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Routine exercise-based cardiac rehabilitation does not increase aerobic fitness: A CARE CR study

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ABSTRACT

Background: Recent evidence suggests that routine exercise-based cardiac rehabilitation (CR) may not lead to a substantial increase in estimated peak oxygen uptake (VO_{2peak}). This could reduce the potential benefits of CR and explain why CR no longer improves patient survival in recent studies. We aimed to determine whether routine exercise-based CR increases VO_{2peak} using gold-standard maximal cardiopulmonary exercise testing (CPET), and to quantify the exercise training stimulus which might be insufficient in patients undertaking CR.
Methods: We studied the effects of a routine, twice weekly, exercise-based CR programme for eight weeks (intervention group) compared with abstention from supervised exercise training (control group) in patients with coronary heart disease. The primary outcome was VO_{2peak} measured using CPET. We also measured changes in body composition using dual X-ray absorptiometry, carotid intima-media thickness, hs-CRP and N-terminal pro B-type natriuretic peptide at baseline, 10 weeks and 12 months. We also calculated the Calibre 5-year all-cause mortality risk score.
Results: Seventy patients (age 63.1 SD 10.0 years; BMI 29.2 SD 4.0 $kg \cdot m^{-2}$; 86% male) were recruited ($n = 48$ intervention; $n = 22$ controls). The mean aerobic exercise training duration was 23 min per training session, and the mean exercise training intensity was 45.9% of heart rate reserve. VO_{2peak} was $23 \cdot 3\ ml \cdot kg^{-1} \cdot min^{-1}$ at baseline, and there were no changes in VO_{2peak} between groups at any time point. The intervention had no effect on any of the secondary endpoints.
Conclusion: Routine CR does not lead to an increase in VO_{2peak} and is unlikely to improve long-term physiological outcomes.

1. Introduction

Cardiac rehabilitation (CR) is a suite of medical and lifestyle secondary prevention measures for patients with heart disease, including coronary heart disease (CHD). Exercise training is a key part of a CR programme in the United Kingdom (UK) [1]. Long-term adherence to exercise-based CR can reduce total cholesterol and LDL-cholesterol, and increases HDL cholesterol [2]. It can reduce the progression of coronary atheroma [3], reduce myocardial remodelling [4], and increases survival [5]. Systematic reviews conducted in 2004 [6] and 2011 [7] reported that compared to standard medical care, exercise-based CR improved survival and reduced the number of hospital admissions by up to 20% and 31%, respectively, in patients with CHD [6,7]. However, a more recent clinical trial [8] and two recent systematic reviews [9,10] suggest that exercise-based CR might not improve all-cause mortality [9], cardiovascular mortality [10], or recurrent cardiovascular events [9] in patients with CHD. This may be because modern revascularisation techniques, such as thrombolysis and percutaneous coronary intervention, improve both short and long-term patient survival [11,12]. However, the authors of a recent systematic review [10], a previous clinical trial [13], and research letters [14,15] have also speculated that low exercise training doses may also be responsible.

The "dose" of exercise training delivered to patients attending exercise-based CR is an important consideration because an

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improvement in peak oxygen uptake (VO_{2peak}) requires an adequate physiological stimulus to invoke positive physiological adaptations. Increasing VO_{2peak} is central to improving patient survival. In patients with CHD, a 1% improvement in VO_{2peak} is associated with a 2% reduction in cardiovascular mortality risk over approximately five years [16], and a 3.5 $ml \cdot kg^{-1}$ min^{-1} increase in VO_{2peak} confers a 25% reduction in all-cause mortality *if* improvements are maintained for more than one year [17].

However, it is not clear whether routine CR results in an increase in VO_{2peak} that is sufficient to improve clinical outcomes, including survival. A UK multi-centre study including 950 patients reported that *estimated* VO_{2peak} increased by as little as 1.8 $ml \cdot kg \cdot^{-1}$ min^{-1} (0.52 METs) following six to eight weeks (6 to 16 sessions) of exercise-based CR [13]. We have shown that estimated VO_{2peak} over-estimates measured changes in VO_{2peak} by 0.7 $ml \cdot kg \cdot^{-1}$ min^{-1} ($-4 \cdot 7$ to $5 \cdot 9$ $ml \cdot kg \cdot^{-1}$ min^{-1}) [18]. Thus, improvements in peak aerobic fitness resulting from routine exercise-based CR in the UK may be minimal. We therefore aimed to assess the short (10 weeks) and longer-term (12 months) effect of standard exercise-based CR on directly measured VO_{2peak} using gold-standard maximal cardiopulmonary exercise testing. We also measured markers of cardiovascular/metabolic health including, dual X-ray absorptiometry (DXA)-derived measurements of body composition, carotid intima-media thickness (C-IMT), high sensitivity C-reactive protein (hs-CRP) and N-terminal pro B-type natriuretic peptide (NT-proBP) and blood lipid/glucose profiles. We hypothesised that a routine, 8 week, 16 session, exercise-based CR programme would lead to an increase in VO_{2peak}, and that the VO_{2peak} of control patients who declined to participate in exercise-based CR would not change.

2. Methods

Reporting of findings adhere to STROBE guidelines (supplementary file). Baseline patient data [19,20] and methods [21] have been reported elsewhere. Clinically stable patients with a recent diagnosis of angina, myocardial infarction (MI), coronary artery bypass graft (CABG) surgery or elective percutaneous coronary intervention (PCI) were recruited between 12th March 2014 and 5th December 2016. All patients were recruited following their referral to a local Phase III CR programme. Patients were free to participate in a routine exercise-based CR programme (intervention group), or to abstain freely from supervised exercise (control group). Patients in the intervention group underwent an initial assessment approximately one week before commencing their CR programme and were followed up approximately one week after completing their CR programme. Patients in the control group were assessed approximately two weeks after they declined their CR programme and were reassessed approximately 10 weeks after their initial assessment. All patients received a follow-up assessment after 12 months. Patients were asked to attend the research laboratory having not participated in strenuous exercise within the previous 24 h.

Ethical approval was obtained from the Humber Bridge NHS Research Ethics Committee – Yorkshire and the Humber (13/YH/0278). Study procedures conform to the 1975 Declaration of Helsinki. Written informed consent was obtained prior to conducting any investigations.

2.1. Anthropometric measurements

Height (cm) was measured using a Leicester Height Measure (SECA, Birmingham, UK). Waist circumference measurements were taken from 1 cm above the iliac crest, and hip measurements were taken from the widest aspect of the buttocks.

2.2. Resting measurements

Resting heart rate was recorded using a 12-lead ECG (GE Healthcare, Buckinghamshire, UK) and resting blood pressure was measured using an automated blood pressure cuff (Tango, SunTech Medical, Eynsham, UK). Pulse wave velocity was then measured using Vascular Explorer (Enverdis GmbH, Düsseldorf, Germany). Measurements were taken between the brachium and ankle by placing a blood pressure cuff above the left cubital fossa (brachial artery) and above the medial malleolus. Photoplethysmographic sensors were placed on the patients left index finger and left hallux. Echocardiography (Vivid 9, GE, USA) was used to measure left ventricular ejection fraction (LVEF) using Simpson's method following the guidelines of Lang and colleagues [22]. Left-ventricular systolic dysfunction was defined as LVEF ≤45%.

2.3. Blood samples

Haematocrit and haemoglobin concentrations, neutrophil and lymphocyte count and NT-proBNP were measured in an accredited National Health Service laboratory on the day that blood samples were collected. Non-fasting plasma glucose and serum hs-CRP were analysed in duplicate using the ABX Pentra 400 biochemistry auto analyser (Horiba, Montpellier, France) using frozen plasma and serum samples. Calibration and quality controls were conducted in accordance with manufacturers' guidelines.

2.4. Dual X-ray absorptiometry

Body composition was determined using DXA (Lunar iDXA, 255 GE Healthcare) as previously described [20,21]. Total body mass (kg), lean body mass (kg) and total fat mass (%) were determined using the Lunar iDXA's integrated software. Appendicular lean mass (ALM; total lean mass in both arms and legs) was calculated (kg) and standardised to their height squared; (skeletal muscle index; SMI $kg \cdot m^{-2}$). ALM was also reported as a percentage of total body mass (appendicular skeletal mass; ASM%). Low skeletal muscle mass was defined as an SMI of <7.0 $kg \cdot m^{-2}$ for men, and <6.0 $kg \cdot m^2$ for women [23].

2.5. Carotid intima-media thickness measurements

Carotid intima-media thickness measurements were made with the Panasonic CardioHealth Station (Panasonic Biomedical Sales Europe BV, Leicestershire, UK), as previously described [21,24].

2.6. Maximal cardiopulmonary exercise testing

The modified Bruce treadmill protocol was used for maximal CPET [25] and our testing practices adhered to established guidelines [26–28]. Heart rate (12-lead ECG) and blood pressure (ECG-gated cuff) were recorded at the second minute of each three minute test stage. Rating of perceived exertion (RPE) scores (6–20) were recorded at peak exercise (Borg, 1982). Breath-by-breath metabolic gas exchange data were collected using an Oxycon Pro metabolic cart (Jaeger, Hoechburg, Germany). Metabolic gas exchange data were exported for offline analysis using Microsoft Excel (Washington, USA). Peak oxygen uptake was defined as the mean VO_2 (ml) over the last 30 s of the CPET, and was adjusted for body mass ($ml \cdot kg^{-1} \cdot min^{-1}$). The ventilatory anaerobic threshold (VAT) was determined by two independent investigators (SN & FN) using the V-slope method [29]. The VAT was analysed using data from the middle five of seven consecutive breaths. The VAT was reported in ml and standardised to body mass ($ml \cdot kg^{-1} \cdot min^{-1}$). Oxygen pulse ($VO_2$/HR), VE/VCO_2 slope and oxygen uptake efficiency slope (OUES) were calculated as previously described [28]. Directly determined metabolic equivalents were calculated by dividing each patient's VO_{2peak} (ml.kg-1.min-1) by 3.5 [30]. Estimated metabolic equivalents were calculated according to the American College of Sport Medicine (ACSM) metabolic equation for walking [31].

2.7. Prognosis – Calibre 5-year all-cause mortality risk

Five-year mortality risk was estimated for each patient using the online (https://www.caliberresearch.org/model) Calibre 5-year risk calculator [32], and reported as a percentage. The model has good calibration and discrimination in internal and external validation (C-Index 0.811) for all-cause mortality. Variables included in the model are shown in Appendix 1. The model does not include any fitness measurements in its calculation.

2.8. Exercise training programme

Patients in the intervention group participated in a physiotherapist-led, eight week, 16 session (twice weekly) personalised exercise training programme, which was prescribed according to UK CR guidelines [33]. Patients were also instructed to participate in additional home-based exercise training sessions at the discretion of the physiotherapist. Each exercise training session incorporated nine exercises which initially alternated between cardiovascular (CV) exercise training and active recovery (AR) stations. Examples of the exercises provided included cycling, treadmill walking, rowing, knee raises, stepping, marching on the spot, arm curls and sit-to-stands. During the course of the eight week CR programme, AR stations were replaced with CV stations to increase difficulty and to increase the total duration of CV exercise training. The aim was for patients to be able to complete a minimum of 20 min of CV exercise training at each exercise session, by the end of the eight week CR programme [33]. Aerobic exercise intensity was prescribed at 40–70% of a patient's heart rate reserve (HRR), which was estimated using the following formula [34]:

((206–0.7 × age) - resting heart rate)

A further 30 beats per minute was deducted from estimated maximal heart for patients who were taking beta-blockers [33]. Patients were asked to record their peak heart rate after each exercise station. The Borg rating of perceived exertion (RPE; 6–20 scale) was used to help patients regulate their exercise intensity [35]. Patients were asked to exercise at an intensity corresponding to an RPE of 11 to 14 [33]. Exercise intensity was up-titrated by increasing cadence or resistance of exercise based on preference and/or the ability of the patient. The total duration of CV training was calculated for each of the 16 exercise sessions. The intensity of aerobic exercise training was characterised by reporting the median *peak* heart rate from each CV exercise station and was expressed relative to HRR, and HR at VAT (determined during CPET).

2.9. Study protocol and statistical analysis

As previously reported [21], an initial calculation assuming 90% power to detect a 2 ml·kg^{-1} min^{-1} (SD 4 ml·kg^{-1} min^{-1}) difference in $\dot{V}O_{2peak}$ between the two groups after the intervention lead to a target sample size of 203 (assuming 15% attrition). As planned [21], the sample size calculation, based on the differences in $\dot{V}O_{2peak}$ (ml·kg·$^{-1}$ min^{-1}) at the 10-week assessment, was repeated after the first 70 patients had completed the study. The mean $\dot{V}O_{2peak}$ in the exercise intervention and control group was 24.1 SD 5.0 ml·kg·$^{-1}$ min^{-1}, and 22.9 SD 5.4 ml·kg·$^{-1}$ min^{-1}, respectively. The allocation ratio was 2/1 in favour of the intervention group. A total sample size of $n = 864$ patients was required to achieve a statistical power of 90% ($n = 288$ in the intervention group and $n = 576$ in the control group). As only 30 patients were being recruited per year, the study was suspended at 70 patients given the unattainable target required.

Statistical analysis was conducted using SPSS version 24 (IBM, New York, NY, USA). Data were visually assessed for normality, and by using the Shapiro-Wilk test. Categorical data are presented as frequency and percentages. Continuous normally distributed data are presented as mean with standard deviation (SD) or 95% confidence intervals (CI), as specified. Where data was missing or participants were lost to follow-up, the last known data point was carried forward. A per-protocol analysis was also conducted on the primary outcome measure ($\dot{V}O_{2peak}$).

Statistically significant differences ($P < 0.05$) were assessed using a one-way analysis of variance (ANOVA) or a repeated measure ANOVA with between group interactions, as appropriate. Corresponding partial eta (ηp^2) effect sizes were used to report the magnitude of group differences. Effect sizes of 0.01, 0.06, and 0.140 denoted small, moderate, and large effect sizes, respectively [36], Friedman and Mann-Whitney U analyses were used to detect significant differences between non-parametric variables. Chi squared analysis was used to detect significant differences between categorical variables.

3. Results

3.1. Patient characteristics

One hundred and forty-nine ($n = 149$) patients who met the study inclusion criteria were invited to participate in the study. Seventy-nine ($n = 79$) patients declined to participate in the study due to lack of interest or time. Seventy patients were recruited (age 63.1 SD 10.0 years; BMI 29.2 SD 4.0 kg·m^{-2}; 86% male). Forty-eight patients were recruited to the intervention group, and 22 patients opted to participate in the control group. Five patients from the intervention group and one from the control group were lost to follow-up at 10 weeks (10 week sample $n = 64$). One patient in the intervention group died from a spontaneous intracranial haemorrhage between 10 weeks and 12 months. One patient in the control group died from pneumonia between 10 weeks and 12 months. A further four patients from the intervention group and five controls were lost to follow-up at 12 months (12 month sample $n = 53$).

Missing data are summarised in Appendix 2. The baseline clinical characteristics of the patients in each group were similar (Table 1), but more control patients had diabetes (36% v 13%; $P = 0.020$), and more control patients were smokers (18% v 0%; $p = 0.023$). There were no differences in prescribed secondary prevention medications between the two groups (Appendix 3). Approximately half the patients (54%) were referred to CR following a MI. The median time between hospital discharge and study consent was 54 days (range 22 to 220).

3.2. Exercise training dose

Patients in the intervention group attended a median of 16 supervised exercise sessions (range: 6 to 16). Thirty-six (75%) patients attended all 16 sessions, and four (8%) attended <14 sessions. Patients in the intervention group took part in a median of one (range: 0 to 8) additional self-directed home-based exercise session per week. However, the cumulative number of weekly supervised and home-based exercise sessions undertaken by patients in the intervention group was still two (range 2 to 10 sessions). In the controls, the total number of reported weekly self-directed home-based exercise sessions was zero (range: 0 to 7; $P = 0.003$). The duration and intensity of self-directed exercise training conducted by control patients was not recorded.

The median CV training duration at the first supervised CR exercise session was 12 min (range: 4 to 28 min), which increased to 23 min at the final exercise session (range: 11 to 50 min; $P < 0.001$). The exercise intensity during CV training increased over the course of the intervention. The mean peak heart rate was 93 bpm (95% CI: 88–98 bpm) during the first session, corresponding to 46% (95% CI: 40–52%) of directly determined HRR, or 97% of mean heart rate at VAT (95% CI: 92–101%). By the end of the 8 week programme, the mean peak heart rate had increased to 97 bpm (95% CI: 92–101 bpm; $P = 0.015$), or 54% of HRR (95% CI: 47–61%; $P = 0.011$), but the mean peak HR as a %HR at the VAT (at 10 weeks), did not increase (102%; 95% CI 97–106%; $P = 0.076$).

3.3. Maximal cardiopulmonary exercise testing

The mean $\dot{V}O_{2peak}$ of patients and controls was similar at baseline (Table 2). There was no change in $\dot{V}O_{2peak}$ in either group after 10 weeks (main effect $P = 0.637$ $\eta_p^2 = 0.004$; interaction effect $P =$

Table 1
Patient characteristics (mean SD standard deviation).

Patient characteristics	All ($n = 70$)	Control group ($n = 22$)	Exercise group ($n = 48$)	P-value
Males (%)	60 (86)	20 (90.9)	40 (83.3)	0.400
Age (years)	63.1 SD 10.1	62.0 SD 10.1	63.7 SD 7.0	0.509
BMI ($kg \cdot m^{-2}$)	29.2 SD 4.0	29.4 SD 4.9	28.9 SD 3.5	0.633
Waist to hip ratio	0.97 SD 0.07	0.98 SD 0.06	0.96 SD 0.07	0.125
Appendicular lean mass (kg)	23.8 SD 4.7	24.3 SD 4.3	23.5 SD 4.9	0.492
SMI ($kg \cdot m^{-2}$)	8.7 SD 1.7	8.9 SD 1.6	8.6 SD 1.8	0.492
ASM (%)	28.1 SD 3.6	28.7 SD 3.5	27.8 SD 3.6	0.290
		Haemodynamic measurements		
Resting HR (bpm)	59 SD 11	59 SD 12	59 SD 12	0.919
Resting systolic BP (mmHg)	128 SD 20	129 SD 24	128 SD 18	0.860
Resting diastolic BP (mmHg)	81 SD 13	84 SD 17	80 SD 11	0.227
LV ejection fraction (%)	55.0 SD 6.9	54.4 SD 8.2	55.3 SD 6.2	0.637
LV end systolic volume (ml)	54.3 SD 17.0	51.8 SD 17.0	55.4 SD 17.1	0.418
LV end diastolic volume (ml)	116.0 SD 28.0	112.4 SD 14.4	117.7 SD 29.7	0.471
LV end systolic diameter (cm)	36.0 SD 5.9	36.4 SD 5.5	35.8 SD 6.2	0.679
LV end diastolic diameter (cm)	50.5 SD 5.6	50.3 SD 4.8	50.6 SD 6.0	0.822
Intraventricular septal thickness (cm)	9.7 SD 1.6	9.9 SD 1.9	9.6 SD 1.6	0.513
		Blood biomarker measurements		
Total cholesterol (mmol/L)‡	3.6 (2.1 to 6.14)	3.5 (2.2 to 5.9)	3.6 (2.1 to 6.1)	0.786
LDL-cholesterol (mmol/L)‡	1.6 (0.8 to 4.0)	1.6 (0.9 to 3.5)	1.6 (0.8 to 4.0)	0.885
HDL-cholesterol (mmol/L)‡	1.1 (0.6 to 2.1)	1.1 (0.8 to 1.8)	1.1 (0.6 to 2.1)	0.815
Triglycerides (mmol/L)‡	1.3 0.5 to 4.6)	1.3 (0.5 to 4.4)	1.4 (0.5 to 4.6)	0.923
High Sensitivity-CRP (mg/L)‡	1.3 (0.1 to 16.6)	1.5 (0.2 to 16.6)	1.3 (0.1 to 9.7)	0.374
Blood Glucose (mmol/L)‡‡	5.6 (3.3 to 22.2)	5.6 (3.3 to 13.8)	5.5 (4.5 to 22.2)	0.775
NT-proBNP (ng/L)‡	187.0 (11.4 to 2735.0)	195.5 (20.3 to 2735.0)	187.0 (11.4 to 1916.0)	0.854
eGFR ($mL/min/1.73m^2$)‡	82.0 (38.0 to 90.0)	83.5 (53.0 to 90.0)	81.5 (38.0 to 90.)	0.144
Haemoglobin (g/L)‡	140.0 (83.0 to 165.0)	140.5 (122.0 to 165.0)	139.5 (83.0 to 165.0)	0.471
Haematocrit (%)‡	41.4 (23.7 to 47.1)	41.1 (36.1 to 45.3)	41.5 (23.7 to 47.1)	0.603
		Spirometry measurements		
Peak expiratory flow (L/s)	7.9 SD 2.1	7.4 SD 2.0	8.1 SD 2.1	0.244
FEV_1 (L)	2.9 SD 0.7	2.9 SD 0.7	2.9 SD 0.7	0.897
FVC (L)	3.8 SD 0.8	3.9 SD 0.9	3.8 SD 0.8	0.736
FEV_1/FVC ratio	0.76 SD 0.08	0.75 SD 0.08	0.77 SD 0.08	0.327
		Presenting diagnosis		
Myocardial infarction (%)	38 (54)	14 (64)	24 (50)	0.710
Percutaneous coronary intervention (%)	19(27)	5 (23)	14 (29)	
Angina (%)	7 (10)	2 (9)	5 (10)	
Coronary artery bypass graft (%)	6 (9)	1 (5)	5 (10)	
		Past medical history		
Myocardial infarction (%)	15 (21)	5 (23)	10 (21)	0.747
Percutaneous coronary intervention (%)	16 (23)	6 (23)	11 (23)	0.793
Coronary artery bypass graft (%	5 (7)	2 (9)	3 (6)	0.668
Cardiac valve surgery (%)	1 (1)	1 (5)	0 (0)	0.137
Cerebrovascular accident (%)	6 (9)	1 (5)	5 (10)	0.415
Atrial fibrillation (%)	5 (7)	1 (5)	4 (8)	0.445
Asthma (%)	8 (11)	1 (5)	7 (15)	0.220
Chronic obstructive pulmonary disease (%)	4 (6)	2 (9)	2 (4)	0.410
Hypertension (%)	33 (47)	13 (59)	20 (42)	0.175
Hyperlipidaemia (%)	47 (67)	14 (64)	33 (69)	0.672
Type II diabetes (%)	14 (20)	8 (36)	6 (13)	0.020*
Cancer (%)	10 14)	4 (18)	6 (13)	0.528
		Behavioural risk factors		
Number of patients achieving 150 min of moderate physical activity per week (%)	32 (46)	8 (36)	24 (50)	0.322
Number of patients achieving 75 min of vigorous physical activity per week (%)	8 (11)	3 (14)	5 (10)	0.660
Weekly alcohol units consumed‡	4 (0 to 70)	4 (0 to 46)	4 (0 to 70)	0.622
Smoker (%)	4 (6)	4 (18)	0 (0)	0.023*
Ex-smoker (%)	43 (61)	13 (59)	30 (63)	
Hospital anxiety and depression score (anxiety)‡	4 (0 to 15)	4 (0 to 11)	4 (0 to 15)	0.670
Hospital anxiety and depression score (depression)‡	2 (0 to 13)	1 (0 to 9)	3 (0 to 13)	0.157

BMI = body mass index; SMI = skeletal muscle index; ASM = appendicular skeletal mass; HR = Heart Rate; bpm = beats per minute; BP = blood pressure; LV = left ventricle; CRP = C-reactive protein; NT-proBNP = N-terminal brain-type natriuretic peptide; eGFR = estimated glomerular filtration rate; FEV_1 = forced expired volume in 1 s; FVC = forced vital capacity.
* Significant difference.
‡ non-parametric data.

Table 2
Cardiopulmonary exercise test variables (mean and 95% confidence intervals).

CPET variable	Control group			Intervention group			P-value		Partial eta squared	
	Baseline	Week 10	Month 12	Baseline	Week 10	Month 12	Main effect	Interaction effect	Main effect	Interaction effect
VO_{2peak} (ml·kg^{-1} min^{-1})	23.0 (20.4 to 25.6)	22.9 (20.4 to 25.3)	23.4 (20.7 to 26.1)	23.5 (21.7 to 25.2)	23.8 (22.2 to 25.5)	24.4 (22.5 to 26.2)	0.108	0.664	0.033	0.005
VO_{2peak} (L)	1.95 (1.70 to 2.20)	1.94 (1.70 to 2.19)	2.01 (1.76 to 2.26)	1.99 (1.82 to 2.16)	2.01 (1.84 to 2.17)	2.05 (1.88 to 2.22)	0.058	0.858	0.042	0.002
Directly measured METs	6.6 (5.8 to 7.3)	6.5 (5.8 to 7.2)	6.7 (5.9 to 7.5)	6.7 (6.2 to 7.2)	6.8 (6.3 to 7.3)	7.0 (6.4 to 7.5)	0.108	0.665	0.033	0.005
VAT (ml·kg^{-1} min^{-1})	15.7 (13.5 to 17.9)	14.9 (12.8 to 17.9)	15.6 (13.6 to 17.7)	17.0 (15.5 to 18.4)	17.0 (15.6 to 18.4)	16.4 (15.1 to 17.8)	0.364	0.070	0.030	0.076
VAT (L)	1.34 (1.14 to 1.54)	1.28 (1.09 to 1.46)	1.36 (1.17 to 1.54)	1.44 (1.31 to 1.58)	1.44(1.31 to 1.56)	1.39 (1.27 to 1.52)	0.307	0.066	0.035	0.078
VE/VCO_2 slope	33.0 (30.4 to 35.7)[b]	32.6 (30.2 to 35.0)[c]	31.7 (29.4 to 34.0)[b,c]	35.4 (33.6 to 37.1)[b]	34.7 (33.1 to 36.4)[c]	34.4 (32.9 to 36.0)[b,c]	0.018[*]	0.667	0.065	0.005
OUES	2.28 (2.02 to 2.53)	2.30 (2.06 to 2.54)	2.37 (2.13 to 2.61)	2.21 (2.03 to 2.38)	2.23 (2.07 to 2.39)	2.23 (2.07 to 2.39)	0.197	0.485	0.024	0.010
Peak VO_2/HR (ml/beat)	15.1 (13.5 to 16.6)	14.8 (13.1 to 16.4)	15.2 (13.6 to 16.8)	14.5 (13.5 to 15.6)	14.7 (13.6 to 15.8)	14.8 (13.7 to 15.9)	0.331	0.514	0.032	0.020
CPET duration (Secs)	801.5 (714.5 to 888.4)[a,b]	827.0 (746.8 to 907.3)[a]	836.7 (748.7 to 924.7)[b]	794.8 (735.9 to 853.6)[a,b]	859.9 (805.6 to 914.3)[a]	866.0 (806.4 to 925.5)[b]	<0.001[*]	0.208	0.140	0.023
Estimated METs	9.0 (7.7 to 10.4)[a,b]	9.6 (8.3 to 10.9)[a]	9.7 (8.3 to 11.1)[b]	9.1 (8.2 to 10.0)[a,b]	10.0 (9.1 to 10.9)[a]	10.1 (9.2 to 11.1)[b]	<0.001[*]	0.583	0.240	0.016
Peak RER	1.05 (1.00 to 1.10)[a,b]	1.08 (1.03 to 1.13)[a]	1.10 (1.05 to 1.15)[b]	1.10 (1.07 to 1.1)[a,b]	1.13 (1.10 to 1.17)[a]	1.14 (1.10 to 1.18)[b]	0.001[*]	0.765	0.114	0.003
Peak HR (bpm)	130 (122 to 139)	131 (124 to 139)	132 (124 to 140)	136 (130 to 141)	136 (131 to 141)	137 (132 to 143)	0.557	0.985	0.017	0.029
Peak systolic BP (mmHg)	178 (166 to 189)	181 (171 to 191)	178 (168 to 189)	179 (172 to 187)	176 (169 to 183)	180 (173 to 187)	0.910	0.289	0.003	0.036
Peak diastolic BP (mmHg)	90 (85 to 95)	87 (81 to 93)	88 (81 to 94)	90 (86 to 93)	87 (83 to 91)	88 (84 to 92)	0.228	0.963	0.022	<0.001
Peak RPE[‡]	17 (13 to 20)	19 (14 to 20)	19 (14 to 20)	18 (12 to 20)	19 (13 to 20)	18 (13 to 20)	0.809	–	–	–

VO_{2peak} = peak aerobic fitness; METs = metabolic equivalents; VAT = ventilatory anaerobic threshold; VE/VCO_2 slope = ventilatory efficiency with respect to VCO_2 elimination; OUES = oxygen uptake efficiency slope; VO_2/HR = oxygen pulse; CPET = cardiopulmonary exercise test; RER = respiratory exchange ratio; HR = heart rate; bpm = beats per minute; BP = blood pressure; RPE = rating of perceived exertion.

[*] Significant difference.
[a] Significant difference between baseline and 10 weeks.
[b] Significant difference between baseline and 12 months.
[c] Significant difference between 10 weeks and 12 months.

0.349; $\eta_p^2 = 0.014$), or 12 months (main effect $p = 0.091$; $\eta_p^2 = 0.052$; interaction effect $P = 0.733$; $\eta_p^2 = 0.006$). Fig. 1 shows the individual changes in VO_{2peak} and VAT at 10 weeks. Approximately 57% ($n = 24$) of intervention patients and 43% ($n = 9$) of controls had a higher VO_{2peak} after 10 weeks. A greater proportion of patients in the intervention (68%; $n = 23$) and control groups (60%; $n = 9$) had a higher VO_{2peak} at 12 months compared with baseline measurements, however the number of patients with a higher VO_{2peak} remained similar (Fig. 1). There were no changes in the VAT at any time point.

There were no differences between groups for other CPET-derived variables. The VE/VCO_2 slope decreased between baseline and week 10 (main effect: -1.1; 95% CI -1.9 to 0.4; $P = 0.003$), and between week 10 and 12 months in both groups (main effect: -0.6; 95% CI -1.2 to −0.1; $P = 0.024$). Peak RER was higher than baseline values at week 10, and 12 months in both groups ($P = 0.001$).

3.4. Cardiovascular/metabolic risk profile

There were no changes in right- ($P = 0.236$), or left-sided, mean C-IMT measurements in either group ($P = 0.401$) at any time point. Body mass index increased in both groups between baseline and 12 months (main effect: 0.4 kg·m^{-2}; 95% CI 0.1–0.7 kg·m^{-2}; $P = 0.011$), and between 10 weeks and 12 months (main effect: 0.3 kg·m^{-2}; 95% CI 0.1–0.5 kg·m^{-2}; $P = 0.016$; Table 3). Appendicular skeletal mass was lower in both groups after 10 weeks compared to baseline (main effect: −0.3%; 95% CI -0.1 to −0.5%; $P = 0.007$). There was a further reduction at 12 months compared to week 10 (main effect: −0.8%; 95% CI -0.1- to −1.5%; $P = 0.018$). Compared to baseline values (187; 11–2735 mg·dl^{-1}), NT-proBNP was significantly lower in both groups after 10 weeks (main effect: 156; 13–1695 mg·dl^{-1}; $P = 0.003$), and decreased further at 12 months (main effect: 137; 9–1695 mg·dl^{-1}; $P = 0.003$). NT-proBNP was also significantly lower after 12 months compared to 10 weeks ($P = 0.011$). Pulse wave velocity, lipids, blood glucose, and NT-proBNP did not differ by group (all $P > 0.050$). There were no differences between the two groups in any of the variables measured.

3.5. Calibre 5-year all-cause mortality risk

The median calculated mortality risk at baseline, 10 weeks, and 12 months is shown in Appendix 4. It was the same in each group at each time point.

4. Discussion

The primary aim of this controlled study was to determine whether a routine 8 week, 16 session, exercise-based CR programme led to an increase in VO_{2peak}. Peak oxygen uptake did not change in our intervention or control group after 10 weeks or 12 months. However, our study did not recruit as many patients as planned [21] and may therefore lack sufficient statistical power to detect a significant difference in our primary outcome measure. It is important to note, however, that the effect sizes for the mean differences between the intervention and control group were small. Furthermore, our planned interim sample size calculation [21] indicated that an additional 794 patients would be required to achieve sufficient statistical power. We estimated that it would take our single centre study another 30 years to recruit this many patients, and we therefore suspended recruitment. The number of patients needed to detect a significant difference between the intervention and control groups is higher than those reported by previous studies [3,37]. Our study therefore provides further evidence [13,18] that the dose of exercise prescribed to patients attending routine CR in the UK may not be high enough to improve VO_{2peak}.

Our data, obtained using gold-standard maximal CPET, agree with previous data showing that exercise-based CR in the UK leads to a small improvement in *estimated* VO_{2peak} [13] when compared to international programmes [38]. However, it is important to consider the

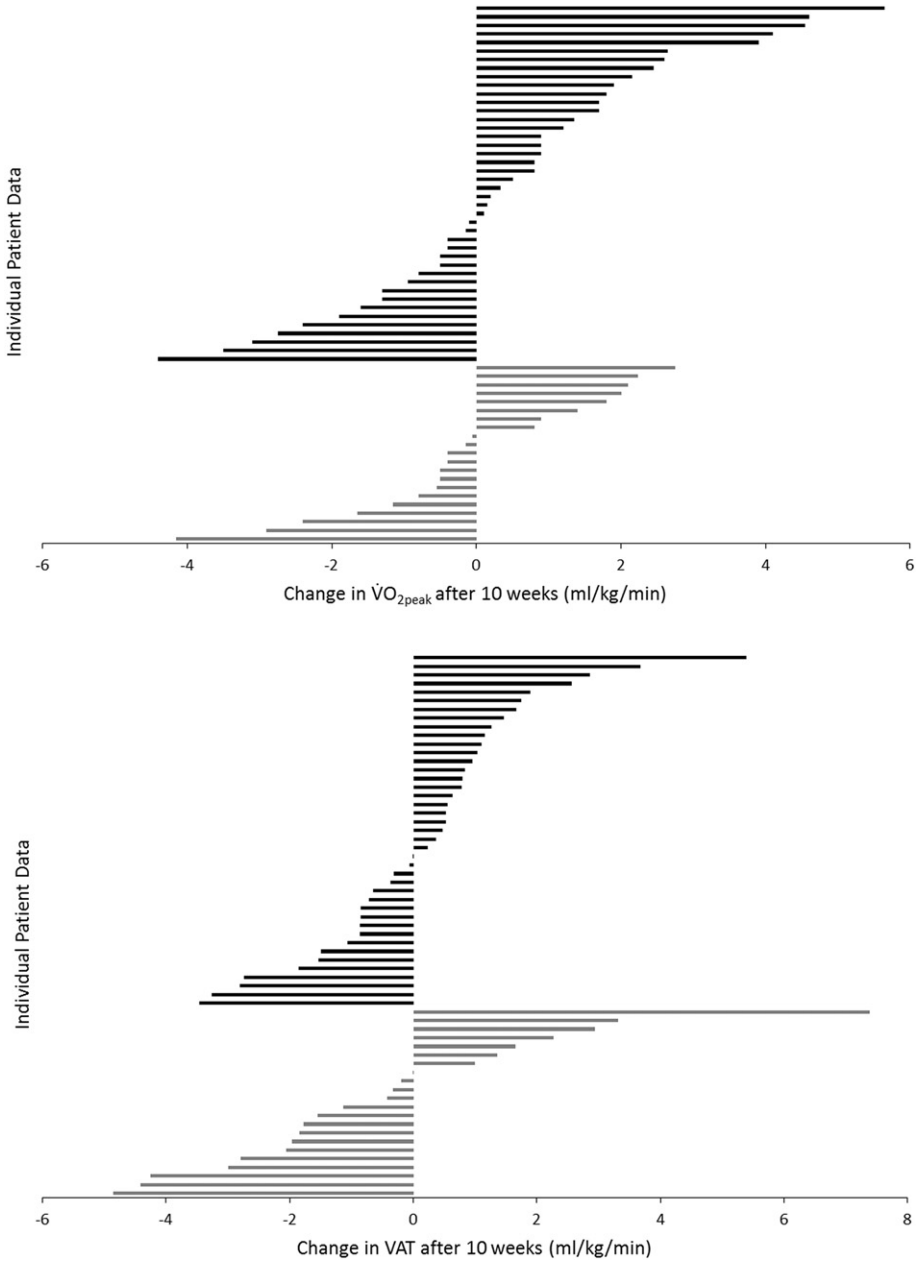

Fig. 1. Individual changes in $\dot{V}O_{2peak}$ and the VAT after 10 weeks. Black lines indicate exercise training responses for patients undertaking the intervention, and grey lines indicate exercise training responses for controls.

measurement error incurred from estimating changes in $\dot{V}O_{2peak}$. Data obtained from walking-based exercise test protocols conducted without metabolic gas exchange shows that UK CR leads to an estimated MET increase of up to 0.76 METs (0.40 to 1.12 METs) [13]. Data from our study suggests that estimated changes in peak aerobic fitness [31] may lead to a 0.7 MET increase without concurrent changes in $\dot{V}O_{2peak}$ (Table 2). This suggests that the changes in $\dot{V}O_{2peak}$ reported in previous studies [13] could be smaller than previously thought. This is important because increasing a patient's $\dot{V}O_{2peak}$ is a key mechanism by which CR was thought to improve patient survival [16,17]. Smaller than expected improvements in $\dot{V}O_{2peak}$ within UK CR programmes [13,18] may therefore partly explain why CR no longer appears to improve patient survival or hospital admissions [9,10].

Recent evidence from the UK showed that patients attending 332 CR exercise training sessions similar to those used in our study, exercised at 37.1% of their HRR [39]. Data from our study shows that the intensity of aerobic exercise training conducted by our patients was slightly higher than this (46–54% HRR), but remained conservatively within UK national guidelines (40–70% HRR) [33]. However, our data were derived from *peak* exercise training heart rate values and is therefore likely to overestimate the average exercise intensity. Furthermore, patients were only exercising for 23 min by the end of the eight week CR programme, which only marginally exceeds the UK's minimum recommendations of 20 min [33]. The low dose of exercise may explain why $\dot{V}O_{2peak}$, markers of cardiometabolic health, C-IMT, and Calibre 5-year all-cause mortality risk did not change following exercise-based CR. Exercise training conducted over 6 [40] to 12 months [3] has been shown to attenuate the progression of atherosclerosis in patients with CHD. Supporting patients to undertake higher doses of exercise training within a structured exercise training programme or as part of a home-based prescription may help to improve these important clinical outcomes.

Table 3
Cardiometabolic risk factors (mean and 95% confidence intervals).

Risk factor	Control group			Intervention group			P-value		Partial eta squared	
	Baseline	Week 10	Month 12	Baseline	Week 10	Month 12	Main effect	Interaction effect	Main effect	Interaction effect
BMI ($kg \cdot m^{-2}$)	29.4 (27.7 to 31.1)[b]	29.6 (27.9 to 31.4)[c]	30.0 (28.1 to 31.9)[b,c]	28.9 (27.8 to 30.1)[b]	28.9 (27.7 to 30.1)[c]	29.1 (27.8 to 30.4)[b,c]	0.010[*]	0.230	0.077	0.022
Waist to hip ratio	0.98 (0.96 to 1.01)	0.98 (0.96 to 1.01)	0.99 (0.96 to 1.01)	0.96 (0.94 to 0.97)	0.95 (0.93 to 0.97)	0.95 (0.93 to 0.97)	0.631	0.802	0.007	0.003
Fat mass (kg)	29.4 (25.8 to 33.1)	29.3 (25.5 to 33.1)	29.0 (24.4 to 33.6)	30.3 (27.9 to 32.8)	29.9 (27.3 to 32.5)	29.6 (26.5 to 32.7)	0.454	0.926	0.012	0.001
Android fat (%)	46.1 (42.7 to 49.4)	45.6 (41.9 to 49.2)	46.0 (42.2 to 49.7)	47.1 (44.8 to 49.4)	46.3 (43.8 to 48.8)	46.4 (43.8 to 48.9)	0.206	0.647	0.023	0.050
Android/gynoid ratio	1.31 (1.22 to 1.39)	1.30 (1.22 to 1.38)	1.31 (1.23 to 1.39)	1.23 (1.17 to 1.28)	1.24 (1.18 to 1.29)	1.23 (1.17 to 1.28)	0.876	0.343	0.002	0.015
Lean body mass (kg)	35.9 (33.0 to 38.7)	36.2 (33.4 to 38.9)	36.2 (33.5 to 38.8)	34.9 (32.9 to 36.8)	34.7 (32.9 to 36.6)	34.6 (32.8 to 36.4)	0.918	0.331	0.001	0.016
Appendicular lean mass (kg)	24.3 (22.3 to 26.3)	24.5 (22.5 to 26.5)	23.9 (21.8 to 26.1)	23.5 (22.1 to 24.9)	23.7 (22.3 to 25.1)	23.2 (21.7 to 24.6)	0.088	0.934	0.041	<0.001
Skeletal muscle index (kg/m^2)	8.9 (8.2 to 9.6)	8.9 (8.2 to 9.7)	8.8 (8.0 to 9.5)	8.6 (8.1 to 9.1)	8.7 (8.2 to 9.2)	8.5 (8.2 to 9.2)	0.088	0.934	0.041	<0.002
Appendicular skeletal mass (%)	28.7 (27.2 to 30.3)[a]	28.9 (27.3 to 30.5)[a,c]	28.0 (26.2 to 29.8)[c]	27.8 (26.7 to 28.8)[a]	28.1 (27.0 to 29.2)[a,c]	27.4 (26.1 to 28.6)[c]	0.035[*]	0.727	0.060	0.002
Resting HR (bpm)	59 (55 to 64)	60 (56 to 64)	60 (56 to 64)	59 (56 to 62)	58 (55 to 60)	58 (55 to 60)	0.940	0.223	0.001	0.022
Resting systolic BP (mmHg)	129 (120 to 137)	126 (117 to 135)	129 (120 to 138)	128 (122 to 134)	121 (115 to 127)	123 (117 to 129	0.060	0.518	0.041	0.010
Resting diastolic BP (mmHg)	84 (79 to 90)[a,b]	77 (72 to 82)[a]	78 (73 to 82)[b]	80 (76 to 84)[a,b]	76 (72 to 79)[a]	79 (76 to 82)[b]	<0.001[*]	0.249	0.109	0.020
LV ejection fraction (%)	54.4 (51.5 to 57.3)	53.4 (50.7 to 56.0)	54.5 (51.9 to 57.2)	55.3 (53.3 to 57.2)	55.6 (53.8 to 57.4)	54.8 (53.0 to 56.6)	0.826	0.224	0.003	0.022
LV end systolic diameter (mm)	36.4 (33.9 to 38.9)	36.0 (33.7 38.3)	35.5 (33.4 to 37.6)	35.8 (34.1 to 37.5)	35.8 (34.2 to 37.3)	37.3 (35.9 to 38.7)	0.695	0.095	0.005	0.034
LV end diastolic diameter (mm)	50.3 (47.9 to 52.7)	50.0 (47.9 to 52.2)	50.2 (48.1 to 52.3)	50.6 (47.0 to 52.2)	50.2 (48.7 to 51.6)	50.5 (49.1 to 51.9)	0.802	0.971	0.003	<0.001
LV end systolic volume (ml)	51.8 (44.6 to 59.1)	55.6 (49.0 to 62.2)	54.4 (47.3 to 61.4)	54.4 (47.3 to 61.4)	55.4 (50.5 to 60.3)	54.1 (49.7 to 58.6)	0.571	0.317	0.008	0.017
LV end diastolic volume (ml)	112.4 (100.4 to 124.4)	118.5 (107.5 to 129.5)	117.5 (106.2 to 128.8)	117.7 (109.6 to 125.8)	120.4 (112.9 to 127.8)	120.3 (112.7 to 128.0)	0.179	0.800	0.025	0.003
Carotid-femoral PWV (m/s)	6.8 (5.9 to 7.7)	6.7 (6.1 to 7.4)	6.9 (6.1 to 7.7)	6.7 (6.1 to 7.3)	6.6 (6.2 to 7.1)	6.7 (6.1 to 7.2)	0.900	0.934	0.002	0.001
Brachium-ankle PWV (m/s)[‡]	14.9 (10.4 to 53.7)	14.6 (10.4 to 29.6)	14.8 (10.4 to 29.6)	14.8 (10.4 to 28.2)	13.9 (10.4 to 21.10)	14.6 (10.4 to 26.5)	0.096	–	–	–
Total cholesterol (mmol/L)[‡]	3.5 (2.2 to 5.9)	3.6 (2.3 to 5.2)	3.6 (2.1 to 5.2)	3.6 (2.1 to 6.1)	3.6 (2.0 to 6.6)	3.6 (2.1 to 7.8)	0.387	–	–	–
LDL-cholesterol (mmol/L)[‡]	1.6 (0.9 to 3.5)	1.7 (0.9 to 3.3)	1.7 (0.8 to 3.3)	1.6 (0.8 to 4.0)	1.5 (0.6 to 4.0)	1.6 (0.9 to 4.0)	0.681	–	–	–
HDL-cholesterol (mmol/L)[‡]	1.1 (0.8 to 1.8)	1.1 (0.7 to 2.1)	1.1 (0.7 to 2.0)	1.1 (0.6 to 2.1)	1.1 (0.6 to 2.0)	1.2 (0.7 to 2.0)	0.534	–	–	–
Triglycerides (mmol/L)[‡]	1.3 (0.5 to 4.4)	1.3 (0.6 to 4.0)	1.3 (0.6 to 4.1)	1.4 (0.5 to 4.6)	1.3 (0.6 to 4.0)	1.2 (0.6 to 5.2)	0.683	–	–	–
High sensitivity-CRP (mg/L)[‡]	1.5 (0.2 to 16.6)	1.4 (0.2 to 18.5)	0.9 (0.2 to 18.5)	1.3 (0.1 to 9.7)	1.2 (0.1 to 19.1)	1.0 (0.1 to 6.0)	0.412	–	–	–
Blood glucose (mmol/L)[‡]	5.6 (3.3 to 13.8)	6.3 to 4.7 to 16.6)	5.9 (4.3 to 19.9)	5.5 (4.5 to 22.2)	5.5 (4.2 to 22.2)	5.7 (4.5 to 22.2)	0.734	–	–	–
NT-proBNP (ng/L)[‡]	195.5 (20.3 to 2735.0)[a,b]	145.5 (20.3 to 1331.0)[a,c]	156.6 (9.1 to 796.0)[b,c]	187.0 (11.4 to 1916.0)[a,b]	155.5 (12.6 to 1695.0)[a,c]	136.0 (19.0 to 1695.0)[a,c]	<0.001[*]	–	–	–

BMI = body mass index; HR = heart rate; bpm = beats per minute; BP = blood pressure; LV = left ventricle; PWV = pulse wave velocity CRP = C-reactive protein; NT-proBNP = N-terminal brain-type natriuretic peptide.
[‡] Non-parametric data.
[*] Significant difference.
[a] Significant difference between baseline and 10 weeks.
[b] Significant difference between baseline and 12 months.
[c] Significant difference between 10 weeks and 12 months.

4.1. Limitations

Our study was only conducted at one site which may limit the generalisability of our findings. Our study sample size was also small, which also limits the conclusions of our findings. However, interim power analysis indicate that we would need to test 864 patients to find a statistically significant improvement in $\dot{V}O_{2peak}$, suggesting that the observed effect signal was small. Furthermore, previous cohort studies which estimated changes in aerobic fitness following routine exercise-based CR and have reported similar findings from CR programmes conducted in other regions of the UK [13]. Finally, we attempted to quantify the dose of exercise prescribed to patients in the routine exercise-based CR programme. However, we did not use 'reference standard' physical activity tracking devices such as accelerometers. Thus, we did not accurately determine the dose of exercise prescribed to our patients. We were therefore unable to determine what dose of exercise *was* likely to increase $\dot{V}O_{2peak}$ in patients attending routine exercise-based CR.

5. Conclusion

Whilst our study was underpowered, our data indicates that the dose of exercise prescribed to patients attending a routine exercise-based CR programme in the UK may be too low to improve $\dot{V}O_{2peak}$ or other markers of cardiovascular health. Our findings should be interpreted with caution, but may partly explain why CR no-longer appears to improve clinical outcomes.

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CRediT authorship contribution statement

S. Nichols: Conceptualization, Methodology, Funding acquisition, Formal analysis, Data curation, Writing - original draft, Project administration.**C. Taylor:**Formal analysis, Data curation, Writing - review & editing, Project administration.**T. Goodman:**Conceptualization, Methodology, Formal analysis, Data curation, Writing - review & editing, Project administration.**R. Page:**Formal analysis, Data curation, Writing - review & editing, Project administration.**A. Kallvikbacka-Bennett:**Formal analysis, Data curation, Writing - review & editing, Project administration.**F. Nation:**Formal analysis, Data curation, Writing - review & editing, Project administration.**A.L. Clark:**Conceptualization, Methodology, Writing - review & editing, Project administration, Funding acquisition.**S.T. Birkett:**Formal analysis, Data curation, Writing - review & editing, Project administration.**S. Carroll:**Conceptualization, Methodology, Funding acquisition, Formal analysis, Data curation, Writing - review & editing, Project administration.**L. Ingle:**Conceptualization, Methodology, Funding acquisition, Formal analysis, Data curation, Writing - review & editing, Project administration.

Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

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Appendix 1. Variables included in the CALIBER 5-year risk score

Categorical variables	Continuous variables
Sex	Age (years)
Belongs to most deprived quintile	Total cholesterol (mmol/L)
CAD diagnosis and severity	HDL (mmol/L)
Interventions (last 6 months)	Heart rate (beats per minute)
Smoking status	Creatinine (micromol/L)
Hypertension/BP lowering medication	White cell count (10^9/L)
Diabetes	Haemoglobin (g/dl)
Heart failure	
Peripheral arterial disease	
Atrial fibrillation	
Stroke	
Chronic renal disease	
COPD	
Cancer	
Chronic liver disease	
Depression	
Anxiety	

CAD = coronary artery disease; HDL high = density lipoprotein; BP = blood pressure; COPD = chronic obstructive pulmonary disease.

Appendix 2. Missing data

Investigation	Number (%) of missing investigations at baseline (total $n = 70$)	Number (%) of missing investigations at 10 weeks (total $n = 64$)	Number (%) of missing investigations at 12 months (total $n = 53$)
CPET	0 (0)	1 (2)	4 (8)
DXA	0 (0)	1 (2)	1 (2)
Echocardiogram	0 (0)	1 (2)	0 (0)
ECG	0 (0)	0 (0)	0 (0)
Spirometry	0 (0)	0 (0)	0 (0)
Cholesterol Measurements	2 (3)	1 (2)	2 (4)
Triglycerides	2 (3)	1 (2)	2 (4)
hs-CRP	2 (3)	1 (2)	2 (4)

(*continued*)

Investigation	Number (%) of missing investigations at baseline (total $n = 70$)	Number (%) of missing investigations at 10 weeks (total $n = 64$)	Number (%) of missing investigations at 12 months (total $n = 53$)
NT-proBNP	2 (3)	3 (5)	2 (4)
Calibre Risk Score	2 (3)	3 (5)	2 (4)
C-IMT	0 (0)	0 (0)	0 (0)

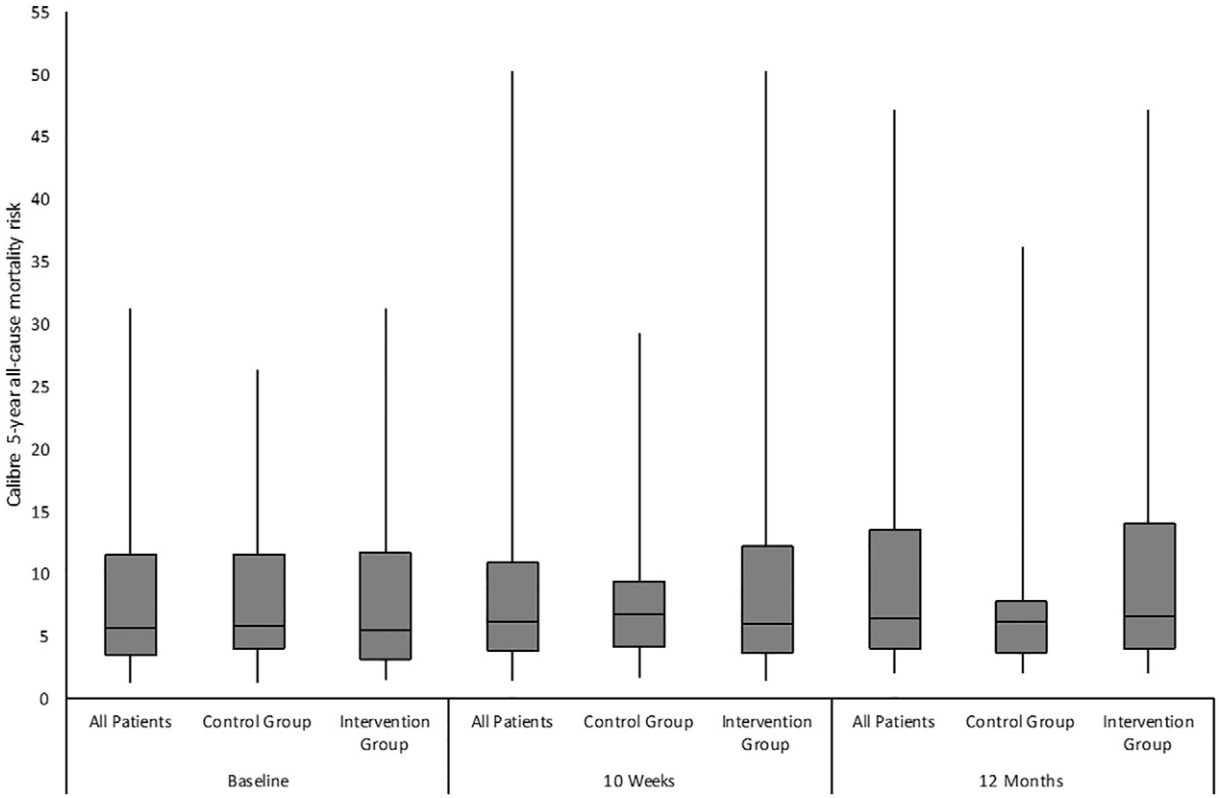
CPET = cardiopulmonary exercise test; DXA = dual X-ray absorptiometry; ECG = electrocardiogram; hs-CRP = high sensitivity C-reactive protein; NT-proBNP = N-terminal brain-type natriuretic peptide; C-IMT = carotid intima-media thickness measurement.

Appendix 3. Patient medications

Medications	All	Control group	Exercise group	*P*-value
Aspirin (%)	68 (97)	21 (95)	47 (98)	0.566
Clopidogrel (%)	21 (30)	4 (18)	17 (35)	0.144
Ticagrelor (%)	35 (50)	14 (64)	21 (44)	0.122
Anti-Coagulants (%)	2 (3)	0 (0)	2 (4)	0.331
Beta-Blockers (%)	60 (86)	19 (86)	41 (85)	0.916
ACE-Inhibitors (%)	42 (60)	15 (68)	27 (56)	0.344
Angiotensin Receptor Blockers (%)	6 (9)	1 (45)	5 (10)	0.415
Statin (%)	67 (96)	21 (95)	46 (96)	0.942
Diuretics (%)	7 (10)	3 (14)	4 (83)	0.492
Calcium Channel Blockers (%)	7 (10)	2 (9)	5 (19)	0.864
Nitrates (%)	16 (23)	5 (23)	11 (23)	0.986

ACE = angiotensin converting enzyme.

Appendix 4. Changes in Calibre 5-year all-cause mortality risk



Appendix 4 – Box-and-whisker plot showing Calibre 5-year all-cause mortality risk at baseline, 10 week, and 12-month follow-up assessment. Lower whisker shows minimum values, lower box line shows 25th percentile, mid-line shows median values, upper box line shows 75th percentile, and upper whisker shows maximum values.

Appendix 5. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.01.044.

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