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SYSTEMATIC REVIEW

Aerobic Interval Training vs. Moderate Continuous Training in Coronary Artery Disease Patients: A Systematic Review and Meta-Analysis

Nele Pattyn · Ellen Coeckelberghs · Roselien Buys · Véronique A. Cornelissen · Luc Vanhees

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Abstract
Background Exercise training improves exercise capacity (peakVO_2), which is closely related to long-term survival in cardiac patients. However, it remains unclear which type and intensity of exercise is most effective for improving exercise tolerance and body weight. Individual studies suggest that aerobic interval training (AIT) might increase peakVO_2 more in this population.
Objective We conducted a meta-analysis to summarize the effects of AIT compared with moderate continuous training (MCT) on peakVO_2, submaximal exercise capacity, and body weight in patients with coronary artery disease (CAD) with preserved and/or reduced left ventricular ejection fraction (LVEF).
Data sources and study selection A systematic search was conducted and we included randomized trials comparing AIT and MCT in CAD patients lasting at least 4 weeks, reporting peakVO_2 results, and published in a peer-reviewed journal up to May 2013. The primary outcome measure was peakVO_2. Secondary outcomes were submaximal exercise capacity parameters and body weight.
Synthesis methods Random- and fixed-effects models were used and data were reported as weighted means and 95 % confidence intervals (CIs).
Results Nine study groups were included, involving 206 patients (100 AIT, 106 MCT). Overall, AIT resulted in a significantly larger increase in peakVO_2 [+1.60 mL/kg/min (95 % CI 0.18–3.02; $p = 0.03$)] compared with MCT. MCT seemed to be more effective in reducing body weight (−0.78 kg; 95 % CI −0.01 to 1.58; $p = 0.05$).
Limitations The small number of studies might have affected the power to reach significance for the secondary outcomes.
Conclusion In CAD patients with preserved and/or reduced LVEF, AIT is superior to MCT for improving peakVO_2, while MCT seems to be more effective in reducing body weight. However, large, well-designed, randomized controlled trials are warranted to confirm these findings.

N. Pattyn and E. Coeckelberghs contributed equally.

N. Pattyn (✉) · E. Coeckelberghs · R. Buys · V. A. Cornelissen · L. Vanhees
Department of Rehabilitation Sciences, KU Leuven, Leuven, Tervuursevest 101, B 1501, 3001 Heverlee, Belgium
e-mail: nele.pattyn@faber.kuleuven.be

1 Introduction

Cardiovascular diseases (CVD) are the most common cause of death in Europe, accounting for over four million deaths or 47 % of all deaths each year [1]. The main causes of CVD deaths are coronary artery disease (CAD) and stroke [1]. The total cost for CVD for the EU is estimated at €195 billion a year [1].

Substantial evidence supports the benefits of exercise-based cardiac rehabilitation in patients with CVD [2]. Exercise-based cardiac rehabilitation increases peak oxygen uptake (peakVO_2), which is an important prognostic parameter for cardiovascular morbidity and mortality [2–4]. Moreover, exercise-based cardiac rehabilitation improves quality of life [2, 5] and various cardiovascular risk factors including blood pressure [2, 4, 6, 7], blood lipids [2, 4, 6, 7], blood glucose, and insulin dynamics [7].

Although the benefits of cardiac rehabilitation have been widely established, there is still controversy regarding the mode and intensity of exercise that yield optimal beneficial effects in patients with CVD [8]. Exercise intensity seems to be an important factor for the effectiveness of a cardiac rehabilitation program as a higher exercise intensity leads to larger improvements in peakVO_2, after adjustment for other training-related variables [9, 10]. However, the positive outcomes of moderate-intensity continuous training (MCT) in cardiac rehabilitation have been supported by many clinical trials and for many years MCT has been the basis of exercise training in patients with stable CAD [8]. It appears that moderate-intensity exercise is sufficient to reduce cardiovascular risk and cardiovascular mortality [10, 11], but it is suggested that higher intensity exercise offers greater cardioprotection [10] in patients with CAD and chronic heart failure (HF) [11]. Higher intensity exercise has been shown to be more effective in improving cardiovascular risk factors and left ventricular ejection fraction (LVEF) than moderate-intensity exercise in patients with HF and CAD [12, 13]. However, a higher intensity of exercise is difficult to maintain for a longer duration. Therefore, during the last decades, the use of aerobic interval training (AIT) gained more interest in the field of cardiac rehabilitation [14]. Interval training consists of periods of high-intensity exercise alternated by periods at lower intensity that make it possible for cardiac patients to complete short exercise bouts at a higher intensity than would be possible during continuous exercise. This higher intensity might challenge the heart's pumping ability, the endothelial system, and the mitochondrial functions in skeletal muscle tissue to a greater extent, and could therefore be more effective in increasing peakVO_2 compared with MCT [15]. Systematic reviews and meta-analyses by Smart et al. [16] and Haykowsky et al. [17] have already demonstrated that AIT is more effective than MCT for improving peakVO_2 in HF patients with reduced ejection fractions caused by CAD as well as by other etiologies [16, 17]. In the largest group of cardiac patients referred to cardiac rehabilitation, namely CAD patients with preserved and/or reduced LVEF, a number of small studies have investigated the effect of AIT compared with MCT, but the results of these small studies are contradictory. Rognmo et al. [18] reported a greater improvement of aerobic exercise capacity following AIT compared with MCT whereas Warburton et al. [19], Rocco et al. [20], and Moholdt et al. [21] reported similar improvements in aerobic exercise capacity. In some studies, differences in the longer term [21] or in the anaerobic exercise performance [22] were found between AIT and MCT, in favor of AIT.

Therefore, this meta-analysis aims to summarize and compare the effect of AIT and MCT on peakVO_2, submaximal exercise measures, and body weight in patients with CAD with preserved and/or reduced LVEF.

2 Methods

2.1 Literature Search

We conducted a systematic literature search in the electronic PubMed database from its inception up to May 2013 using the following terms: (aerobic interval training OR high intensity interval training OR interval training OR intermittent training OR high intensity exercise OR interval training) AND (coronary artery disease OR coronary heart disease OR heart failure OR myocardial infarction OR coronary artery bypass surgery OR ischemic heart disease OR angina pectoris), without any limitations. From this search, we only included papers addressing the effect of AIT compared with MCT in CAD patients with preserved and/or reduced LVEF. In addition, the reference lists from published original and review articles were searched manually to identify other possible eligible studies.

2.2 Study Selection

The inclusion criteria for this meta-analysis were: (1) randomized intervention studies, (2) comparing supervised AIT, defined as an alternation of intervals at high intensity according to Vanhees et al. [23] with periods of relative rest on treadmill, bicycle, or other exercise devices, with supervised MCT, (3) with a duration of at least 4 weeks, (4) in CAD patients with preserved and/or reduced LVEF, (5) reporting pre- and post-intervention mean and standard deviations (SDs) (or standard errors) or mean change and SDs (or standard errors) of peakVO_2, and (6) published in a peer-reviewed journal up to May 2013. Exclusion criteria included any studies not meeting all the criteria above.

2.3 Measured Outcomes

The primary outcome measure was change in peakVO_2 (mL/kg/min). Secondary outcomes included submaximal exercise capacity parameters, i.e., VO_2 at the first threshold (i.e., anaerobic threshold or ventilatory threshold) and the slope of increase of ventilation relative to carbon dioxide production (V_E/VCO_2), and changes in body weight.

2.4 Data Extraction

Two unblinded reviewers (N.P. and E.C.) independently conducted data extraction. A specific developed data extraction sheet was used to extract data on study source, study design, study quality, sample size, characteristics of the participants, exercise training interventions, and the different outcomes in each study. Using Cohen's kappa statistic, the overall agreement rate prior to correcting discrepant items was 0.86. Disagreements were resolved by consensus.

2.5 Study Quality

Study quality was assessed using an adapted PEDro-scale [24], which is an 11-item questionnaire designed to collect data on eligibility criteria, random allocation, concealed allocation, similarity of baseline values, blinding of participants/therapists/assessors, key outcomes, intention-to-treat analysis, between group differences, and point and variability measures. All questions were binary [yes (1) or no (0)]. We regarded the quality criteria 'blinding of participants' and 'blinding of therapists' as not applicable in the cardiac rehabilitation intervention studies and therefore omitted these criteria. Considering the above, the minimum score was 0 and the maximum was 9, with a higher number reflecting a better study quality. The PEDro-scale has been reported to be valid and reliable [25, 26]. All assessments were conducted by the first two authors (N.P. and E.C.), independent of each other. Using Cohen's kappa statistic, overall inter-rater agreement was 0.96. Disagreements were resolved by consensus. Trials were not excluded based on quality.

2.6 Statistical Analysis

Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA) and Review Manager Software (RevMan 5.1; Cochrane Collaboration, Oxford, UK). Descriptive data are reported as mean ± SD or median and range. The mean baseline values were calculated by combining mean values from the intervention groups, weighted by the number of participants included in the final analysis in each study group.

For secondary outcomes, a minimum of three study groups were needed before an analysis was performed. Effect sizes for primary and secondary outcomes were calculated by subtracting the pre-intervention value from the post-intervention value (post − pre). The net treatment effect was then obtained by subtracting the change score difference in the MCT group from the change score difference in the AIT group. Review Manager Software calculated the variances from the inserted pooled SDs of change scores in the intervention groups. However, some studies reported only the SDs or standard errors at baseline and post-intervention. Therefore, missing change score SDs were calculated from pre -and post-SD values, using the following formula: $\text{SDchange} = \sqrt{[(\text{SDpre})^2 + (\text{SDpost})^2 - 2 \times \text{corr(pre, post)} \times \text{SDpre} \times \text{SDpost}]}$ [27], for which we used a calculated correlation coefficient (corr) for each outcome, using the pre- and post-SD and the SD of the change of the study of Moholdt et al. [28] in the following formula: $\text{corr} = (\text{SDpre}^2 + \text{SDpost}^2 - \text{SDchange}^2)/(2 \times \text{SDpre} \times \text{SDpost})$. For exercise capacity outcomes that were not available in Moholdt et al. [28], that is, VO_2 at first threshold and V_E/VCO_2 slope, we used the correlation coefficient of peakVO_2. Given the small number of studies, the small study groups and the differences in study populations, we used random-effects models to combine all primary and secondary outcomes [29, 30]. Each effect size was weighted by the inverse of its variance. The results are reported as weighted means and 95 % confidence intervals (CIs). Two-sided tests for overall effects were considered significant at $p \leq 0.05$.

Statistical heterogeneity among the trials was assessed using Cochrane's Q statistic and an alpha value for statistical significance of 0.10 indicated significant heterogeneity. In addition, the I^2 parameter was used to quantify inconsistency of treatment effects across trials ($I^2 = [(Q - df)] \times 100$ %, where Q is the χ^2 statistic and df are the degrees of freedom). A value for $I^2 > 50$ % has been considered to be substantial heterogeneity.

To examine the influence of each study on the overall results, sensitivity analyses were also performed with each study deleted from the model once.

Subgroups of CAD patients with preserved or reduced LVEF were compared using a fixed effect model. If the p value was $\leq$0.05, we further checked for non-overlapping CI to decide which groups significantly differ from each other.

Finally, funnel plots were used to assess small publication bias.

3 Results

3.1 Literature Search

A PRISMA flow diagram of literature search and selection is presented in Fig. 1. From 1,655 potentially relevant studies retrieved from our main and additional manual search, we identified 15 trials that fulfilled the inclusion criteria [15, 18–22, 31–39]. However, four studies were a duplicate of another study [31, 32, 34, 36], i.e., using the same population and intervention. In those cases, we included the most complete publication in terms of exercise capacity outcomes. Further, the authors of four studies that investigated the effects of AIT vs. MCT in patients with reduced LVEF due to different etiologies, were contacted and asked to provide us with the data of the subset of CAD patients only [22, 33, 35, 38]. Two authors provided these data [22, 38] and their studies could be included as well. Hence, nine studies in CAD patients [15, 18–22, 36, 38, 39] could be included in the quantitative analysis, of which five compared AIT with MCT in CAD patients with preserved LVEF [18–21, 39] and four in CAD patients with reduced LVEF [15, 22, 36, 38].

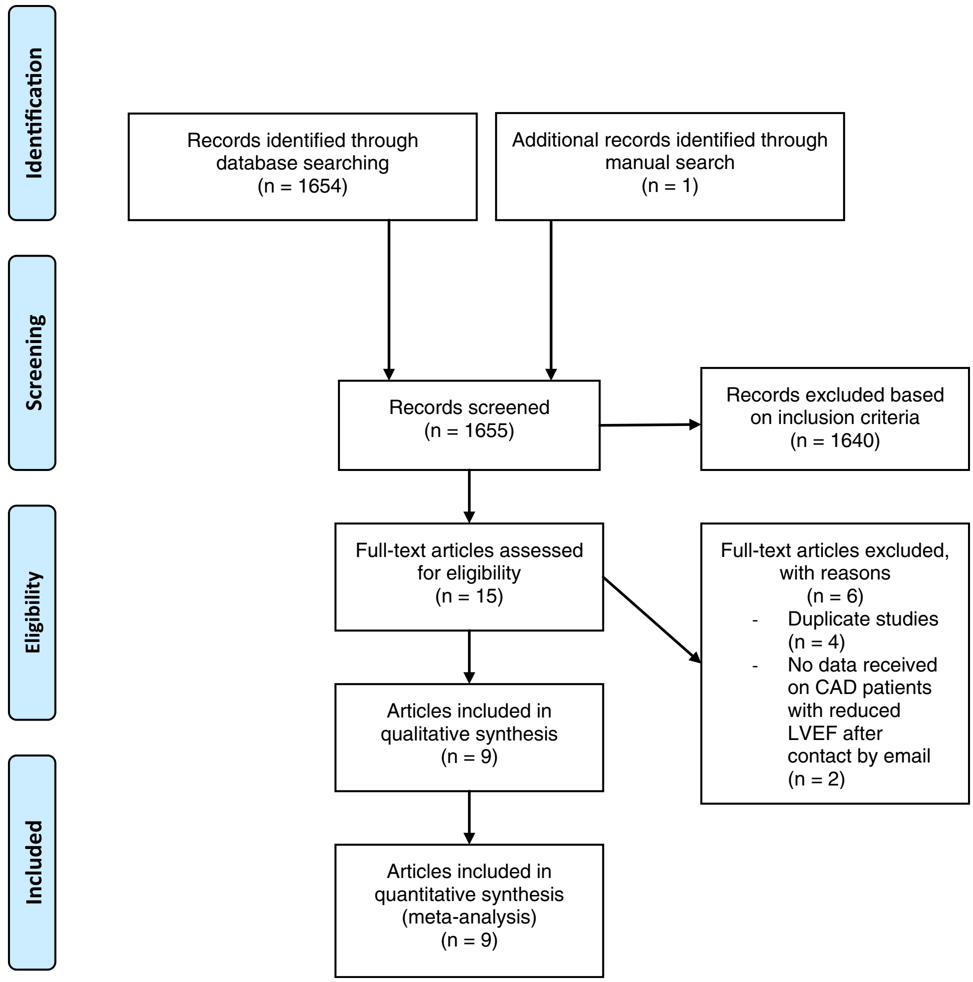

Fig. 1 PRISMA flow chart of the literature search. *CAD* coronary artery disease, *LVEF* left ventricular ejection fraction

3.2 Characteristics of the Participants and Study Design

A general description of each included study is shown in Table 1. One study was a randomized controlled trial [15] whereas the other eight studies were not controlled [18–22, 36, 38, 39]. All studies used a parallel design and were published between 2004 and 2013. Three studies were conducted in Norway [15, 18, 22]; two studies in Canada [19, 39]; and the remaining four studies were conducted in Brazil [20], Greece [22], Italy [36], and Australia [38], respectively.

Median sample size of the studies was 17 (range 11–59). A total number of 234 participants were randomized to AIT (n = 114) or MCT (n = 120). There was an average drop out of 12.0 %, resulting in a total of 206 participants that could be included in the final analysis: 100 completed the AIT intervention (71 CAD with preserved LVEF and 29 CAD with reduced LVEF; average drop out 12.3 %, range 0–27 %), 106 completed the MCT intervention (77 CAD with preserved LVEF and 29 CAD with reduced LVEF; average drop out 11.7 %, range 0–33 %). Mean age was 62.5 years (range 56.0–75.5). Seven studies included both men and women [15, 18, 19, 21, 22, 38, 39], two studies were restricted to men only [19, 36]. No study reported on race. Seven studies did not report on smoking [15, 18–22, 36], one excluded smokers [39], and one did not exclude smokers [38]. All studies allowed the intake of medication, with beta-blockers, ACE inhibitors, statins, diuretics, and antiplatelet agents being the most often reported. Four studies included also patients with type 2 diabetes mellitus [20–22, 38], one study excluded patients with type 2 diabetes [36], and the remaining four studies did not specifically report this but also did not exclude this [15, 18, 19, 39].

3.3 Intervention Characteristics

A description of the intervention characteristics of each study is shown in Table 1. Study duration ranged between

Table 1 Descriptive characteristics of the study groups at baseline and characteristics of the intervention

References	Subgroup	Country	Inclusion criteria	Subjects analyzed (*n*)	Age (years) (mean ± SD)	Duration (weeks)	Intervention
Rognmo et al. [18]	CAD	Norway	Angiographically documented CAD in at least one major epicardial vessel; previous MI, CABG, PCI, or ischemia in ECG	AIT 6M + 2F MCT 8M + 1F	AIT 62.9 ± 11.2 MCT 61.2 ± 7.3	10	3×/week Uphill treadmill walking AIT 33 min 5-min warm-up (50–60 % peakVO_2 − 65–75 % HR_{max}) 4 × 4 min interval (80–90 % peakVO_2 − 85–95 % HR_{max}) 3 × 3 min rest period (50–60 % peakVO_2) 3-min cool-down MCT 41 min 41 min (50–60 % peakVO_2) Programs are isocaloric[a]
Warburton et al. [19]	CAD	Canada	Men; At least 6 months post-PCI or -CABG	AIT 7 M MCT 7 M	AIT 55 ± 7 MCT 57 ± 8	16	2×/week Treadmill, stairclimber, arm or leg cycle ergometry AIT 50 min 10-min warm-up 8 × 2 min interval (90 % HRres/VO_2res) 7 × 2 min rest period (40 % HRres/VO_2res) 10-min cool-down MCT 50 min 10-min warm-up 30 min (65 % of HRres/VO_2res) 10-min cool-down No information on caloric expenditure reported
Moholdt et al. [21]	CAD	Norway	4–16 weeks post-CABG	AIT 24M + 4F MCT 24M + 7F	AIT 60.2 ± 6.9 MCT 62 ± 7.6	4	5×/week Treadmill AIT 38 min 8-min warm-up 4 × 4 min interval (90 % HR_{max}) 3 × 3 min rest period (70 % HR_{max}) 5-min cool-down MCT 46 min 46 min (70 % HR_{max}) Programs are isocaloric[a]

Table 1 continued

References	Subgroup	Country	Inclusion criteria	Subjects analyzed (*n*)	Age (years) (mean ± SD)	Duration (weeks)	Intervention
Rocco et al. [20]	CAD	Brazil	Angiographically documented CAD	AIT 14M + 3F MCT 15M + 5F	AIT 56.5 ± 3.0 MCT 62.5 ± 2.0	12	3×/week Treadmill AIT 47 min 5-min warm-up 7 × 3 min interval (RCP) 7 × 3 min rest period (VAT) 5-min cool-down MCT 60 min 5-min warm-up 50 min (VAT) 5-min cool-down Programs are isocaloric[a]
Currie et al. [39]	CAD	Canada	Angiographically documented stenosis ≥50 % in at least on major coronary artery; MI or PCI or CAGB; positive exercise test (positive nuclear scan, chest discomfort, ECG changes of >1 mm)	AIT 10M + 1F MCT 9M + 1F	AIT 62 ± 11 MCT 68 ± 8[b]	12	At least 3×/week Cycling AIT 30 min 5-min warm-up 10 × 1 min interval (89–102–110 % peakWR) 10 × 1 min rest period (10 % peakWR) 5-min cool-down MCT 40–60 min 5-min warm-up 30 min (week 1–4), 40 min (week 5–8), 50 min (week 9–12) (58 % peakWR) 5-min cool-down Programs are not isocaloric[a]
Dimopoulos et al. [22]	CAD: ischemic HF	Greece	Stable CHF of ischemic origin	AIT 6M MCT 4M + 1F	AIT 59.2 ± 12.2[c] MCT 61.5 ± 7.1[c]	12	3×/week Cycling AIT 40 min 40 × 30 s interval (100–110–120 % peakWR) 40 × 30 s rest period MCT 40 min 40 min (50–55–60 % peakWR) Programs are isocaloric[a]

Table 1 continued

References	Subgroup	Country	Inclusion criteria	Subjects analyzed (*n*)	Age (years) (mean ± SD)	Duration (weeks)	Intervention
Wisløff et al. [15]	CAD: ischemic HF	Norway	LVEF <40 %; Post-infarction HF (MI ≤12 months)	AIT 7M + 2F MCT 7M + 2F[d]	AIT 76.5 ± 9 MCT 74.4 ± 12	12	3×/week Uphill treadmill walking AIT 38 min 10-min warm-up (50–60 % peakVO_2 − 60–70 % HRpeak) 4 × 4 min interval (90–95 % HR_{max}) 3 × 3 min rest period (50–70 % HR_{max}) 3-min cool-down MCT 47 min 47 min (70–75 % HR_{max}) Programs are isocaloric[a]
Iellamo et al. [36]	CAD: ischemic HF	Italy	LVEF <40 %; Post-infarction HF; NYHA class II or III; no hospital admission in the last 3 months	AIT 8M MCT 8 M	AIT 62.2 ± 8 MCT 62.6 ± 9	12	2×/week (week 1–3), 3×/week (week 4–6), 4×/week (week 7–9), 5×/week (week 10–12) Uphill treadmill walking AIT 37 min 9-min warm-up 4 × 4 min interval (75–80 % HRres) 4 × 3 min rest period (45–50 % HRres) MCT 30–45 min 30–45 min (45–60 % HRres) Programs are isocaloric[a]
Smart et al. [38]	CAD: ischemic HF	Australia	LVEF <35 %; At least two minor and one major Framingham criteria	AIT 4M + 2F MCT 8 M	AIT 57.7 ± 11.8 MCT 65 ± 11.4	16	3×/week Cycling AIT 60 min 30 × 60 s interval (70 % peakVO_2) 30 × 60 s rest period MCT 30 min 30 min (70 % peakVO_2) Programs are isocaloric[a]

CAD coronary artery disease, *MI* myocardial infarction, *CABG* coronary artery bypass surgery, *PCI* percutaneous coronary intervention, *ECG* electrocardiogram, *AIT* aerobic interval training, *MCT* moderate continuous training, *M* male, *F* female, *peak*VO_2 peak oxygen uptake, HR_{max} maximal heart rate, *HRres* heart rate reserve, VO_2res VO_2 reserve, *RCP* respiratory compensation point, *VAT* ventilator anaerobic threshold, *HF* heart failure, *CHF* chronic heart failure, *peakWR* peak work rate, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association

[a] As reported by the investigators

[b] Data from 11 patients in the MCT group

[c] Data from the entire group of patients included in the study

[d] One drop-out, sex unknown

Table 2 PEDro-scores for the included intervention trials

References	Eligibility criteria	Randomly allocated	Allocation concealed	Baseline similar	Blinding assessors	Key outcome 85 %	Intention to treat	Between group	Point + variability measure	Total PEDro score
Currie et al. [39]	1	1	0	1	0	0	1	1	1	6
Dimopoulos et al. [22]	0	1	0	1	0	0	1	1	1	5
Iellamo et al. [36]	1	1	0	1	0	0	1	1	1	6
Moholdt et al. [21]	1	1	0	1	1	1	1	1	1	8
Rocco et al. [20]	1	1	0	1	0	1	1	1	1	7
Rognmo et al. [18]	1	1	0	1	0	0	1	1	1	6
Smart et al. [38]	1	1	0	1	1	1	1	1	1	8
Warburton et al. [19]	0	1	0	1	0	1	1	1	1	6
Wisløff et al. [15]	1	1	0	1	1	1	1	1	1	8

4 [21] and 16 [19, 38] weeks (median 12). The frequency of exercise training varied between 2 and 5 sessions weekly (median 3), with an average duration of the total training session (with warm-up and cool-down) of 41 min per session for the AIT intervention (range 30–60) and 45 min for the MCT intervention (range 30–60). Mode of exercise involved walking/jogging on a treadmill in five studies [15, 18, 20, 21, 36], cycling in three studies [22, 38, 39], and a combination of exercises on a treadmill, stair climber, and leg and arm ergometers in one remaining study [19]. Intensity of the endurance exercise programs was expressed as a percentage of maximal heart rate (HR_{max}) [15, 18, 21], as a percentage of maximal workload [22, 39], as a percentage of peakVO_2 [18, 38], as a percentage of heart rate reserve or VO_2 reserve [19, 36], or as an intensity corresponding to the ventilatory anaerobic threshold and the respiratory compensation point [20]. The mean intensity was 90.8 % of HR_{max} for AIT (range 85–95 %) and 71.3 % of HR_{max} for MCT (range 70–75 %), which corresponds to a high and moderate intensity of exercise, respectively [23]. In seven studies, participants performed only supervised training [18–22, 36, 38], while in two studies, two supervised and (at least) one home-based exercise session weekly were provided [15, 39]. Data on compliance were reported in four studies [15, 18, 21, 36] and ranged between 82 % [21] and 100 % [36] for the AIT group and 83.5 % [21] and 100 % [36] for the MCT group. Seven out of the nine studies provided information on adverse events, in which no major complications were reported [15, 18, 19, 21, 36, 38, 39].

PeakVO_2 was assessed using a graded maximal cardiopulmonary exercise test on a treadmill in six studies [15, 18–21, 36] and on a cycle ergometer in the remaining three studies [22, 38, 39]. Criteria for a maximal exercise test were described as leveling off in VO_2 while workload is still increasing [15, 19], peak respiratory exchange ratio >1.05 [15], standard clinical criteria according to Fletcher et al. [40], or subjective exhaustion as leg fatigue or dyspnea [19, 20, 23, 38].

Table 2 shows the results of the study quality using the adapted PEDro-scale. The median PEDro score was 6.6, with a range from 5 [22] to 8 [15, 21, 38].

3.4 Primary Outcome: Effect of AIT vs. MCT on peakVO_2

As shown in Fig. 2, AIT resulted in a significantly larger increase in peakVO_2 (+1.60 mL/kg/min; 95 % CI 0.18–3.02; $p = 0.03$; $I^2 = 83\%$) compared with MCT. Overall, CAD patients increased their peakVO_2 with 4.26 ± 2.47 mL/kg/min (+20.5 %) after AIT and 2.61 ± 2.12 mL/min/kg (+12.8 %) after MCT. In the subgroup of CAD patients with preserved LVEF, AIT

Study or Subgroup	AIT Mean	AIT SD	AIT Total	MCT Mean	MCT SD	MCT Total	Weight	Mean Difference IV, Random, 95% CI
Currie 2013	4.7	1.99	11	3.6	2.46	10	11.9%	1.10 [-0.83, 3.03]
Dimopoulos 2006	0.92	2.13	6	0.26	2.13	5	10.3%	0.66 [-1.87, 3.19]
Iellamo 2012	4.24	2	8	4.09	1.9	8	12.0%	0.15 [-1.76, 2.06]
Moholdt 2009	3.3	2.44	28	2.3	2.26	31	13.8%	1.00 [-0.20, 2.20]
Rocco 2012	4.4	1.98	17	4.2	2.34	20	13.4%	0.20 [-1.19, 1.59]
Rognmo 2004	6	5.72	8	2.7	2.3	9	6.5%	3.30 [-0.94, 7.54]
Smart 2012	3.5	3.17	6	0.21	1.24	8	9.9%	3.29 [0.61, 5.97]
Warburton 2005	5.25	4.14	7	4.25	2.79	7	7.5%	1.00 [-2.70, 4.70]
Wisloff 2007	6	0.96	9	1.9	0.46	8	14.8%	4.10 [3.40, 4.80]
Total (95% CI)			**100**			**106**	**100.0%**	**1.60 [0.18, 3.02]**

Heterogeneity: Tau² = 3.41; Chi² = 47.23, df = 8 (P < 0.00001); I² = 83%
Test for overall effect: Z = 2.22 (P = 0.03)

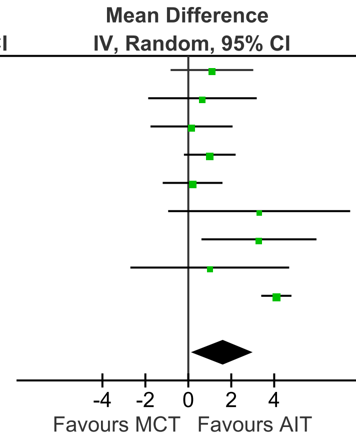

Fig. 2 Forest plot of the mean effect sizes and corresponding 95 % confidence intervals for peakVO_2. *Peak*VO_2 peak oxygen uptake, *AIT* aerobic interval training, *MCT* moderate continuous training, *IV* intervention, *CI* confidence interval, *SD* standard deviation

Study or Subgroup	AIT Mean	AIT SD	AIT Total	MCT Mean	MCT SD	MCT Total	Weight	Mean Difference IV, Random, 95% CI
Dimopoulos 2006	-1.74	2.71	6	2.28	4.7	5	8.9%	-4.02 [-8.68, 0.64]
Iellamo 2012	-2	1.3	8	-0.75	1.8	8	27.9%	-1.25 [-2.79, 0.29]
Rocco 2012	-2.7	1.22	17	-3.3	1.56	20	33.7%	0.60 [-0.30, 1.50]
Smart 2012	-7.08	7.88	6	-0.2	4.71	8	4.4%	-6.88 [-13.98, 0.22]
Warburton 2005	0	1.79	7	1	1.74	7	25.0%	-1.00 [-2.85, 0.85]
Total (95% CI)			**44**			**48**	**100.0%**	**-1.06 [-2.65, 0.53]**

Heterogeneity: Tau² = 1.74; Chi² = 11.55, df = 4 (P = 0.02); I² = 65%
Test for overall effect: Z = 1.31 (P = 0.19)

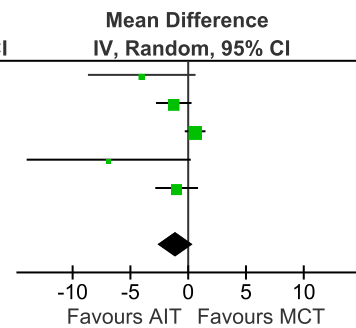

Fig. 3 Forest plot of the mean effect sizes and corresponding 95 % confidence intervals for V_E/VCO_2 slope. V_E/VCO_2, the slope of increase of ventilation relative to carbon dioxide production; *AIT* aerobic interval training, *MCT* moderate continuous training, *IV* intervention, *CI* confidence interval, *SD* standard deviation

resulted in significantly larger improvements in peakVO_2 than MCT (0.84 mL/kg/min; 95 % CI 0.05–1.63; $p = 0.04$; $I^2 = 0\%$). In the subgroup of CAD with reduced LVEF, AIT and MCT groups did not differ significantly (2.14 mL/kg/min; 95% CI −0.15 to 4.43; $p = 0.07$; $I^2 = 85\ \%$), but there was a trend in favor of AIT. In percentages, the peakVO_2 increase in CAD with preserved LVEF was 18.2 % after AIT and 13.6 % after MCT, while the effect for CAD patients with reduced LVEF was 25.6 % after AIT and 10.9 % after MCT. Subgroup analysis revealed no significantly different responses between CAD patients with preserved and reduced LVEF ($p = 0.29$; $I^2 = 9.5\ \%$). With each trial deleted from the model once, overall results of peakVO_2 remained statistically significant with an overall effect size ranging from 0.90 to 1.82 mL/kg/min, except for Rognmo et al. [18] (1.48 mL/kg/min; 95 % CI −0.01 to 2.97; $p = 0.05$) and Smart et al. [38] (1.41 mL/kg/min; 95 % CI −0.12 to 2.95; $p = 0.07$).

Only one study reported absolute changes in peakVO_2 [18], which made a meta-analytical approach on these data impossible.

3.5 Secondary Outcomes: Effect of AIT vs. MCT on Other Exercise Capacity Parameters and Other Cardiovascular Risk Factors

Overall, no differences were observed between AIT and MCT on the different submaximal exercise parameters. As shown in Figs. 3 and 4, no significant differences were found for the V_E/VCO_2 slope and the VO_2 at first threshold in the total group or the subgroups. However, there was a trend in favor of AIT for the V_E/VCO_2 slope in the subgroup of CAD patients with reduced LVEF (−2.71; 95 % CI −5.60 to 0.17; $p = 0.07$; $I^2 = 40\ \%$).

As shown in Fig. 5, the overall effect size for body weight was 0.78 kg (95 % CI −0.01 to 1.58; $p = 0.05$; $I^2 = 0\ \%$) in AIT vs. MCT, showing a trend towards a larger decrease in body weight in the MCT group compared with the AIT group.

3.6 Publication Bias

Funnel plots did not show any significant publication bias for the primary outcome peakVO_2, meaning that there was

Study or Subgroup	AIT Mean	AIT SD	AIT Total	MCT Mean	MCT SD	MCT Total	Weight	Mean Difference IV, Random, 95% CI
Currie 2013	3.3	1.48	11	2.1	1.56	10	15.2%	1.20 [-0.10, 2.50]
Dimopoulos 2006	0.46	1.83	6	0.37	1.85	5	11.2%	0.09 [-2.09, 2.27]
Iellamo 2012	2.34	1.1	8	3.65	0.96	8	16.6%	-1.31 [-2.32, -0.30]
Rocco 2012	1.7	1.27	17	2.5	1.29	20	17.4%	-0.80 [-1.63, 0.03]
Smart 2012	1.8	1.19	6	2.13	1.56	8	14.6%	-0.33 [-1.77, 1.11]
Warburton 2005	7	4.73	7	2	1.42	7	6.4%	5.00 [1.34, 8.66]
Wisloff 2007	3.4	0.45	9	2.1	0.38	8	18.7%	1.30 [0.91, 1.69]
Total (95% CI)			**64**			**66**	**100.0%**	**0.35 [-0.78, 1.48]**

Heterogeneity: Tau² = 1.74; Chi² = 44.77, df = 6 (P < 0.00001); I² = 87%
Test for overall effect: Z = 0.61 (P = 0.54)

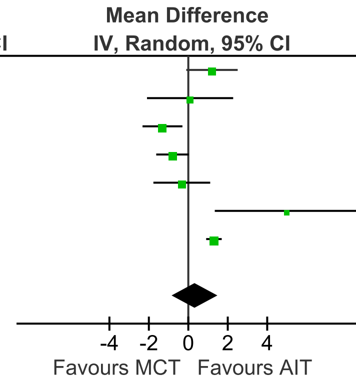

Fig. 4 Forest plot of the mean effect sizes and corresponding 95 % confidence intervals for VO_2 at the first threshold. VO_2 oxygen uptake, *AIT* aerobic interval training, *MCT* moderate continuous training, *IV* intervention, *CI* confidence interval, *SD* standard deviation

Study or Subgroup	AIT Mean	AIT SD	AIT Total	MCT Mean	MCT SD	MCT Total	Weight	Mean Difference IV, Random, 95% CI
Currie 2013	-0.6	2.2	11	-1.2	1.8	10	21.5%	0.60 [-1.11, 2.31]
Moholdt 2009	0.2	3.27	28	-0.8	2.06	31	31.6%	1.00 [-0.41, 2.41]
Rocco 2012	0.3	2.88	17	-0.1	6.54	20	6.2%	0.40 [-2.78, 3.58]
Rognmo 2004	-0.1	1.63	8	-0.8	1.33	9	31.0%	0.70 [-0.73, 2.13]
Warburton 2005	-3	1.4	7	-4	3.14	7	9.7%	1.00 [-1.55, 3.55]
Total (95% CI)			**71**			**77**	**100.0%**	**0.78 [-0.01, 1.58]**

Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 4 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.94 (P = 0.05)

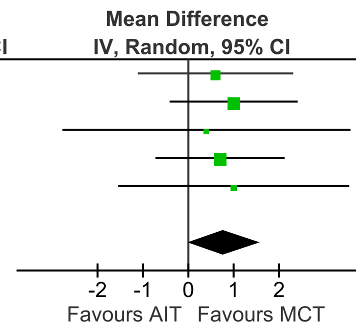

Fig. 5 Forest plot of the mean effect sizes and corresponding 95 % confidence intervals for body weight. *AIT* aerobic interval training, *MCT* moderate continuous training, *IV* intervention, *CI* confidence interval, *SD* standard deviation

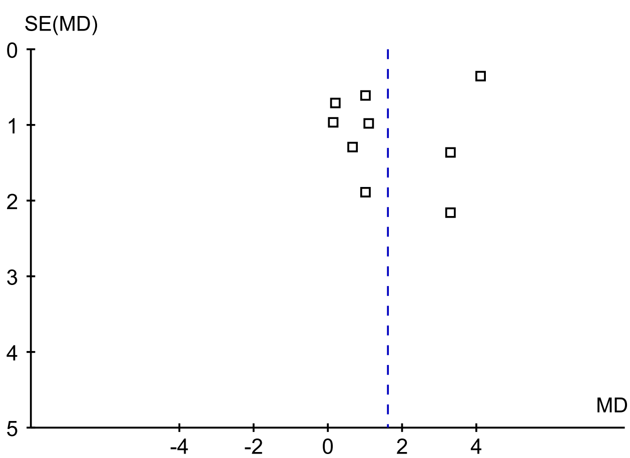

Fig. 6 Funnel plot for peakVO_2 of the included studies. *SE* standard error, *MD* mean differences, *peakVO₂* peak oxygen uptake

no asymmetric relationship between treatment effects and study size (Fig. 6).

4 Discussion

Exercise training is a cornerstone in cardiac rehabilitation; however, there is still controversy regarding the mode and intensity of exercise that can yield optimal beneficial effects in CAD patients [8]. The results of our meta-analysis suggest that (1) AIT elicits larger benefits on peakVO_2 than MCT in CAD patients; and (2) body weight tends to decrease more after MCT than AIT.

Cardiopulmonary exercise testing is an important tool to directly measure peakVO_2 in cardiac patients, which is used for clinical evaluation, prognostic stratification, and for the prescription of an individual exercise training program [3, 4, 41]. Low aerobic capacity has been shown to be a stronger predictor of CVD and mortality compared with other established cardiovascular risk factors [4]. In this meta-analysis, the AIT intervention resulted in a 1.60 mL/kg/min larger improvement in peakVO_2 than the MCT program. This is of clinical relevance, as each 1 mL/kg/min increment in peakVO_2 results in a 17 % decrease in all-cause mortality and a 16 % decrease in CVD mortality in men with CAD [42]. For women with CAD, this is 14 % for both all-cause and CVD deaths [42].

It has to be taken into account that CAD patients with preserved and/or reduced LVEF might respond differently to exercise training [8]. Patients with reduced LVEF often have symptoms such as shortness of breath, edema, fatigue, and even more important, they have exercise intolerance because of a limited pumping ability of the heart (LVEF

<40 %) and thus a lower provision of oxygen to the muscular tissue. Therefore, we investigated the CAD patients with reduced LVEF as a subgroup. The peakVO_2 increase in CAD patients with preserved LVEF was relatively small but significant (18.2 % after AIT and 13.6 % after MCT) while the effect for CAD patients with reduced LVEF was larger but only resulted in a trend in favor of AIT (25.6 % after AIT and 10.9 % after MCT). These results suggest that AIT significantly increases peakVO_2 more than MCT in CAD patients. Our results for peakVO_2 are in line with the findings of a recent review of Cornish et al. [12] in CAD patients, of Smart et al. [16] and Haykowsky et al. [17] in patients with HF of different etiologies, and of Hwang et al. [43] in patients with cardiometabolic diseases. The mean duration of one training session of the intervention studies included in our meta-analysis was comparable for both groups (41 min for AIT vs. 45 min for MCT), while the mean intended intensity was higher in the AIT group compared with the MCT group (90.8 % of HR_{max} vs. 71.3 % of HR_{max}). Therefore, the biological mechanisms and physiological adaptations through which AIT results in higher changes in peakVO_2 may be due to intensity-dependent improvements in exercise cardiovascular and skeletal muscle function. First, exercise training influences the hemodynamics of the heart and arteries. It has been shown that cardiac output and stroke volume increase more after 12 weeks of AIT compared with MCT [33]. In addition, systemic vascular resistance seems to decrease significantly more after an acute bout of AIT compared with MCT [44] and also long-lasting decreases occur after 3 [45] or 12 weeks [33] of an AIT program in patients with HF. Second, Wisløff et al. [15] in CAD patients with reduced LVEF and Tjonna et al. [46] in metabolic syndrome patients showed significantly better improvements in peripheral endothelial function measured by flow-mediated dilation after an AIT intervention compared with an MCT intervention. Third, improved skeletal muscle oxidative capacity may play an important role in the larger increase in peakVO_2 after AIT compared with MCT, as Wisløff et al. [15] showed in CAD patients with reduced LVEF and Tjonna et al. [46] in metabolic syndrome patients. Both studies reported a larger increase in peroxisome proliferative activated receptor-γ coactivator-1α in AIT groups, which is an indicator of mitochondrial biogenesis. Mitochondrial biogenesis results in more mitochondria, which increase metabolic enzymes for glycolysis, oxidative phosphorylation, and ultimately a greater metabolic capacity.

The inconsistency of the explanatory mechanisms by which peakVO_2 improves after exercise training, and more specifically after AIT, is largely based on small studies and therefore needs to be further elucidated in large, well-designed, randomized controlled trials.

While previous investigations demonstrating a significant improvement in peakVO_2 following exercise training are numerous, the benefit on the V_E/VCO_2 slope is less investigated [47]. Van De Veire et al. [48] documented a relationship between the V_E/VCO_2 slope and indices of progressive LV remodeling, systolic dysfunction, and neurohormonal activation in patients with CAD. This slope is, in addition to peakVO_2, an important independent prognostic marker in cardiac patients [49], especially in HF patients [50, 51]. In our overall group and in the subgroup of CAD patients with preserved LVEF, there was no significant difference between AIT and MCT in decreasing the V_E/VCO_2 slope; in the group of CAD patients with reduced LVEF, there was a trend in favor of AIT. The non-significance of our results can be because of the small number of studies included in the analysis. More research is needed in this domain of submaximal exercise parameters, especially for HF patients.

Furthermore, our study results suggest that body weight tends to decrease more after MCT than after AIT. This is partly in line with Vanhees et al. [23], stating that increasing exercise volume and program prolongation are effective strategies to augment fat loss. It is known that with lower exercise intensity and longer exercise duration, fat metabolism is activated for the provision of energy, while at higher intensities; more carbohydrates are used at first. However, fat mass loss is determined by the total caloric expenditure of the training programs [52]. If the total caloric expenditure of the MCT programs was larger compared with AIT, then this can partly explain our findings. However, it is also possible that because of the higher workloads, and possibly higher training volumes, CAD patients in the AIT group might effectively lose fat mass but might increase their muscle mass and therefore might maintain or increase their body weight. Unfortunately, because we could not extract data on caloric expenditure of all training programs, we cannot make any statements on this issue based on our data.

Meta-analytical statistics on other cardiovascular risk factors, including blood glucose, total cholesterol, blood triglycerides, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and blood pressure, were not possible because of the limited number of studies reporting them. Iellamo et al. [36] and Moholdt et al. [21] found no significant decreases for HDL-C, LDL-C, and blood triglycerides after both training programs. Blood glucose decreased significantly after MCT but not after AIT in Iellamo et al. [36] but did not change after both interventions in Moholdt et al. [21]. Total cholesterol was only reported in one study and did not change significantly after AIT or MCT [21]. Systolic and diastolic blood pressure before and after training were available in only two studies. While Rognmo et al. [18] found no significant decreases after training, Currie et al. [39] showed significant reductions in diastolic blood pressure but not in systolic blood pressure for both intervention groups.

To the best of our knowledge, this is the first meta-analysis comparing the effects of AIT and MCT in CAD patients. Based on our results, AIT seems to be more effective to improve exercise capacity and therefore may be more appropriate for use in a cardiac rehabilitation setting. Furthermore, Guiraud et al. [14] suggested that AIT is both very efficient and particularly cost effective. Nevertheless, AIT in cardiac patients is sometimes considered to be controversial, because of the potential risk for adverse events with exercising at higher intensities [53]. However, in a review of Rognmo et al. [54], it has been shown in 4846 CAD patients that the risk of cardiovascular events during AIT and MCT is low: one fatal cardiac arrest occurred during MCT (129,456 exercise hours), two non-fatal cardiac arrests during AIT (46,364 exercise hours), and no myocardial infarctions. Based on these findings, AIT seems to be safe in a cardiac rehabilitation setting.

4.1 Limitations

Results from meta-analyses have to be interpreted with some caution, but, although meta-analyses are no substitute for large, well-designed, controlled trials, the meta-analytical technique is probably the best method to systematically review previous work. Advantages are the greater precision of the estimates and the enhanced statistical power [55]. Potential disadvantages are the heterogeneity of studies and publication bias [55]. With regard to the latter, we observed high heterogeneity and inconsistency between the interventions. Although mostly random-effects models that take into account heterogeneity into their model were used, some caution might be warranted with the interpretation given also the small number of studies. This small number of studies might have affected the power to reach significance for the secondary outcomes, and limited further investigation on the role of sex, age, and exercise (mode, intensity, duration, frequency) for the primary outcome measure. In addition, the AIT and MCT protocols were different throughout the nine studies. Some studies compared isocaloric AIT and MCT programs; others did not provide information on total caloric expenditure and the necessary information to calculate caloric expenditure was not provided in all studies. This made it impossible to investigate the impact of caloric expenditure of the different exercise protocols on the studied training effects.

4.2 Future Research

Future research must focus on the effects of AIT compared with MCT in larger groups, both in CAD patients with preserved and/or reduced LVEF, on exercise-related parameters and cardiovascular risk factors. In addition, research should focus more on the underlying mechanisms that can explain the differences in improvement of exercise capacity and cardiovascular risk factors between AIT and MCT. In addition, it remains unclear whether it is the high intensity of the exercise or the interval character of the exercise leading to larger improvements in peakVO_2. And last but not least, different AIT protocols should be investigated and compared with each other to document which protocol generates the highest benefit in terms of training response, long-term health, quality of life, and patient satisfaction.

5 Conclusion

The findings from this meta-analysis suggest that in CAD patients, AIT is superior to MCT for improving peakVO_2, while MCT seemed to be more effective in reducing body weight.

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Conflict of interest None.

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