).

High-intensity exercise was a strong and independent marker of VA, even when adjusted for the interaction with long-duration exercise (odds ratio: 3.8; 95% confidence interval: 1.3 to 11.0, $p < 0.001$), whereas long-duration exercise was not.

CONCLUSIONS High-intensity exercise was a strong and independent marker of life-threatening VA in AC patients, independent of exercise duration. AC patients could be advised to restrict their exercise intensity. (J Am Coll Cardiol EP 2018;4:744–53) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Regular physical activity is a cornerstone of a healthy lifestyle and is recommended to healthy adults (4). Athletes commonly exercise in vast excess of the recommended minimum doses (5) for healthy individuals. Vigorous exercise aggravates and accelerates AC disease, and athletes are overrepresented in AC patient cohorts (6–8). Athletes are accustomed to an active lifestyle and are often concerned about the inactivity and exercise restrictions recommended in the treatment guidelines during the past decade (9–11). There is no established exercise threshold associated with adverse outcome in AC, and data considering harmful effects of different types of exercise are lacking. Previous studies have reported the total exercise dose or perceived activity level of AC patients (6,12) without separating the impact of exercise intensity and exercise duration. We aimed to explore the impact of exercise intensity, exercise duration, and exercise dose on outcome in AC patients.

METHODS

STUDY POPULATION. We included consecutive patients diagnosed with AC at the Department of Cardiology, Oslo University Hospital, Rikshospitalet, Oslo, Norway, between January 2008 and November 2016 in an observational cohort study. Probands fulfilling AC diagnosis by the current Task Force Criteria (1) underwent genetic testing, and family members of probands with pathogenic mutations were screened and included if mutation positive (1). We defined a proband as the first person in a family to exhibit clinical symptoms or signs that triggered an evaluation of AC. Patients with heart or lung comorbidities were excluded. We performed a clinical examination and recorded any use of AC-related medication. VA, the primary outcome, was defined as a history of 1 or more of the following events: aborted cardiac arrest, documented sustained ventricular tachycardia (>100 beats/min, >30 s) (13) on electrocardiogram or Holter recordings or appropriate implantable cardioverter-defibrillator (ICD) therapy at last clinical follow-up. Appropriate ICD therapy was defined as anti-tachycardia pacing or shock therapy for documented ventricular tachycardia or ventricular fibrillation. VA and age at the first documented VA were recorded retrospectively by an independent observer blinded to exercise data. Cardiac function and dimensions, the secondary outcomes, were assessed by echocardiography and cardiac magnetic resonance imaging (CMR). Written informed consent was given by all patients, and the study complied with the Declaration of Helsinki and was approved by the Regional Committee for Medical Research Ethics in Norway.

EXERCISE. At time of diagnosis, we advised our AC patients to abstain from competitive sports (11). We interviewed all patients about their exercise habits immediately before their AC diagnosis, either by direct interview during their clinical visit or by telephone calls. Exercise was defined as physical activity performed on a regular basis during the past 3 years (14). Duration of exercise was defined as the actual time in motion and was expressed as average hours per week, which allowed for seasonal variation. Median duration of exercise in our cohort served as the cutoff to categorize exercise duration as short or long. Exercise intensity was assigned from the main reported exercise activity using the 2011 Compendium of Physical Activities (15) and was expressed as metabolic equivalents (METs). Patients were classified as regularly engaging in high-intensity exercise (>6 METs), for example, running, aerobics, fast swimming, or competitive sports (16), or low-intensity exercise (3 to 6 METs), for example, walking, dancing, or weight lifting. Regular physical activity <3 METs was not recorded as exercise. On the basis of exercise intensity and duration, we categorized patients into 4 groups:

1. Low-intensity and short-duration exercise (low/short);  
2. Low-intensity and long-duration exercise (low/long);  
3. High-intensity and short-duration exercise (high/short);  
4. High-intensity and long-duration exercise (high/long)

The exercise dose was calculated by multiplying the exercise intensity in METs by the weekly exercise duration in hours and was expressed as MET-h/week (14).

ELECTROCARDIOGRAM. All patients underwent a 12-lead electrocardiogram (ECG) at the time of diagnosis, and major and minor criteria according to the 2010 AC Task Force Criteria (1) were assessed. A signal-averaged ECG was also obtained at the time of diagnosis (MAC 5000, GE Medical Systems, Milwau-kee, Wisconsin) in a subgroup of patients. A pathological signal-averaged ECG was defined according to the 2010 AC Task Force Criteria (1).

CARDIAC MAGNETIC RESONANCE IMAGING. A subgroup of patients without contraindications, including noncompatible ICD leads, underwent CMR
By cardiac imaging, we defined the secondary outcomes as left ventricular (LV) dysfunction (top), right ventricular (RV) dilation (bottom left), and RV dysfunction (bottom right). (Top) LV dysfunction was defined as (a) ejection fraction <54% in female patients and <52% in male patients or (b) global longitudinal strain (GLS) worse than -18%. (Bottom left) RV dilation was defined as (a) proximal RV outflow tract (RVOT) diameter $\geq 32$ mm in parasternal short-axis view, (b) basal RV diameter (RVD) $> 41$ mm in RV focused apical 4-chamber view (blue arrows), or (c) major criterion indexed RV end-diastolic volume (RVEDVi) by cardiac magnetic resonance imaging. (Bottom right) RV dysfunction was defined as (a) fractional area change $\leq 40\%$, (b) tricuspid annular systolic excursion $< 17$ mm, or (c) major criterion RV ejection fraction by cardiac magnetic resonance imaging. Blue arrows and areas are end-diastolic measures, and red are end-systolic measures.
on clinical indication in a 1.6-T unit (Magnetom Sonata, Vision Plus or Avanto Siemens, Erlangen, Germany) using a phased-array body coil as reported previously (7). The presence of RV contraction abnormalities was recorded, and the major Task Force Criteria (1) were included in the imaging endpoints of RV dilation and dysfunction.

**Echocardiography.** All participants underwent echocardiography at the time of AC diagnosis (Vivid 7, E9 or E95, GE, Vingmed, Horten, Norway), and datasets were analyzed offline (EchoPac 201, GE, Vingmed) by 2 independent observers blinded to clinical and exercise information. LV ejection fraction was assessed by the Simpson biplane method. LV global longitudinal strain was assessed by the speckle tracking technique and calculated as the average peak global longitudinal strain was assessed by the Simpson biplane method. LV function was assessed by the Vingmed (EchoPac 201, GE, Vingmed) by 2 independent observers blinded to clinical and exercise information. LV ejection fraction was assessed by the Simpson biplane method. LV global longitudinal strain was assessed by the speckle tracking technique and calculated as the average peak negative longitudinal strain in a 16-segment model (17). LV dysfunction was defined as ejection fraction <54% in females and 52% in males or global longitudinal strain worse than –18% (Figure 1) (18–20).

RV function and dimensions were assessed by echocardiographic RV fractional area change, tricuspid annular plane systolic excursion, proximal diameter of RV outflow tract, RV basal diameter (21), and CMR parameters. RV dilation was defined as RV basal diameter >41 mm, RV outflow tract ≥32 mm (Figure 1), or indexed RV end-diastolic volume ≥100 ml/m² in females and ≥110 ml/m² in males with concomitant RV akinesia/dyskinesia by CMR (1). RV dysfunction was defined as fractional area change ≥40%, tricuspid annular plane systolic excursion <17 mm (Figure 1) (22), or RV ejection fraction ≤40% with concomitant RV akinesia/dyskinesia by CMR (1).

**Genetic analyses.** Genomic DNA was isolated from peripheral blood, and testing was performed as a part of the diagnostic workup as described previously (7).

**Statistical analysis.** Values are expressed as mean ± SD, frequencies with percentages, or median with interquartile range (IQR) and were compared by unpaired Student’s t-test, chi-square test, Fisher exact test, or Mann-Whitney U test as appropriate (SPSS version 21.0, SPSS Inc., Chicago, Illinois). Receiver operating characteristic (ROC) curves were computed for exercise parameters to identify patients with adverse outcome, and the curve coordinate closest to the upper left corner was defined as the statistical optimal threshold value. Logistical regression analyses were performed in patients with long- and short-duration exercise, in patients with high- and low-intensity exercise, and in patients with and without VA. Possible confounders (p < 0.10) were added to multivariable logistical regression for the primary endpoint, including an interaction term for high-intensity and long-duration exercise. Multicollinearity was defined by correlation coefficients >0.7 or variance inflation factor >5 (23). The distributions of outcomes across the 4 groups of high- or low-intensity and short- or long-duration exercise were presented as modified radar plots that reflected the prevalence of outcomes as a percentage of the length from the center of the diagram to the respective corner. Distributions of outcomes around the axes were compared by chi-squared test. The p values were 2-sided, and values <0.05 were considered significant.

**Results.**

Of 191 patients diagnosed with AC at our center, 11 had heart or lung comorbidities and 7 were unavailable for exercise interview, which left 173 included patients (53% probands; 44% female; 41 ± 16 years of age) (Table 1) with detailed exercise information and data on the primary outcome. An ECG was available in all 173 patients, and a satisfactory signal-averaged
Table 2: Clinical and Cardiac Imaging Characteristics of 173 AC Patients Divided by Short and Long Exercise Duration

<table>
<thead>
<tr>
<th></th>
<th>≤2.5 h/week (n = 87)</th>
<th>&gt;2.5 h/week (n = 86)</th>
<th>p Value</th>
<th>Adjusted* OR (95% CI) p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>42 ± 18</td>
<td>39 ± 14</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.9 ± 0.2</td>
<td>1.9 ± 0.2</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>24 (28)</td>
<td>&lt;0.001</td>
<td>0.5 (0.2-1.1)</td>
</tr>
<tr>
<td>Probands</td>
<td></td>
<td>34 (39)</td>
<td>&lt;0.001†</td>
<td></td>
</tr>
<tr>
<td>High intensity</td>
<td></td>
<td>25 (29)</td>
<td>&lt;0.001</td>
<td>4.6 (2.0-11)</td>
</tr>
<tr>
<td>VA</td>
<td>Total VA</td>
<td>27 (31)</td>
<td>&lt;0.001</td>
<td>1.6 (0.6-3.9)</td>
</tr>
<tr>
<td></td>
<td>ACA</td>
<td>4 (5)</td>
<td></td>
<td>13 (16)</td>
</tr>
<tr>
<td></td>
<td>VT</td>
<td>19 (22)</td>
<td>&lt;0.001†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ICD therapy</td>
<td>10 (12)</td>
<td>&lt;0.001†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age at VA, yrs</td>
<td>46 ± 16</td>
<td>0.03‡</td>
<td>10 (3-9)</td>
</tr>
</tbody>
</table>

Cardiac imaging

| LV dysfunction | 24 (29) | 42 (49) | 0.008 | 1.3 (0.6-2.8) | 0.54 |
| EF, %          | 58 ± 5  | 54 ± 9  |       | 0.002‡       |      |
| GLS, %        | −19.5 ± 3.0 | −18.3 ± 3.5 | 0.02† |               |      |
| RV dilation    | 53 (63) | 75 (87) | <0.001 | 2.5 (0.9-6.4) | 0.07 |
| RVD, mm       | 40 ± 7  | 44 ± 9  |       | 0.001†       |      |
| RVOT, mm      | 33 ± 7  | 38 ± 9  |       | 0.001†       |      |
| CMR RV EDVi, ml/m² | 103 ± 41 | 109 ± 32 | 0.51 |               |      |
| RV dysfunction | 47 (53) | 62 (71) | 0.02 | 0.9 (0.4-2.1) | 0.81 |
| FAC, %        | 41 ± 10 | 37 ± 10 | 0.01‡ |               |      |
| TAPSE, mm     | 20 ± 5  | 19 ± 6  | 0.36  |               |      |
| CMR RV EF, %  | 49 ± 12 | 46 ± 11 | 0.30  |               |      |

Values are mean ± SD, or n (%). Unpaired Student’s t-test, chi-squared, Fisher exact test, and multivariable logistical regression. *Multivariable logistical regression including significant variables from univariable analyses and age. †Proband status was not retained in multivariable analyses because of multicollinearity with VA. Adjusted: * OR (95% CI) p Value

ECG was available in 139 (80%). Five patients had unsatisfactory echocardiographic acquisitions of either LV or RV, and thus, 168 patients (97%) were analyzed for all the secondary outcomes (LV and RV dysfunction and RV dilation). CMR was performed in 134 patients (79%). Genetic analyses had been performed in 170 patients, of whom 125 (72%) had pathogenic mutations (109 [87%] in plakophilin-2, 8 [6%] in desmoplakin, 7 [6%] in desmoglein-2, and 2 [2%] in desmocollin-2 genes). Forty-five patients were mutation-negative probands with definite AC, and 3 probands with definite AC were not genetically tested. As expected, probands had more severe disease than family members (Table 1).

Seventeen patients had experienced aborted cardiac arrest, 70 had documented sustained ventricular tachycardia, and 49 had received appropriate ICD therapy (Online Table). In total, VA had occurred in 83 patients (34% female; age 40 ± 16 years). Patients with VA were more frequently probands (86% vs. 6%, p < 0.001) and had more prevalent LV dysfunction (52% vs. 27%; p = 0.001), RV dysfunction (83% vs. 47%, p < 0.001), and RV dilation (93% vs. 59%; p < 0.001) than patients without VA.

EXERCISE DURATION: LONG VERSUS SHORT. Median weekly exercise duration was 2.5 h (IQR: 2.0 to 5.5 h). According to the predefined cutoff, 86 patients were classified as regularly engaging in long-duration exercise (>2.5 h/week), and 87 as participating in short-duration exercise (≤2.5 h/week) (Table 2).

Ventricular arrhythmia. Long-duration exercise was more common in males and in probands and was associated with VA, but none of these markers remained when adjusted for confounders (Table 2). Exercise duration ≥2.3 h/week was the statistical threshold associated with VA (C-statistic, 0.69; 95% CI: 0.61 to 0.77).

Functional and structural alterations. Patients with long-duration exercise had worse LV and RV function, and more RV dilation, than patients with short exercise duration. There was a trend towards an association between long-duration exercise and RV dilation in multivariable analysis (p = 0.07). The statistical threshold associated with RV dilation was ≥2.8 h of exercise per week, ≥3.2 h/week with RV dysfunction, and ≥3.4 h/week with LV dysfunction.

EXERCISE INTENSITY: HIGH VERSUS LOW. The mean exercise intensity was 6.7 ± 1.9 METs. High-intensity exercise (>6 METs) was reported by 91 patients, and 82 reported low-intensity exercise (3 to 6 METs) (Table 3). High-intensity exercise was more common in males, probands, and patients reporting long-duration exercise.

Ventricular arrhythmia. Patients with high-intensity exercise had more prevalent VA than patients with low-intensity exercise, an association that remained strong in multivariable analysis (Table 3). Male sex, long-duration exercise, and high-intensity exercise were markers of VA in univariable logistical regression, and higher age was a possible confounder. High-intensity exercise and the interaction between high-intensity and long-duration exercise were independent markers of VA in multivariable analysis (Table 4). In a subgroup analysis of mutation-positive family members (n = 82), VA occurred in 5 (6%), and all of them reported high-intensity exercise (23% vs. 0%, p = 0.001).

Functional and structural alterations. Patients reporting high-intensity exercise had worse LV and RV function and more RV dilation than patients reporting low-intensity exercise, but not when adjusted for confounders (Table 3). ROC analyses
suggested exercise intensities between 6 and 7 METs as the optimal statistical threshold values for detecting VA (C-statistic, 0.78; 95% CI: 0.70 to 0.85) and for all secondary outcomes (LV and RV dysfunction and RV dilation).

**COMBINATIONS OF EXERCISE DURATION AND INTENSITY.** The distributions of outcomes in the 4 groups stratified by high or low intensity and long or short duration of exercise shown on the modified radar plots (Figure 2) revealed that VA was most prevalent in high/long exercise (Figure 2A). Interestingly, VA was more prevalent among patients with high/short exercise than patients with low/long exercise (Figure 3). LV dysfunction was most prevalent in high/long exercise and significantly more prevalent than in low/short exercise (Figure 2B). RV dysfunction was also more prevalent in high/long exercise than in both groups of low-intensity exercise (Figure 2C). RV dilation was more prevalent in high/long exercise than in both groups of short duration but not different from patients with low/long exercise (Figure 2D).

**EXERCISE DOSE.** Median exercise dose was 18 MET·h/week (IQR: 12 to 41 MET-h/week) and was higher in probands (Table 1) and men (36 MET-h/week [IQR: 14 to 55 MET-h/week] vs. 12 MET-h/week [IQR: 9 to 22 MET-h/week]) in women, p < 0.001.

**Ventricular arrhythmia.** Patients with exercise doses above median had more prevalent VA (67% vs. 30%, p < 0.001) than patients with lower exercise doses. ROC analysis suggested ≥21 MET-h/week to be associated with VA (C-statistic, 0.74 [95% CI: 0.67 to 0.82]).

**Functional and structural alterations.** Patients with exercise doses above median had more prevalent LV dysfunction (49% vs. 29%, p = 0.01), RV dysfunction (75% vs. 55%, p = 0.006), and RV dilation (88% vs. 63%, p < 0.001) than patients with lower exercise doses. A total of ≥13 MET-h/week was associated with RV dilation, ≥17 MET-h/week with RV dysfunction, and ≥25 MET-h/week with LV dysfunction.

**DISCUSSION**

This study supports the previously reported relationship between exercise and AC disease and shows for the first time that high-intensity exercise has a stronger association with adverse outcome than long exercise duration. These findings suggest that high-intensity exercise is the main premise for harmful effects of exercise in AC and could be helpful when giving exercise advice to AC patients.

**TABLE 3 Clinical and Cardiac Imaging Characteristics of 173 AC Patients and Mutation Carriers With History of Low-Intensity and High-Intensity Exercise**

<table>
<thead>
<tr>
<th></th>
<th>≤6 METs (n = 82)</th>
<th>&gt;6 METs (n = 91)</th>
<th>p Value</th>
<th>Adjusted* OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>41 ± 17</td>
<td>40 ± 15</td>
<td>0.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.9 ± 0.2</td>
<td>1.9 ± 0.2</td>
<td>0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>52 (63)</td>
<td>24 (26)</td>
<td>&lt;0.0001</td>
<td>0.3 (0.1-0.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>Probands</td>
<td>22 (27)</td>
<td>69 (76)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long duration</td>
<td>20 (24)</td>
<td>66 (73)</td>
<td>&lt;0.0001</td>
<td>4.7 (2.0-11)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total VA</td>
<td>16 (20)</td>
<td>67 (74)</td>
<td>&lt;0.0001</td>
<td>14.5 (1.3-39)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACA</td>
<td>4 (5)</td>
<td>13 (15)</td>
<td>0.03†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VT</td>
<td>12 (15)</td>
<td>58 (66)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD therapy</td>
<td>6 (7)</td>
<td>43 (49)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at VA, yrs</td>
<td>45 ± 14</td>
<td>39 ± 16</td>
<td>0.20</td>
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</table>

Cardiac imaging

<table>
<thead>
<tr>
<th></th>
<th>≤6 METs (n = 82)</th>
<th>&gt;6 METs (n = 91)</th>
<th>p Value</th>
<th>Adjusted* OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV dysfunction</td>
<td>21 (27)</td>
<td>45 (50)</td>
<td>0.002</td>
<td>1.4 (0.6-3.5)</td>
<td>0.45</td>
</tr>
<tr>
<td>EF, %</td>
<td>58 ± 5</td>
<td>55 ± 9</td>
<td>0.01†</td>
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<tr>
<td>GLS, %</td>
<td>−19.9 ± 2.6</td>
<td>−18.0 ± 3.5</td>
<td>&lt;0.0001</td>
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<tr>
<td>RV dilation</td>
<td>52 (64)</td>
<td>76 (85)</td>
<td>0.001</td>
<td>0.7 (0.2-1.8)</td>
<td>0.42</td>
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<tr>
<td>RVD, mm</td>
<td>39 ± 7</td>
<td>45 ± 9</td>
<td>&lt;0.0001</td>
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<td>RVOT, mm</td>
<td>34 ± 6</td>
<td>37 ± 9</td>
<td>0.004†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMR RVEDVI, ml/m²</td>
<td>96 ± 30</td>
<td>117 ± 39</td>
<td>0.02†</td>
<td></td>
<td></td>
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<tr>
<td>RV dysfunction</td>
<td>42 (52)</td>
<td>67 (76)</td>
<td>0.001</td>
<td>0.8 (0.3-2.2)</td>
<td>0.70</td>
</tr>
<tr>
<td>FAC, %</td>
<td>42 ± 9</td>
<td>36 ± 10</td>
<td>&lt;0.0001</td>
<td></td>
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</tr>
<tr>
<td>TAPSE, mm</td>
<td>21 ± 5</td>
<td>18 ± 6</td>
<td>0.005†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMR RV EF, %</td>
<td>50 ± 11</td>
<td>45 ± 12</td>
<td>0.07</td>
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</tr>
</tbody>
</table>

**EXERCISE DURATION.** Long-duration exercise was associated with adverse outcome; however, the majority of patients with a history of long-duration exercise also had a history of high-intensity exercise. Adjusted for high-intensity exercise and other potential confounders, long-duration exercise was

**TABLE 4 Clinical Markers of VA (n = 83) in 173 AC Patients**

<table>
<thead>
<tr>
<th></th>
<th>Univariable</th>
<th>Multivariable</th>
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<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>Age, 1 yr</td>
<td>1.02 (1.00-1.04)</td>
<td>0.05</td>
</tr>
<tr>
<td>BSA, 0.1 m²</td>
<td>1.06 (0.92-1.22)</td>
<td>0.45</td>
</tr>
<tr>
<td>Female</td>
<td>0.37 (0.20-0.68)</td>
<td>0.002</td>
</tr>
<tr>
<td>High-intensity exercise</td>
<td>11.52 (5.62-23.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Long-duration exercise</td>
<td>4.15 (2.20-7.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interaction of high-intensity and long-duration exercise</td>
<td>12.75 (1.86-87.29)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Logistic regression of clinical and exercise variables. High-intensity and long-duration exercise correlated moderately and were retained in multivariable analysis with other potential confounders (p < 0.10) from univariable analysis and an interaction term of high-intensity and long-duration exercise.

Abbreviations as in Tables 1 and 2.
FIGURE 2  Distribution of Outcomes

(A) Ventricular arrhythmia, n = 83  p < 0.001

(B) LV dysfunction, n = 66  p = 0.007

(C) RV dysfunction, n = 109  p = 0.001

(D) RV dilatation, n = 128  p = 0.001

Modified radar plots of the distributions of life-threatening ventricular arrhythmia (VA), LV dysfunction, RV dysfunction, and RV dilatation across 4 groups of high- and low-intensity exercise (x-axis) and long- and short-duration exercise (y-axis). The p value by chi-squared test for the distribution of outcomes across 4 groups of intensity/duration as stated. (A) VAs (red): VA was more prevalent in high-intensity/long-duration exercise than in high-intensity/short-duration (82% vs. 52%, p = 0.004), low-intensity/long-duration (82% vs. 10%, p < 0.001), or low-intensity/short-duration exercise (82% vs. 23%, p < 0.001) and more prevalent in patients reporting high-intensity/short-duration exercise than in low-intensity/long-duration (52% vs. 10%, p = 0.003) or low-intensity/short-duration exercise (52% vs. 23%, p = 0.007). (B) LV dysfunction (blue): LV dysfunction was more prevalent in high-intensity/long-duration exercise than in low-intensity/short-duration exercise (55% vs. 25%, p = 0.001). (C) RV dysfunction (green): RV dysfunction was more prevalent in patients reporting high-intensity/long-duration exercise than in low-intensity/short-duration exercise (83% vs. 40%, p < 0.001) and low-intensity/short-duration exercise (83% vs. 56%, p = 0.001). (D) RV dilatation (orange): RV dilatation was more prevalent in patients with high-intensity/long-duration exercise than in high-intensity/short-duration exercise (91% vs. 70%, p = 0.01) and low-intensity/short-duration exercise (91% vs. 61%; p < 0.001). METs = metabolic equivalents.
not a marker of VA. In the adjusted model, there was only a trend towards an association between long-duration exercise and RV dilation. Increased RV dimensions are acknowledged effects of endurance training in healthy athletes (24) but are also associated with disease progression in AC (25). Therefore, RV dilation was considered a soft secondary outcome. This was further supported by the finding that the exercise duration thresholds associated with VA and RV dilation were shorter than for RV and LV dysfunction. This is well in line with the progressive nature of AC, in which VA and RV dilation are early phenomena that could be followed by later development of myocardial dysfunction (26).

**EXERCISE INTENSITY.** High-intensity exercise was strongly associated with adverse outcome. AC patients reporting high-intensity exercise had aggravated phenotypes according to echocardiography and CMR, indicative of more severe disease. Combining high-intensity with long-duration exercise was the strongest marker of VA, which implies that high-intensity exercise performed for long durations was the most harmful form of exercise. The majority of patients reporting high-intensity exercise also reported long-duration exercise. High-intensity exercise remained a strong and independent marker of VA when adjusted for long-duration exercise and other potential confounders. Interestingly, high-intensity exercise of short duration was a strong and independent marker of adverse outcome, whereas low-intensity exercise of long duration was not.

The more harmful effects of high intensity compared with long duration could have several possible explanations. During high-intensity exercise, the increase in RV wall stress exceeds LV wall stress because of the thinner wall of the RV (27). This incremental increase in wall stress has been proposed as an explanation of the harmful effects of vigorous exercise and the RV predilection observed in AC (7,28). The wall stress increase is less pronounced during low-intensity exercise, which might therefore be tolerated, even for longer durations. Our results are in line with previous reports of harmful effects of exercise in AC (6,28,29) and add important information by highlighting the role of exercise intensity in AC. Therefore, the advice to AC patients to abstain from competitive sport should be more specific. The threshold for harmful exercise intensity in our study was around 6 to 7 METs for all adverse outcomes, which suggests that AC patients should not perform activities such as soccer, aerobics, or fast swimming on a regular basis, even noncompetitively.

Although VA occurred rarely in mutation-positive family members, it occurred exclusively in family members reporting high-intensity exercise. This finding adds to previous studies reporting more prevalent VA in an AC mutation-positive family with high exercise doses (7,29) and indicates that high-intensity exercise has also an impact on disease progression in family members with no or mild disease manifestation (7).

Low-intensity exercise, reflecting an active everyday lifestyle (e.g., walking, gardening), was associated with myocardial function and RV dimensions within the normal range. Low-intensity exercise seemed to be tolerated better, even when performed for long durations. However, one-fifth of patients reporting low-intensity exercise had experienced VA, which might reflect the high prevalence of VA in AC independently of exercise (6,28). Data on the safety of moderate-intensity exercise is sparse in AC. There were no results in our study that suggested that low-intensity exercise had an adverse impact in AC; however, further studies should explore safe exercise thresholds in AC, preferably in experimental studies, because randomized exercise training trials in AC patients are unfeasible for ethical reasons.

**EXERCISE DOSE.** Patients with high exercise doses had more prevalent VA, LV dysfunction, RV
dysfunction, and RV dilation than patients with lower doses. The threshold of exercise doses ranged from approximately 13 MET h/week for RV dilation, equivalent to the upper American Heart Association-recommended level for healthy adults of 30 min of low-intensity exercise 5 days per week (4), to almost double that dose (25 MET h/week) for LV dysfunction. We demonstrated that exercise intensity had a stronger association with outcome in AC patients than exercise duration, which implies that sheer multiplication of the two might not give an appropriate estimation of the exercise load in these patients. Interestingly, female patients in our study had lower exercise doses than male patients, which might be one of several explanations of the lower disease penetrance in females.

**CLINICAL IMPLICATIONS.** Our study showed that exercise at >6 METs was associated with VA and a more severe AC phenotype than low-intensity exercise and underscores the advice that AC patients should avoid high-intensity exercise. Low-intensity exercise, even for long durations, was not associated with an unfavorable outcome and might be an acceptable alternative for patients diagnosed with AC who wish to maintain an active lifestyle.

**STUDY LIMITATIONS.** The observational single-center study design limited external validity. Exercise duration was self-reported, and intensity was assigned on the basis of the reported exercise activity. The categorization of exercise duration by median was arbitrary but coincidentally reflected the minimum exercise duration recommended for healthy adults (4). We reported exercise habits during the immediate 3 years before AC diagnosis and did not include lifelong exercise data in analyses because exercise habits can change over time and are subject to recall bias. At diagnosis, patients were advised to restrict their exercise (11), and exercise after diagnosis was not assessed. High-intensity exercise was often combined with long-duration exercise, but the 2 parameters were only moderately correlated. The high odds of an adverse outcome in high-intensity exercise was independent of the interaction between the two, which further strengthens the impact of high-intensity exercise.

**CONCLUSIONS**

High-intensity exercise and long-duration exercise were both associated with unfavorable outcome in AC patients, but high-intensity exercise was a strong marker of VA independent of exercise duration. Low-intensity exercise, even for long durations, was associated with a milder phenotype and can be advised for patients with AC. Further research should explore the safety of low-intensity exercise and the effects of exercise intensity restriction on AC diagnosis.

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**ADDRESS FOR CORRESPONDENCE:** Dr. Kristina H. Haugaa, Department of Cardiology, Oslo University Hospital, Rikshospitalet, PO Box 4950 Nydalen, 0424 Oslo, Norway. E-mail: kristina.haugaa@medisin.uio.no.

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KEY WORDS arrhythmia, arrhythmogenic
right ventricular cardiomyopathy, athletes
heart, exercise intolerance, ventricular arrhyth-
mia, myocardial function

APPENDIX For a supplemental table, please
see the online version of this paper.