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Aerobic interval training and continuous training equally improve aerobic exercise capacity in patients with coronary artery disease: The SAINTEX-CAD study ☆

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ABSTRACT

Background: Exercise-based cardiac rehabilitation increases peak oxygen uptake (peak VO_2), which is an important predictor of mortality in cardiac patients. However, it remains unclear which exercise characteristics are most effective for improving peak VO_2 in coronary artery disease (CAD) patients. Proof of concept papers comparing Aerobic Interval Training (AIT) and Moderate Continuous Training (MCT) were conducted in small sample sizes and findings were inconsistent and heterogeneous. Therefore, we aimed to compare the effects of AIT and Aerobic Continuous Training (ACT) on peak VO_2, peripheral endothelial function, cardiovascular risk factors, quality of life and safety, in a large multicentre study.
Methods: Two-hundred CAD patients (LVEF > 40%, 90% men, mean age 58.4 ± 9.1 years) were randomized to a supervised 12-week cardiac rehabilitation programme of three weekly sessions of either AIT (90–95% of peak heart rate (HR)) or ACT (70–75% of peak HR) on a bicycle. Primary outcome was peak VO_2; secondary outcomes were peripheral endothelial function, cardiovascular risk factors, quality of life and safety.
Results: Peak VO_2 (ml/kg/min) increased significantly in both groups (AIT 22.7 ± 17.6% versus ACT 20.3 ± 15.3%; p-time < 0.001). In addition, flow-mediated dilation (AIT +34.1% (range –69.8 to 646%) versus ACT +7.14% (range –66.7 to 503%); p-time < 0.001) quality of life and some other cardiovascular risk factors including resting diastolic blood pressure and HDL-C improved significantly after training. Improvements were equal for both training interventions.
Conclusions: Contrary to earlier smaller trials, we observed similar improvements in exercise capacity and peripheral endothelial function following AIT and ACT in a large population of CAD patients.

1. Introduction

Coronary artery disease (CAD) is the main cause of death worldwide [1] and in Europe [2]. The benefits of exercise-based cardiac rehabilitation on cardiovascular risk factors [3,4], on quality of life (QoL) [5], on exercise tolerance (peak VO_2) [6–9], and on cardiac morbidity and mortality [3,4] have been widely established in CAD patients. However, there is still controversy regarding the optimal exercise characteristics that yield the most beneficial effects in patients with CAD [10,11]. The "traditional" approach is to prescribe training at an intensity of 60 to 80% of peak VO_2, which results in an average increase of 20% for peak VO_2 [12]. Intensity seems to be an important predictor of the effectiveness of cardiac rehabilitation programmes since a higher intensity leads to larger improvements in peak VO_2, even after adjustment for other training-related variables [12,13]. However, a higher intensity is difficult to maintain for a longer period; therefore an interval structure is suggested by Mezzani et al. [11]. Interval training consists of periods of high-intensity exercise alternated by periods of relative rest that makes it possible for patients to complete short work periods at higher intensities. From a physiological point of view, high intensity interval training stimulates cardiac contractility and poses a larger impact on the endothelium and skeletal muscle mitochondrial function compared to continuous training at moderate intensity (MCT), which could add to a more favourable effect on peak VO_2 [14]. Whereas the implementation of high intensity aerobic interval training (AIT) is common practice in sports medicine, only relatively small, single centre trials have tested this approach in CAD patients [15,16]. A recent meta-analysis, comprising 9 studies and 206 patients, concluded that AIT results in a 1.60 ml/kg/min larger benefit in peak VO_2 compared to MCT in patients with CAD [16]. The AIT group showed an improvement of 20.5% in peak VO_2 compared to only 12.8% in the MCT group, the latter being low compared to the average increases after three months of "traditional" cardiac rehabilitation [12]. Given the small sample sizes and the large inconsistency and heterogeneity between the study results, this meta-analysis highly recommended that a sufficiently powered randomized multicentre study is warranted to 1) assess efficacy and safety of AIT [16], and to 2) investigate if the aerobic continuous training (ACT) can be performed at intensities higher than 70–75% of peak heart rate (HR) resulting in better improvements.

Therefore, the aim of the present study [17] was to assess whether a 12-week programme of three weekly, supervised sessions of AIT is superior to aerobic continuous training (ACT) in terms of 1) peak VO_2, 2) peripheral endothelial function, 3) cardiovascular risk factors, 4) QoL and 5) safety.

2. Methods

A detailed description of study design, eligibility and participants of the Study on Aerobic INTerval EXercise training in CAD patients (SAINTEX-CAD) has been published previously [17].

2.1. Participants

Two hundred CAD patients (aged between 40–75 years) referred for cardiac rehabilitation were enrolled in a longitudinal, randomized prospective clinical study at the University Hospital of Antwerp (Centre 1) and the University Hospital of Leuven (Centre 2), 100 patients at each site. Inclusion criteria were: [17] 1) angiographically documented CAD or previous acute myocardial infarction (AMI), 2) left ventricular ejection fraction (LVEF) >40%, 3) on optimal medical treatment, 4) stable with regard to symptoms and medication for at least 4 weeks and 5) included between 4 and 12 weeks following AMI, Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Grafting (CABG). After obtaining written informed consent, patients were randomized to AIT or ACT on a 1:1 base. The study complied with the World Medical Association Declaration of Helsinki on ethics in medical research [18] and was approved by the local medical ethics committees.

2.2. Measurements

Anthropometric measurements, echocardiography and blood analyses were performed at baseline and after 12 weeks. The cardiopulmonary exercise test (CPET),

flow-mediated dilation (FMD) and QoL were assessed at baseline, 6 weeks and 12 weeks. The CPET at 6 weeks was performed to adjust the training intensity according to the achieved peak HR.

2.2.1. Anthropometric measurements

Height (cm) and weight (kg) were measured before the CPET using a stadiometer (Seca model) and a scale (Centre 1, ADE; Centre 2, Tefal, Sensitive Computer). Body mass index (BMI) was calculated as the weight (kg) over the height squared (m^2). Waist circumference (cm) was measured end-expiratory at a level midway between the lowest rib and the iliac crest.

2.2.2. Cardiopulmonary exercise test

As described previously [17], a maximal graded exercise test (20 W + 20 W/min or 10 W + 10 W/min) on a bicycle ergometer was performed. Twelve-lead ECG and gas exchange measurements were recorded continuously, and blood pressure was measured every 2 min. Peak VO_2 was determined as the mean value of VO_2 during the final 30 s of exercise.

2.2.3. Flow-mediated dilation by brachial artery ultrasound scanning

Endothelium-dependent and -independent vasodilation of the right brachial artery were measured by ultrasound scanning (Centre 1, AU5 Ultrasound System, Esaote; Centre 2, GE Healthcare, Vivid 7), in standardized conditions as described in the guidelines [19]. A high resolution linear-array vascular probe was used (Centre 1, 10 MHz; Centre 2, 5–13 MHz). Patients were positioned supine with the right arm resting on an arm support; the brachial artery was imaged above the antecubital fossa in the longitudinal plane. Blood pressure was obtained after 10 min of rest with an automated blood pressure monitor (Omron M6). To determine the endothelium-dependent vasodilation, the forearm was occluded for 5 min at a cuff pressure of at least 200 mm Hg or 60 mm Hg higher than the resting systolic blood pressure. Images were continuously recorded before cuff inflation for 1 min, and after cuff deflation for 3 min. Endothelium-independent vasodilation was measured after administering 1 dose (0.4 mg) of nitroglycerine (Nitrolingual® Pumpspray) sublingually. Images were continuously recorded from the 3rd until the 9th minute after administering nitroglycerine. Images were analysed using edge-detection software FMD-i by Flomedi (Flomedi, Brussels, Belgium). FMD and Nitroglycerine-mediated dilation (NMD) were expressed as the change in post-stimulus diameter as a percentage of the baseline diameter. Analyses were blinded in both study centres.

2.3. Echocardiography

Patients were examined by experienced cardiologists, at rest in the left lateral supine position using an ultrasound machine (Centre 1, GE Healthcare, Vivid 7; Centre 2, GE Healthcare, Vivid E9) and a 1.5–4.5 MHz probe. Left ventricular ejection fraction (LVEF) was calculated using the biplane Simpson's method on the 4- and 2-chamber views of the left ventricle. The average of these two measurements was used in the statistical analysis. Analyses were blinded and were performed by one cardiologist (CDM).

2.3.1. Blood analyses

Venous blood samples were drawn after an overnight fast. Total cholesterol, serum triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and glucose were analysed by the biochemical laboratories using standard procedures at both University Hospitals. High sensitivity C-reactive protein (hs-CRP) was analysed using standard procedures in Centre 1 on all blood samples. Laboratory personnel were blinded to treatment allocation.

2.3.2. Quality of life

The Short Form-12 (SF-12) was used as a generic health status measure [20] and comprises a physical component summary (PCS) and a mental component summary (MCS) that refer to self-reported physical and mental health status, respectively [21].

2.3.3. Safety

All adverse events were reported immediately to the project coordinating committees (Safety Committee and Adverse Event Committee) composed of two independent researchers for each committee. Adverse events were defined as all-cause mortality, hospitalization for cardiovascular disease, atrial tachycardia, atrial fibrillation or frequent ventricular arrhythmias.

2.4. Exercise training

The training intervention (Fig. 1) was previously described by Conraads et al. [17]. In short, patients followed a supervised training programme 3 times a week during 12 weeks of either AIT (90–95% of peak HR) or ACT (at least 70–75% of peak HR) on a bicycle (Centre 1, Technogym XT; Centre 2, Ergo-fit, Gymna). Besides 36 exercise sessions, 6 additional multi-disciplinary education sessions were organized.

Patients in Centre 1 exercised using a key, in which their target HR zones were programmed. The key was connected to the bicycle, and workload was adapted continuously according to the actual training HR. In Centre 2, a workload-based approach was used, where workloads were determined for each training session, and HR was measured 4 times during each session. If the HR was no longer close to the upper border of the target HR zone, the workload for the next session was adapted. The Borg 6–20 scale and blood pressure were measured after each training session.

A. AIT programme (38 min)

B. ACT programme (47 min)
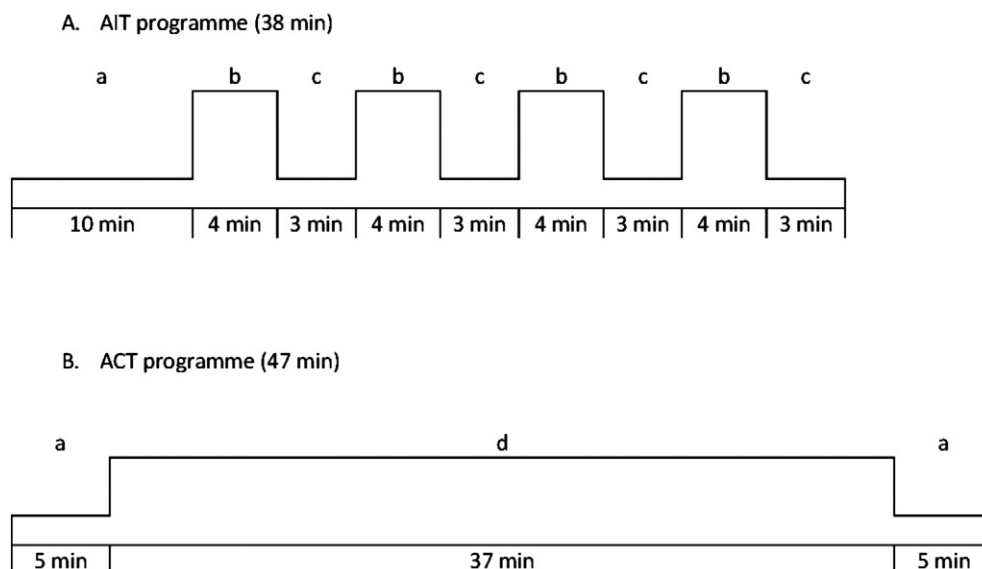
Fig. 1. Visual presentation of the AIT (A) and ACT (B) programme. a = 50–60% of peak VO₂, 60–70% of peak heart rate, 11–13 Borg scale, no shortness of breath. b = 85–90% of peak VO₂, 90–95% of peak heart rate, 15–17 Borg scale, shortness of breath. c = 50–70% of peak heart rate. d = at least 60–70% of peak VO₂, at least 65–75% of peak heart rate.

2.5. Statistical analyses

Data are presented as mean ± standard deviation (SD) or as number; in the figure mean ± standard error of measurement (SEM) was used. All statistical analyses were performed using SAS (SAS® 9.3, Sas Institute, Inc., Cary, NC, USA). Based on an effect size of 0.5 (increase in peak VO₂ of 3.5 ml/kg/min, SD 7 ml/kg/min), we calculated that a total number of 172 patients would be needed to detect a larger benefit with AIT, with a significance level of 0.05 and a statistical power of 0.90 [17]. To anticipate for potential drop-outs, 100 patients were enrolled in each treatment arm.

Baseline characteristics were calculated for the total group and the AIT and ACT group separately. Group differences and differences between inclusions and non-inclusions were tested by ANOVA for continuous variables and by chi-square test for dichotomous variables. As there were group differences for age and pathology (Acute Myocardial Infarction (AMI), Coronary Artery Bypass Surgery (CABG), and Percutaneous Coronary Intervention (PCI)) at baseline, an ANCOVA was performed to test the effects after 6 and 12 weeks of training with age and pathology as covariates. Patients who had only AMI or AMI + PCI, were categorized in the AMI group. The CABG group comprised all patients who had CABG, AMI + CABG, or the combination of AMI + PCI + CABG. The PCI group consisted of patients that only had PCI. The Scheffé test for multiple comparisons was used as a post hoc test. Pearson correlation coefficients were calculated between baseline values and changes of the primary outcome peak VO₂ (ml/kg/min) and secondary outcome FMD (%).

For the primary and the secondary outcome (peak VO₂ in ml/kg/min and FMD in %), the effect of the centre of enrolment was calculated using an ANCOVA with centre as covariate, in addition to age and pathology. No centre-effect was found for peak VO₂ (p = 0.81) but FMD resulted in a significantly higher mean value in Centre 2 (p < 0.001). Therefore, ANCOVA for FMD included age, pathology and centre as covariates. Percentual changes of FMD were skewed and therefore expressed as median and range.

Intention-to-treat analysis [22], in which the results from all patients assigned to AIT or ACT were taken into account, including drop-outs, was done for the primary outcome (peak VO₂ in ml/kg/min). The baseline data of the drop-outs were used as the missing data at 6 and/or 12 weeks of the intervention. This intention-to-treat analysis usually reflects the effects of treatment in everyday practice. As we aimed to investigate the results of the treatment, we performed a per protocol analysis for the training effects.

All statistical tests were 2-sided at a significance level of ≤0.05.

Mean training HRs and workloads for session 1 to 18 and 19 to 36 were calculated by averaging the 4 HRs/workloads of each training session (AIT: HR/workload measured at the end of each 4-minute interval; ACT: HR/workload measured at 10′, 20′, 30′ and 37′ of the moderate intensity bout) and dividing it by the number of training sessions (=18). These mean HRs/workloads were expressed as % of the peak HR/workload of the first exercise test (peak HR 1/workload 1) for sessions 1–18 and of the second exercise test (peak HR 2/workload 2) for sessions 19–36.

hs-CRP values were not detectable if <0.160 mg/l and these values were thus replaced by 0.160 mg/l. In addition, hs-CRP data were skewed and were therefore log transformed before analyses.

3. Results

A flowchart of the trial is presented in Fig. 2. One thousand thirty seven patients were referred to cardiac rehabilitation between November 2010 and March 2013 (Centre 1, n = 392; Centre 2, n = 645). Four hundred seventy seven patients were eligible according to the inclusion and exclusion criteria [17], of which 175 refused participation, 102 could not be included for other reasons, and 200 were randomized to AIT or ACT. Age was not significantly different (p = 0.23) between the included patients (n = 200) and the eligible but non-included patients (n = 277), respectively 58.4 ± 9.1 years versus 59.4 ± 8.9 years, but significantly (p = 0.0035) less females were included (included: 180 M and 20 F versus non-included: 222 M and 55 F): 45% of all men compared to 27% of all women participated.

Baseline characteristics of the included patients are presented in Table 1. Age and pathology differed significantly, with younger age, more post-AMI and less post-PCI patients in the AIT group, while other baseline values were similar between AIT and ACT.

As shown in Fig. 2, 26 patients dropped out (13%) during the 12 weeks of training, of which 15 from the AIT group (6 in Centre 1; 9 in Centre 2; NS) and 11 from the ACT group (5 in Centre 1; 6 in Centre 2; NS). The drop-out rate in women (7 out of 20; 5 AIT and 2 ACT) was higher than the drop-out rate in men (19 out of 180; 10 AIT and 9 ACT; p = 0.002). According to previous calculations [17], a number of 174 patients were still sufficient to detect significant differences between AIT and ACT.

As shown in Table 2, peak VO₂, peak workload, peak HR and O₂ pulse increased significantly over time (p < 0.001). Similar responses were found after AIT and ACT. Peak VO₂ increased with 14.5 ± 20.1% after 6 weeks and 22.7 ± 17.6% after 12 weeks of AIT; peak VO₂ improved with 13.1 ± 12.8% after 6 weeks and 20.3 ± 15.3% after 12 weeks of ACT (Fig. 3). Results of the intention-to-treat analysis for peak VO₂ did not differ significantly from the per protocol analysis.

We observed a significant increase in FMD following training with no difference between both training groups (Table 3). Flow-mediated dilation increased with 12.3% (range −78.9 to 454%) after 6 weeks and 34.1% (range −69.8 to 646%) after 12 weeks of AIT; FMD increased with 16.9% (range −80.8 to 503%) after 6 weeks and 7.14% (range −66.7 to 503%) after 12 weeks of ACT. Baseline FMD was inversely correlated with changes in FMD (r = −0.51; p < 0.001). Changes in peak VO₂ (ml/kg/min) correlated significantly with changes in FMD (r = 0.17; p = 0.035).

As shown in Table 4, HDL-C and total cholesterol increased significantly after the 12-week intervention, with no difference between both training groups. Diastolic blood pressure and hs-CRP decreased significantly over time, while systolic blood pressure tended to decrease.
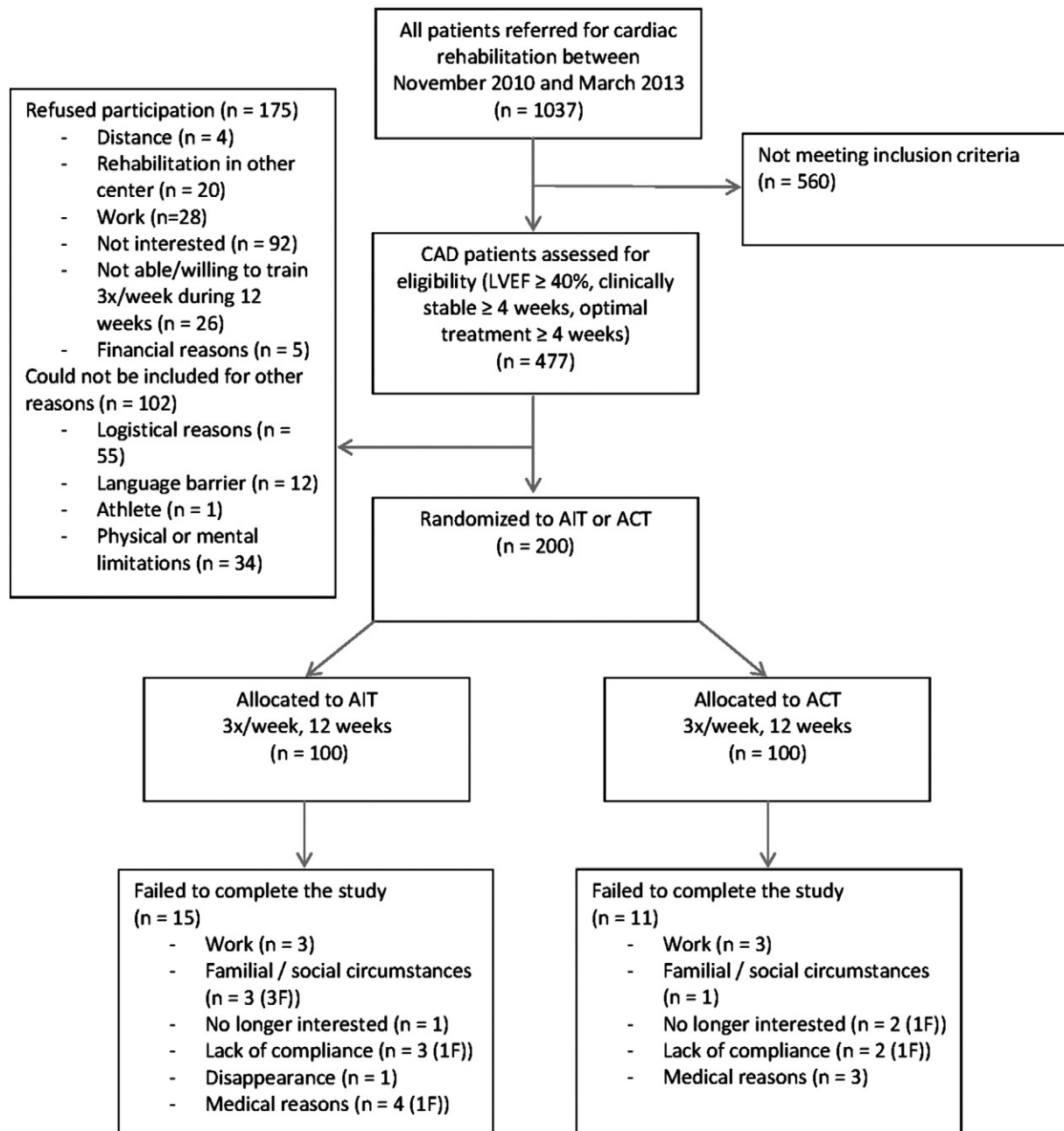
Fig. 2. Flowchart of the trial. n = number of patients; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; AIT = aerobic interval training; ACT = aerobic continuous training; F = female.

Quality of life improved significantly on the physical and mental domain following AIT and ACT, with no group differences (Table 4). Increases from baseline to 6 weeks were significant, with no further significant improvements from 6 to 12 weeks (data at 6 weeks not shown).

Beta-blocker dose was changed in 32 patients during the intervention period: the dose was doubled in 17 (5 AIT, 12 ACT) and halved in 8 (5 AIT, 3 ACT), stopped in 3 (1 AIT, 2 ACT) and started in 4 (2 AIT, 2 ACT) patients. When excluding these 32 patients, similar results were found for all exercise- and endothelial-related variables, for cardiovascular risk factors and QoL, except for resting diastolic blood pressure (p-time > 0.05).

Overall compliance for the AIT group was 35.7 ± 1.1 training sessions and for the ACT group 35.6 ± 1.5 training sessions. The analyses of the training intensities were done for the total group of patients (n = 172), as it did not differ from the analyses excluding patients changing their beta-blocker dose. Mean training intensity for the AIT group was around 88% of peak HR and for the ACT group around 80% of peak HR during the 12 week intervention (Supplemental Table 5). Mean training workloads for the AIT group were 86% of peak workload and for the ACT group 63% of peak workload (Supplemental Table 6). There were significant group differences between the training intensities (p-group < 0.001), the training workloads (p-group < 0.001) and the Borg scores (p-group < 0.001; AIT: 13.5 ± 1.6 vs ACT: 12.5 ± 1.5), with higher values for the AIT group.

No adverse events were reported during the training sessions. One patient (ACT) had an AMI, >24 h after his last training session, after which PCI was performed. Two other patients (both ACT) had a significant ST-depression during the exercise test at 6 weeks and underwent PCI.

Table 1
Baseline characteristics of the participants.

	Total group	AIT	ACT	Significance
Sample size	200	100	100	
Characteristics				
Gender (M/F)	180/20	91/9	89/11	NS
Age (years)	58.4 ± 9.1	57.0 ± 8.8	59.9 ± 9.2	P = 0.023
Height (cm)	173 ± 8.0	174 ± 7.6	173 ± 8.4	NS
Weight (kg)	84.9 ± 14.0	84.7 ± 14.4	85.0 ± 13.7	NS
BMI (kg/m^2)	28.3 ± 4.3	28.0 ± 4.4	28.5 ± 4.3	NS
Waist (cm)	99.7 ± 11.7	100 ± 12.0	99.4 ± 11.6	NS
Peak VO$_2$ (ml/kg/min)	22.7 ± 5.69	23.3 ± 5.78	22.2 ± 5.56	NS
FMD (%)[a]	5.62 ± 2.84	5.53 ± 3.15	5.71 ± 2.50	NS
Reason for referral				
AMI	115	67	48	P = 0.007
PCI	25	7	18	P = 0.019
CABG	60	26	34	NS
Duration of CAD				NS
≤3 months	156	83	73	
>3 months	44	17	27	
LVEF (%)	56.9 ± 8.1	57.1 ± 8.5	56.8 ± 7.7	NS
Cardiovascular risk factors				
Hypertension	104	58	46	NS
Diabetes	38	20	18	NS
History of COPD	4	3	2	NS
Familial predisposition	50	21	29	NS
Smoking				NS
Never	53	27	26	
Ex	122	59	63	
Current	25	14	11	
Alcohol consumption (drinks/week)	4.2 ± 5.7	4.7 ± 6.5	3.7 ± 4.7	NS
Medication				
Beta-blockers	167	84	83	NS
Anti-hypertensive medication	149	77	72	NS
Nitrates	9	5	4	NS
Diuretics	25	10	15	NS
Anti-arrhythmics	4	3	1	NS
ASA	188	93	95	NS
Anti-thrombotics	147	76	71	NS
Vitamin K antagonists	15	9	6	NS
Digitalis	2	1	1	NS
Statins	196	97	99	NS
Antidiabetic medication	37	18	19	NS

Data are expressed as means ± standard deviation (SD) for continuous variables or as percentages for dichotomous variables.

AIT = aerobic interval training; ACT = aerobic continuous training; M = male; F = female; NS = not significant; BMI = body mass index; peak VO$_2$ = peak oxygen uptake; FMD = flow-mediated dilation; AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; COPD = chronic obstructive pulmonary disease; ASA = acetylsalicylic acids.

[a] FMD data were available in 188 patients (AIT and ACT, n = 94).
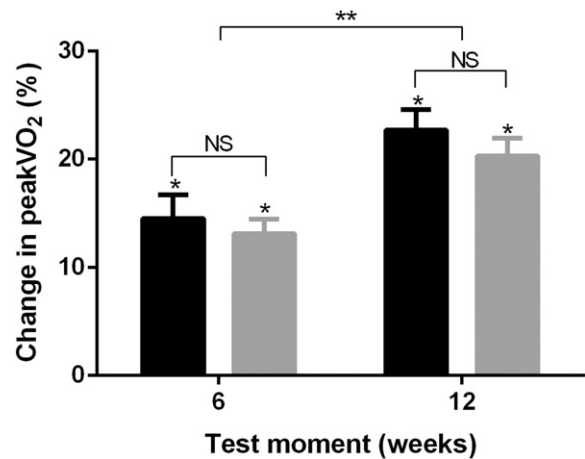
Fig. 3. Percent changes in peak VO$_2$ in AIT and ACT after 6 and 12 weeks. Data are means ± SEM; * = significantly different from baseline (p < 0.001); ** = 6 weeks differs significantly from 12 weeks (p = 0.0231); NS = not significant; black bars = AIT; grey bars = ACT.

4. Discussion

Exercise training is a cornerstone in cardiac rehabilitation; however, there is still controversy regarding the exercise characteristics that are most effective for improving peak VO$_2$ in CAD patients [10]. Proof of concept papers comparing AIT and MCT were conducted in small sample sizes and findings were inconsistent and heterogeneous [16]. The results of the present large randomized multicentre study in CAD patients demonstrate that AIT and ACT are equal in improving peak VO$_2$, peripheral endothelial function, QoL, and some cardiovascular risk factors. In addition, both programmes seem to have beneficial effects within the first 6 weeks of training and are safe in CAD patients.

Peak VO$_2$ increased with 5.06 ± 4.06 ml/kg/min or 22.7 ± 17.6% after AIT and with 4.35 ± 3.21 ml/kg/min or 20.3 ± 15.3% after ACT. These increases are probably of clinical relevance, as suggested by a large observational study, where each 3.5 ml/kg/min increment in peak VO$_2$ resulted in a 12% improvement in survival [7]. This 22.7% increase in peak VO$_2$ after AIT is comparable to the increments reported in the meta-analysis of Pattyn et al. [16] (20.5%) and to other large intervention studies [12,23], while the 20.3% increase after ACT in our study is larger than the 12.8% increase in peak VO$_2$ described in the same meta-analysis [16]. The difference with earlier publications might be explained by the on average lower training intensity observed in these ACT groups [16] (range 70–75% of peak HR) resulting in relatively lower gains in peak VO$_2$. Analyses of the present study showed that our ACT group trained at average intensities of 80% of peak HR. The fact that none of the patients had to terminate the exercise prematurely

Table 2
Peak exercise capacity parameters at baseline, after 6 and after 12 weeks of AIT or ACT.

	AIT (n = 85)			ACT (n = 89)				F-values	
Parameter	0 weeks	6 weeks	12 weeks	0 weeks	6 weeks	12 weeks	Time	Group	Interaction
VO$_2$ (ml/min)	1965 ± 503	2232 ± 548	2395 ± 560	1887 ± 473	2116 ± 527	2238 ± 550	31.69***,a,b,c	3.34§	0.31^{NS}
VO$_2$/kg (ml/kg/min)	23.5 ± 5.7	26.7 ± 6.7	28.6 ± 6.9	22.4 ± 5.6	25.2 ± 6.2	26.8 ± 6.7	28.18***,a,b,c	3.87*	0.16^{NS}
HR (bpm)	134 ± 21.0	140 ± 19.0	145 ± 18.2	129 ± 21.1	134 ± 22.3	138 ± 21.5	12.84***,a,b	10.38**	0.13^{NS}
Workload (Watt)	154 ± 38.8	177 ± 44.9	192 ± 46.9	145 ± 41.0	169 ± 47.9	180 ± 46.6	39.42***,a,b,c	3.98*	0.17^{NS}
RER	1.26 ± 0.12	1.27 ± 0.12	1.28 ± 0.11	1.26 ± 0.11	1.26 ± 0.09	1.27 ± 0.09	0.84^{NS}	0.28^{NS}	0.20^{NS}
O$_2$ pulse	14.8 ± 3.6	16.0 ± 3.5	16.6 ± 3.5	14.7 ± 2.9	15.9 ± 3.3	16.2 ± 3.2	12.32***,a,b	0.04^{NS}	0.07^{NS}

Data are expressed as means ± standard deviation (SD). All data are corrected for age and pathology.

AIT = aerobic interval training; ACT = aerobic continuous training; n = number of patients; VO$_2$ = oxygen uptake; NS = not significant; HR = heart rate; bpm = beats per minute; RER = respiratory exchange ratio; *p < 0.05; **p < 0.01; ***p < 0.001; §p = 0.068; a = 6 weeks differed significantly from baseline; b = 12 weeks differed significantly from baseline; c = 12 weeks differed significantly from 6 weeks.

suggests that they were still working aerobically. We can conclude for ACT that if a higher intensity can be sustained, the workloads and HR zones need to be adapted to achieve the best improvements possible.

In contrast, the average intensity of the AIT group was 88% of peak HR, which is lower than the prescribed intensity. In practice, we had to decrease training intensity in several patients in order to avoid extreme hyperventilation or discontinuation of pedalling. In accordance with our results, Guiraud et al. demonstrated that a shorter high-intensity interval (15 s) was at least as efficient in the time spent at peak VO_2 and much better tolerated than the longer ones (60 s) in CAD patients [24]. However, our patients in the AIT group perceived shortness of breath and scored significantly higher on the Borg scale than the ACT group. Though, we think that the results of the Borg scale were not reliable and did not reflect real exercise intensity. This is in agreement with a recently published paper [25], in which the authors concluded that rating of perceived exertion results in an exercise intensity below target (Borg score 17) during high-intensity interval training bouts, and that HR monitors should be used for accurate intensity guidance. We can conclude that AIT training at 90–95% of peak HR is hardly feasible in most of the CAD patients, at least not for the full 4 min.

Nevertheless, if we calculated the relative intensity of sessions 19–36 using peak HR1, patients in the AIT group trained at >90% of peak HR1, as prescribed (Supplemental Table 5). Since peak HR increased (Table 2) following training, target HR zones needed adaptation. The relative intensity of sessions 19–36 was only 84% of peak HR3 (Supplemental Table 5), which suggests that not changing the target HR zones result in low intensities of training and probably smaller improvements after the intervention.

Following these results and observations, we suggest that in clinical practice, it is necessary to adjust the objectively defined target HR zones and workloads according to the patient's subjective feelings as [11] 1) ACT programmes can be sustained at intensities higher than 70–75% of peak HR, and 2) AIT programmes with 4-minute intervals at 90–95% of peak HR are hardly feasible for 4 min. Further we recommend an intermediate exercise test to adapt target HR zones.

Endothelial dysfunction is an important early precursor of atherosclerosis and is an independent predictor of cardiovascular events [26]. Previous studies have shown that FMD improves after exercise-based cardiac rehabilitation in CAD patients [27–29]. In accordance to our results, Currie et al. [30] found similar improvements after AIT and MCT, while Wisløff et al. [14] and Tjonna et al. [31] found larger increases after AIT compared to MCT. At the moment, there is no consensus for a clinical relevant cut off value for brachial artery FMD [32]. However, it has been shown that persistent impairment of FMD, defined as FMD <5.5%, is an independent predictor of cardiovascular morbidity and mortality in CAD patients [33]. The mean pre-training value for the total group in our study was 5.44% (n = 156), which can be classified as borderline impaired FMD and results in a 2.9 times higher risk of cardiovascular events compared to an FMD >5.5% [33]. This implies that the improvement in FMD to 6.58% is of clinical relevance. The endothelial function increased significantly during the first 6 weeks of the intervention, while further improvements were diminished between 6 and 12 weeks. It seems that endothelial function adapts fast following

exercise training, which confirms the statement made in a review by Green et al. [34].

The absolute change in FMD correlated inversely with baseline FMD and positively with the increase in peak VO_2. These findings were also reported by Luk et al. [28] and Wisløff et al. [14], and support the finding that endothelial function is a possible underlying mechanism in the improvement of exercise capacity. Indeed, changes in peak VO_2 following exercise training result from increased O_2 delivery (due to increased stroke volume and exercise-induced vasodilation) and enhanced O_2 consumption (increased oxidative capacity of skeletal muscles). We observed no change in NMD following AIT or ACT, which is in line with other studies [14,30]. It seems that exercise primarily corrects the endothelial dysfunction and does not improve the vascular smooth muscle cell responsiveness [28].

Self-perceived QoL increased significantly and to a similar extent after AIT and ACT. There is evidence that post-AMI patients have significant and clinically relevant poorer scores than healthy subjects [21,35]. Our CAD patients scored lower on the physical and mental component compared to normative scores of the general Dutch population, even after the training intervention [21]. Our patients showed similar PCS scores [21] but lower MCS scores [21] compared to a large sample of Dutch post-AMI patients. It seems reasonable to suggest that more psychological support is necessary to normalize the self-perceived mental health.

HDL-C improved significantly in both groups, which is in contrast with findings in meta-analyses on exercise training in CAD patients [3,4] and other AIT versus MCT trials [36]. Total cholesterol, which consists of HDL-C, LDL-C and very LDL-C, increased after the intervention, probably caused by the significant increment of HDL-C. Yet, the total/HDL cholesterol ratio seems to be more informative about CAD mortality than total cholesterol or HDL-C either, with a lower ratio predicting a lower mortality rate [37]. In our study, the ratio showed a non-significant decrease following the intervention. Hs-CRP decreased after the intervention, which is in line with results of a meta-analysis of Swardfager et al. who found a significantly reduced inflammatory activity after exercise training in CAD patients [38]. Other laboratory parameters did not change significantly because most of the patients were optimally treated with lipid-lowering medication and anti-diabetic medication if necessary (see Table 1).

Finally, our results show that 6 weeks of three-weekly sessions of 38 min (duration of one AIT session) are already sufficient to obtain clinically relevant improvements in peak VO_2, peripheral endothelial function and QoL. This is of interest to the patient as these observed improvements might be an extra stimulus to continue a physically active lifestyle. Furthermore we confirm that a longer training period resulted in further significant increases in peak VO_2, which stresses the need of encouraging a life-long physically active lifestyle not only to further improve but at least to maintain the obtained improvements [39].

4.1. Strengths and limitations

This study is strengthened by the large sample size (n = 200), the repeated CPET after 6 weeks to adapt the training intensity, the objective

Table 3
Endothelial function parameters at baseline, after 6 and after 12 weeks of AIT or ACT.

Parameter	0 weeks	AIT (n = 76)		0 weeks	ACT (n = 84)		F-values Time	F-value Group	Interaction
		6 weeks	12 weeks		6 weeks	12 weeks			
Resting diameter (mm)	3.96 ± 0.56	4.00 ± 0.56	4.00 ± 0.50	3.93 ± 0.56	3.95 ± 0.58	3.99 ± 0.65	0.32[NS]	0.11[NS]	0.04[NS]
FMD (%)	5.26 ± 3.02	6.33 ± 3.22	6.47 ± 2.79	5.61 ± 2.36	6.46 ± 2.87	6.68 ± 3.09	7.28***,a,b	1.69[NS]	0.06[NS]
NMD (%)	22.6 ± 6.57	22.5 ± 6.55	22.2 ± 7.19	22.1 ± 7.30	21.2 ± 7.77	22.1 ± 6.92	0.21[NS]	0.40[NS]	0.28[NS]

Data are expressed as means ± standard deviation (SD). All data are corrected for age and pathology. Data for FMD are corrected for age, pathology and centre of enrolment.
AIT = aerobic interval training; ACT = aerobic continuous training; n = number of patients; NS = not significant; FMD = flow-mediated dilation; NMD = nitrate-mediated dilation; **p < 0.01; ***p < 0.001; a = 6 weeks differed significantly from baseline; b = 12 weeks differed significantly from baseline.

Table 4
Cardiovascular risk factors and quality of life at baseline and after 12 weeks of AIT or ACT.

Parameter	AIT (n = 85)		ACT (n = 89)		F-values		
	0 weeks	12 weeks	0 weeks	12 weeks	Time	Group	Interaction
Weight (kg)	84.6 ± 14.5	85.1 ± 14.2	85.1 ± 13.9	84.6 ± 13.4	0.00^{NS}	0.13^{NS}	0.07^{NS}
BMI (kg/m^2)	27.9 ± 4.1	28.0 ± 3.9	28.5 ± 4.3	28.2 ± 4.2	0.01^{NS}	0.92^{NS}	0.11^{NS}
Waist (cm)	99.7 ± 11.7	98.8 ± 11.5	99.5 ± 11.3	97.6 ± 10.9	1.66^{NS}	0.34^{NS}	0.15^{NS}
Resting HR	57.7 ± 7.9	55.4 ± 7.4	59.4 ± 10.5	55.4 ± 8.1	6.48^{**}	0.01^{NS}	0.80^{NS}
SBP (mm Hg)	125 ± 14.3	125 ± 14.3	128 ± 17.2	122 ± 13.3	$2.45^{\$}$	0.85^{NS}	2.18^{NS}
DBP (mm Hg)	75.8 ± 8.4	74.7 ± 8.4	76.2 ± 10.6	72.5 ± 8.2	3.08^{*}	1.08^{NS}	0.83^{NS}
Fasting glucose (mmol/l)	5.40 ± 1.04	5.59 ± 1.42	5.29 ± 0.81	5.47 ± 1.32	2.20^{NS}	2.49^{NS}	0.00^{NS}
Cholesterol (mmol/l)	3.61 ± 0.71	3.78 ± 0.74	3.60 ± 0.78	3.76 ± 0.78	4.36^{*}	1.20^{NS}	0.01^{NS}
HDL-C (mmol/l)	1.13 ± 0.27	1.21 ± 0.26	1.11 ± 0.28	1.20 ± 0.31	9.25^{**}	2.63^{NS}	0.10^{NS}
Cholesterol/HDL-C ratio	3.33 ± 0.96	3.23 ± 0.85	3.41 ± 0.96	3.27 ± 0.89	1.38^{NS}	0.92^{NS}	0.03^{NS}
LDL-C (mmol/l)	1.88 ± 0.51	1.97 ± 0.53	1.98 ± 0.66	2.05 ± 0.66	1.57^{NS}	0.55^{NS}	0.01^{NS}
Triglycerides (mmol/l)	1.49 ± 0.99	1.47 ± 0.90	1.28 ± 0.49	1.25 ± 0.47	0.09^{NS}	4.42^{*}	0.00^{NS}
hs-CRP (log mg/l)§	0.21 ± 0.44	0.12 ± 0.52	0.24 ± 0.57	0.07 ± 0.52	5.67^{*}	0.20^{NS}	0.51^{NS}
QoL Physical component	43.5 ± 8.1	47.7 ± 7.5	42.4 ± 7.7	46.8 ± 6.1	14.62^{***}	0.35^{NS}	0.74^{NS}
QoL Mental component	36.1 ± 7.8	38.6 ± 7.7	35.8 ± 7.5	38.8 ± 5.7	7.98^{***}	0.05^{NS}	0.15^{NS}

Data are expressed as means $\pm$ standard deviation (SD). All data are corrected for age and pathology.
AIT = aerobic interval training; ACT = aerobic continuous training; n = number of patients; NS = not significant; BMI = body mass index; HR = heart rate; bpm = beats per minute; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; hs-CRP = high sensitivity C-reactive protein; QoL = quality of life (AIT n = 76, ACT n = 83); $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; $^{\$}p = 0.066$; §data for hs-CRP were log transformed.

evaluation combined with the subjective perception of the patients during the training sessions, and the multicentre design. Yet, multicentre studies have limitations including the variability in assessments, analyses, and implementation of training between the centres. In addition, caloric expenditure was not measured, which could have been useful to compare the efficiency of the programmes. Flow-mediated dilation differed significantly between the centres ($p < 0.001$) and was therefore corrected in the analysis. Another limitation is the larger participation rate of men compared to women, and moreover a larger drop-out in women.

4.2. Future research

Future research must focus on 1) the comparison of AIT and ACT performed at representative and feasible intensities, 2) the underlying mechanisms responsible for peak VO$_2$ improvements, 3) the measurement of caloric expenditure of AIT and ACT or MCT used in the present and in previous studies, and 4) the comparison of AIT and ACT protocols with other cardiac rehabilitation programmes in terms of training response, long-term health, QoL and patient satisfaction.

5. Conclusion

We can conclude that a 12-week AIT and ACT intervention equally improve peak VO$_2$, peripheral endothelial function, QoL and some cardiovascular risk factors in CAD patients. In addition, both programmes seem to be safe for CAD patients. In our experience, sustained AIT at 90–95% of peak HR during 4 min is hardly feasible in CAD patients. When using continuous exercise training, a sufficient training intensity should be performed, which may be more than the 70–75% of peak HR of the baseline evaluation as used in a number of previous studies. These conclusions should be taken into account when prescribing exercise training programmes in clinical practice.

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Potential conflicts of interest

There are no conflicts of interests to declare.

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