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ORIGINAL ARTICLE

Interval Training Versus Continuous Exercise in Patients with Coronary Artery Disease: A Meta-Analysis

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Background High aerobic capacity is inversely related to cardiovascular disease morbidity and mortality. Recent studies suggest greater improvements in aerobic capacity with high-intensity interval training (interval) compared to moderate-intensity continuous aerobic exercise (continuous). Therefore we perform a meta-analysis of randomised controlled trials comparing the effectiveness of INTERVAL versus CONTINUOUS in aerobic capacity, amongst patients with stable coronary artery disease (CAD) and preserved ejection fraction

Methods We searched PubMed, EMBASE, CINAHL, the Australia and New Zealand Clinical Trials Register, clinicaltrials.gov and TROVE for randomised controlled trials comparing INTERVAL with CONTINUOUS in patients with CAD. Studies published in the English language up to December 2013 were eligible for inclusion. Aerobic capacity, quantified by peak oxygen consumption (VO_{2peak}) post exercise training was extracted and compared post-intervention between INTERVAL and CONTINUOUS by way of a fixed model meta-analysis. Secondary outcomes including anaerobic threshold, blood pressure and high-density lipoproteins (HDL) were also analysed.

Results Six independent studies with 229 patients (n = 99 randomised to INTERVAL) were included in the meta-analysis. There was a significantly higher increase in VO_{2peak} following INTERVAL compared to CONTINUOUS (Weighted Mean Difference = 1.53 ml•kg^{-1}min^{-1}, 95% CI 0.84 to 2.23) with homogeneity displayed between studies (Chi Squared = 2.69; P = 0.7). Significant effects of INTERVAL compared to CONTINUOUS were also found for anaerobic threshold but not systolic blood pressure.

Conclusion In patients with CAD, INTERVAL appears more effective than CONTINUOUS for the improvement of aerobic capacity in patients with CAD. However, long-term studies assessing morbidity and mortality following INTERVAL are required before this approach can be more widely adopted.

Keywords Rehabilitation • Myocardial infarction • Coronary artery bypass graft • Risk factors • Oxygen uptake

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Introduction

Exercise-based cardiac rehabilitation is an effective strategy for reducing total and cardiovascular mortality in patients with coronary artery disease (CAD) [1]. Furthermore, aerobic fitness has been established as a strong predictor of cardiovascular [2,3] and all-cause mortality [4]. Defining aerobic fitness by way of cardiopulmonary exercise testing has become increasingly available in many rehabilitation settings, where peak oxygen consumption (VO_{2peak}) can be directly measured as the gold standard for aerobic capacity. Increases in VO_{2peak} have been shown to relate to improvements in mortality risk [5], where every 1-metabolic equivalent (1-MET = 3.5 ml•kg^{-1}min^{-1} VO_2) increase yields a 13% improvement in survival. Exercise training-induced increases in aerobic capacity are therefore highly desirable for the improvement of patient outcomes.

Optimising exercise rehabilitation to maximise the potential increase in aerobic capacity is an important factor in the prescription of exercise. In patients with CAD, traditional exercise prescription has included continuous aerobic exercise, such as walking or cycling, at a moderate intensity (40-80% VO_{2peak}) for 30-60 minutes [6]. However, recent evidence in healthy participants [7,8], heart failure patients [9,10] and patients with cardiometabolic disease [11] suggests that high-intensity interval training (INTERVAL) may be a more effective strategy for the improvement of aerobic capacity than continuous, moderate intensity exercise training (CONTINUOUS).

High-intensity interval training is characterised by brief intermittent bursts of exercise interspersed by active recovery periods, and has shown a number of benefits in patients with CAD, including improvements in aerobic capacity, anaerobic threshold, endothelial function and cardiac function [9,12].

Studies comparing INTERVAL with CONTINUOUS training in patients with heart disease typically prescribe intervals of up to four minutes duration at an intensity of approximately 85-95% peak heart rate (HR_{peak}) [9,13,14]. Alternatively, shorter durations of one to two minutes have also been applied with a 1:1 work:rest ratio [15,16]. Likewise, both shorter [7] and longer intervals [8] have been shown to increase aerobic capacity compared to CONTINUOUS in healthy participants.

In many instances, the benefits on aerobic capacity of INTERVAL appear to exceed the improvements seen with CONTINUOUS training. Previous meta-analyses of studies recruiting heart failure [10] and cardiometabolic disease patients [11] indicate that INTERVAL results in increases of approximately 2-3 ml/kg/min VO_{2peak} greater than that observed with CONTINUOUS training.

Previous systematic reviews have included studies comparing INTERVAL with no exercise [17] or patients with metabolic and/or other lifestyle diseases in addition to those with CAD [11]. More recently, a meta-analysis revealed greater improvements in aerobic capacity with INTERVAL compared with CONTINUOUS in patients with CAD [18]. However, since publication of this meta-analysis, a further study has been published comparing the two approaches. Importantly, the meta-analysis by Pattyn et al, included studies in which patients had ischaemic heart failure and ejection fractions <40% [9]. Additionally, in some studies analysed, there were no differences in the actual exercise intensity between the two training methods. The aim of the present study was to perform a meta-analysis of all randomised controlled trials studies comparing the effectiveness of INTERVAL with CONTINUOUS on aerobic capacity, defined using VO_{2peak}, amongst patients diagnosed with stable CAD in the absence of disclosed heart failure.

Methods

Study Selection

The search aimed to find both published and unpublished studies. The search was restricted to studies published in the English language prior to December 2013. A three-step search strategy was employed; an initial limited search of PubMed and CINAHL was undertaken followed by analysis of text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms was then undertaken across PubMed, EMBASE, CINAHL, the Australia and New Zealand Clinical Trials Register, clinicaltrials.gov and TROVE (Fig. 1). Thirdly, the reference lists of all identified reports and articles were searched for additional studies. At this time, one further study came to the attention of the authors.

Keywords used in the search included those relating to the exercise intervention (e.g. exercise rehabilitation, interval exercise, high-intensity exercise) combined with those specific to the population (e.g. coronary artery disease, ischemic heart disease, myocardial infarction). Full-text articles were retrieved after review of the title and abstract. Criteria for inclusion were all of the following; i) randomised controlled trials comparing INTERVAL with CONTINUOUS in patients with stable CAD in the absence of heart failure, ii) studies prescribing an exercise program for at least four weeks, and iii) studies including aerobic capacity as a reported outcome. Secondary outcomes for this study included the cardiovascular risk factor profile including resting systolic blood pressure, low-density lipoprotein (LDL) and high-density lipoprotein (HDL). To be eligible for inclusion, INTERVAL was defined as brief (1-4 mins), intermittent bouts of high-intensity (>85% HR_{peak} or equivalent) rhythmic exercise such as cycling, jogging, or walking, interspersed by periods of active recovery. Both supervised and home-supervised exercise was considered for inclusion. Continuous, moderate-intensity exercise was defined as at least 30 minutes of rhythmic aerobic exercise, such as cycling, walking, running or swimming, performed at a moderate-intensity (<80% HR_{peak} or equivalent) that is sustainable for the duration of the session.

Assessment of Methodological Quality

Studies selected for inclusion were assessed for methodological validity by two independent reviewers (A.D.E and D.J.B)

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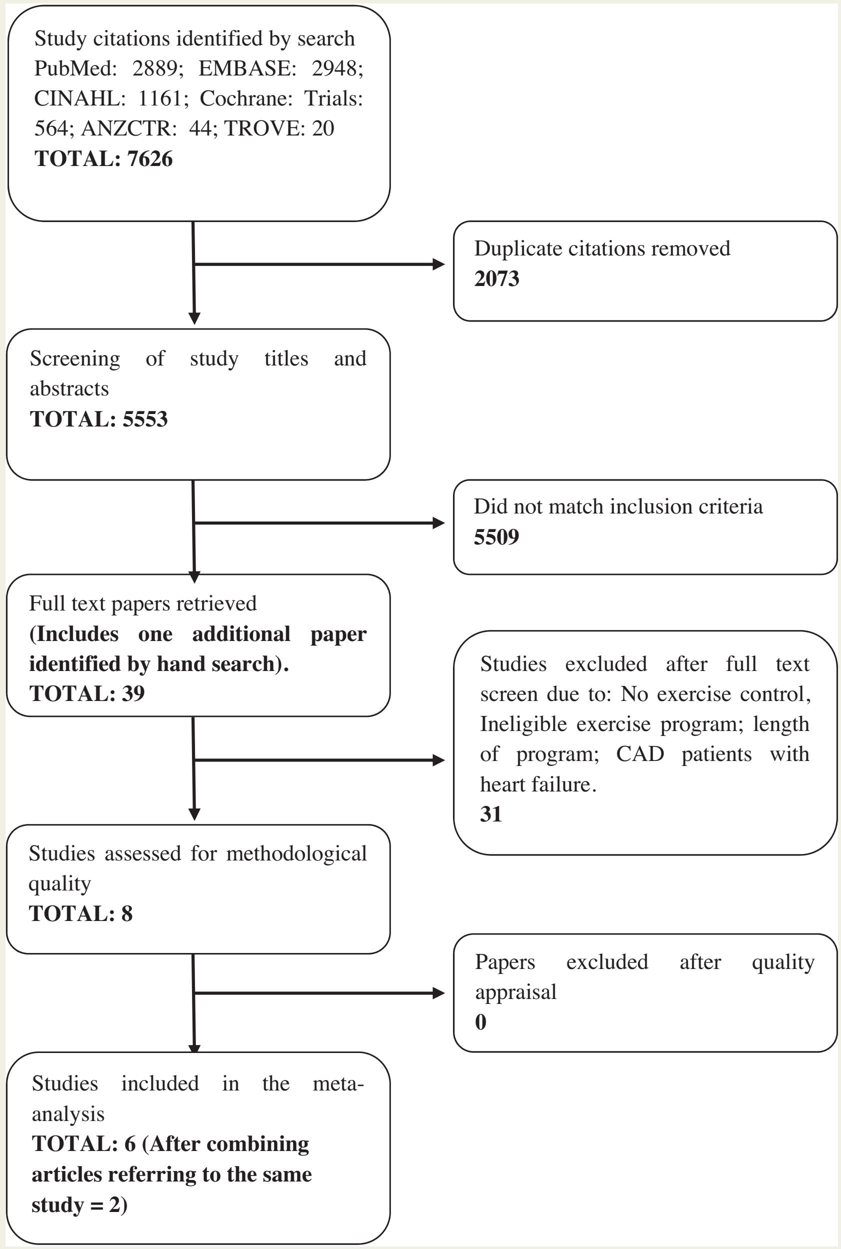

Figure 1 Flow diagram of the search and study inclusion process.

using standard critical appraisal instruments for randomised controlled trials from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment for Review Instrument (JBI-MAStARI, Joanna Briggs Institute, University of Adelaide, Australia). For inclusion in the review, both reviewers agreed that a cut-off score of five out of 10 be used to determine acceptable quality for inclusion.

Data Extraction

All data was extracted by a single investigator (A.D.E) using a standardised form. For each study, the citation details, sample size, details of exercise interventions and outcomes were extracted. The primary outcome extracted was aerobic capacity, namely VO_{2peak}. Secondary outcomes extracted included anaerobic threshold, lipid profile (LDL and HDL), and systolic blood pressure.

Statistical Analysis

The JBI-MAStARI was used to pool results from the included studies. A fixed effect meta-analysis was used to determine the weighted mean difference (WMD) and 95% confidence intervals of outcomes compared between INTERVAL and

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Table 1 Characteristics of included studies.

Study	Sample	n	INT	CONT	Duration	Mode
Rognmo et al (2004); Amundsen et al (2008)	CAD	17 (INT = 8)	3d/wk - 4x4mins @ 80-90% VO_2peak, 3min recovery.	3d/wk – 41 mins@50-60% VO_2peak.	10 weeks	TM Walking
Warburton et al (2005)	CAD (previous CABG or AP)	14 (INT = 7)	2d/wk - 2mins @ 90% VO2R, 2min recovery. 30 mins total. Additional 3d/wk 30mins & 65%VO2R	2d/wk - 30 mins@65%VO_2R Additional 3d/wk 30mins & 65%VO_2R	16 weeks	TM, Stairclimber, Arm and Leg Ergometer
Moholdt et al (2009)	Post-CABG	59 (INT = 28)	5d/wk – 4x4mins @ 90%HR_{peak}, 3min recovery.	5d/wk – 46min walking @ 70%HRmax.	4 weeks	TM Walking
Moholdt et al (2011, 2012)	Post-MI	89 (INT = 30)	3d/wk - 4x4mins @ 85-95%HR_{peak}, 3min recovery.	3d/wk – 35min aerobic group exercise	12 weeks	TM Walking (INT), Aerobic exercises (Control)
Currie et al (2013)	Recent CAD event	22 (INT = 11)	2d/wk – 10x1min @ 89%PPO, 1min recovery	2d/wk – 30-50min @ 58%PPO	12 weeks	Cycling
Keteyian et al (2014)	Post-MI, CABG and/or PCI	28 (INT = 15)	3d/wk - 4x4mins @ 80-90% HRR, 3min recovery	3d/wk - 30mins@ 60-80% HRR	10 weeks	TM

CAD Coronary Artery Disease; CABG Coronary artery bypass graft; AP Angioplasty; MI Myocardial infarction; PCI Percutaneous coronary intervention; INT Interval training; CONT Moderate continuous training; HR_{peak} Peak heart rate; HRR Heart rate reserve; VO_{2peak} Peak oxygen consumption; VO_2R VO_2 reserve determined as difference between resting and peak VO_2; PPO peak power output; TM Treadmill.

CONTINUOUS measured upon completion of the relevant exercise program. Statistical heterogeneity was evaluated using chi-squared.

Results

Identified Studies

Following the initial search, 5553 studies were reviewed by their title and abstract (Fig. 1). Of these, 39 were retrieved in full-text, 32 of which did not match the eligibility criteria for the study. Following assessment of methodological quality, eight articles were included in the meta-analysis. In two instances, two articles were reporting outcomes from the same study [12,13,19,20]. In these instances, both articles were treated as a single study such that the final analysis included six independent research studies.

The characteristics of the included studies are shown in Table 1. Three studies were from the same institution in Norway [13,14,20], with the remaining three studies from Canada [15,16] and the United States [21]. A total of 229 patients with CAD were analysed (Table 2), 99 of which were randomised to INTERVAL. Sample size in the included studies ranged from 14 to 89 patients (Table 1). Exercise program duration ranged from four to 16 weeks with a frequency of exercise training ranging from two to five days per week (Table 1). The methodological quality of each study is reported in Table 3.

VO_{2peak}

Pooling of studies using a fixed-effects meta-analysis revealed that INTERVAL is significantly more effective than CONTINUOUS for increasing VO_{2peak} in CAD patients (Fig. 2). Patients in the INTERVAL group improved their VO_{2peak} by 1.53 ml•kg^{-1}min^{-1} (95% CI 0.84 to 2.23) more than the CONTINUOUS group (Overall Z = 4.33, $P = 0.0001$). Homogeneity was observed between studies (chi squared = 2.69, $P = 0.7$).

Anaerobic Threshold

Three of the six studies [15,16,21] reported the VO_2 at anaerobic threshold post exercise training (Fig. 3). The WMD was 1.95 ml•kg^{-1}min^{-1} (95% CI 1.23 to 2.67) in favour of INTERVAL (Overall Z = 5.31, $P = 0.0001$). Statistical heterogeneity was observed between studies (chi-squared = 4.95, $P < 0.05$).

Cardiovascular Risk Factors

Three studies with a combined sample of 67 patients [13,16,21] reported systolic blood pressure following exercise training (Fig. 4). The WMD was -3.44 mmHg (95% CI -7.25 to

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0.36), with an overall Z effect of 1.77 indicating a non-significant effect ($P = 0.07$). Two studies with a combined sample of 148 patients revealed no statistically significant difference in plasma HDL [14,22]; a WMD of 0.04 (95% CI 0.00 to 0.07) was determined ($Z = 1.8$; $P = 0.1$). Only one study [14] reported LDL following exercise training. Meta-analysis was unable to be performed on this outcome.

Discussion

The findings of this meta-analysis indicate that INTERVAL is more effective than CONTINUOUS for the improvement of both VO_{2peak} and the anaerobic threshold in patients with stable CAD in the absence of heart failure. The greater improvement in VO_{2peak} following INTERVAL compared to CONTINUOUS (4.6 ± 3.1 versus 2.8 ± 2.4 ml•kg^{-1}min^{-1}) is important in the context of a 10-25% survival advantage with every 3.5 ml•kg^{-1}min^{-1} improvement in VO_{2peak} [23]. These findings are in agreement with previous meta-analyses comparing INTERVAL with CONTINUOUS in heart failure patients [10], and cardiometabolic disease [11] although the magnitude of the effect reported here is lower than that seen in these other populations. The greater effect seen in studies of heart failure (~2.14 ml•kg^{-1}min^{-1}) is likely mediated by impaired cardiac function at baseline in that population. However, the meta-analysis by Weston et al (2013) in patients with 'cardiometabolic' disease indicated a >3 ml•kg^{-1}min^{-1} increase in VO_{2peak} with INTERVAL compared to CONTINUOUS. Although not widely reported, many of the included studies would have enrolled patients without heart failure, thus suggesting that the presence of heart failure may not be a critical factor in determining the magnitude of benefit with INT. One should note that many of the studies of INTERVAL in heart failure included studies in which INTERVAL was prescribed intermittent exercise with no difference in exercise intensity. Therefore, the precise description of high-intensity interval training may underlie some of the observed differences between studies. Nonetheless, these findings indicate that INTERVAL may be widely incorporated into exercise-based cardiac rehabilitation programs where a primary aim is to increase aerobic capacity. Analysis of the studies reporting blood pressure and HDL, indicate no significant effect of INTERVAL when compared with CONTINUOUS. However, these outcomes were reported in only three and two studies respectively, thus potentially limiting statistical power, although no trends were apparent for either variable.

The possible mechanisms underlying the greater improvements in aerobic capacity with INTERVAL are unclear, although the training intensity-dependence of VO_{2peak} [24] has been established previously and is evident even in groups performing INTERVAL within the desired range of 85-95% HR_{peak} [25]. There is considerable evidence that high-intensity exercise training yields a number of beneficial adaptations with regards to cardiac function including improved stroke volume [8], systolic [9] and diastolic left ventricular function [12]. Additionally, greater improvements in endothelial function have been reported with INTERVAL [9,14,26]

Table 2 Patient characteristics and disease status for included studies.

Study	**Rognmo et al.**		**Warburton et al**		**Moholdt et al**		**Moholdt et al**		**Currie et al**		**Keteyian et al**	
Group	*INT*	*CONT*	*INT*	*CONT*	*INT*	*CONT*	*INT*	*CONT*	*INT*	*CONT*	*INT*	*CONT*
Disease Status	**Angiographically documented CAD**		**Previous CABG or AP**		**Post-CABG (4-16 weeks)**		**Post-MI (2-12 weeks)**		**Angiographically documented CAD**		**Previous PCI, CABG or MI**	
Age (Yrs.)	62.9 ± 11.2	61.2 ± 7.3	55 ± 7	57 ± 8	60.2 ± 6.9	62 ± 7.6	56.7 ± 10.4	57.7 ± 9.3	62 ± 11	68 ± 8	60 ± 7	58 ± 9
Gender (Male/Female)	6/2	8/1	7/0	7/0	24/4	24/7	25/5	49/10	10/1	10/1	11/4	12/1
Baseline VO_{2peak} (ml•kg^{-1}min^{-1})	31.8 ± 9.3	32.1 ± 5.3	33.3 ± 7.7	29.8 ± 2.3	27.1 ± 4.5	26.2 ± 5.2	31.6 ± 5.8	32.2 ± 6.7	18.7 ± 5.7	19.8 ± 3.7	22.4 ± 4.2	21.8 ± 4
MI (no.)	4	4	3	2	NR	NR	30	59	7	6	8	9
PCI (no.)	1	2	3	3	NR	NR	23	47	6	8	11	8
CABG (no.)	2	3	3	3	28	31	NR	NR	4	3	3	4
1-2 Diseased Vessels	6	6	4	3	NR	NR	NR	NR	NR	NR	NR	NR
3+ Diseased Vessels	2	3	3	4	NR	NR	NR	NR	NR	NR	NR	NR

INT Interval Training; **CONT** Continuous Training; **CAD** Coronary Artery Disease; **MI** Myocardial Infarction; **PCI** Percutaneous Coronary Intervention; **CABG** Coronary Artery Bypass Graft; **NR** Not Reported.

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Table 3 Methodological quality of included studies.

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Warburton et al, 2005	N	N	N	N	N	Y	Y	Y	Y	Y
Rognmo et al, 2004	Y	N	Y	N	N	Y	Y	Y	Y	Y
Moholdt et al, 2009	Y	N	Y	N	N	Y	Y	Y	Y	Y
Moholdt et al, 2012	Y	N	Y	N	N	Y	Y	Y	Y	Y
Currie et al, 2013	U	N	N	N	N	Y	Y	Y	Y	Y
Keteyian et al (2014)	Y	N	Y	N	Y	Y	Y	Y	Y	Y
%	67%	0%	67%	0%	17%	100%	100%	100%	100%	100%

Y Represents criteria achieved; **N** Represents criteria not achieved; **U** Represents criteria unable to be determined.
1. Was the assignment to treatment groups truly random?
2. Were participants blinded to treatment allocation?
3. Was allocation to treatment groups concealed from the allocator?
4. Were the outcomes of people who withdrew described and included in the analysis?
5. Were those assessing outcomes blind to the treatment allocation?
6. Were the control and treatment groups comparable at entry?
7. Were groups treated identically other than for the named interventions?
8. Were outcomes measured in the same way for all groups?
9. Were outcomes measured in a reliable way?
10. Was appropriate statistical analysis used?

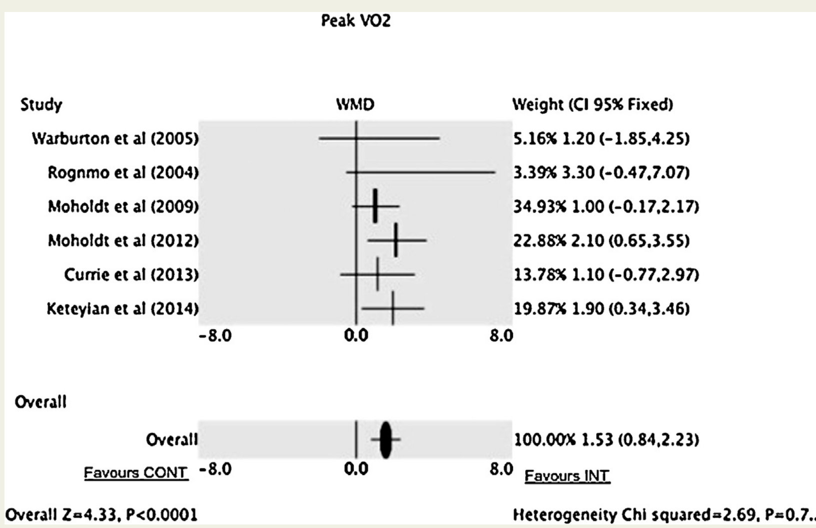

Figure 2 Effect of interval versus continuous exercise training on VO_{2peak} (ml•kg^{-1}min^{-1}). **CONT** moderate intensity continuous training; **INT** Interval training; **WMD** weighted mean difference; **95% CI** 95% confidence intervals.

most likely due to an increased vascular shear stress associated with greater peripheral blood flow. Previously, greater skeletal muscle oxidative capacity has been reported with shorter sprint, interval training compared to traditional endurance training in healthy participants [7], an effect which may also be apparent with INTERVAL of longer duration (four minute intervals). Together, these findings indicate that both central and peripheral factors may mediate the greater VO_{2peak} improvements although no studies have directly assessed this hypothesis.

The absence of any significant effect of INTERVAL compared to CONTINUOUS on blood pressure is perhaps unsurprising given recent findings that have shown either a positive [26,27] or no effect [9] in similar populations. Furthermore, the systolic BP recorded in the studies by Currie et al [16] and Keteyian et al [21] did not exceed 130 mmHg, indicating that high BP was not a characteristic in the population sample upon entry. Previously, it has been suggested that despite the benefits of moderate-intensity exercise for the reduction of blood pressure, additional increases in the exercise intensity confer little added benefit [28,29].

Despite the role of HDL as a positive risk factor, there was minimal overall difference between INTERVAL and CONTINUOUS following exercise training, despite a

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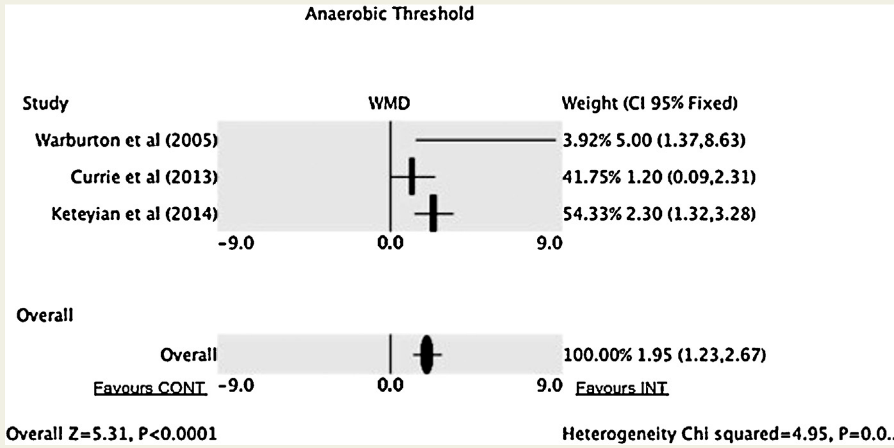

Figure 3 Effect of interval versus continuous exercise training on the VO_2 (ml•kg^{-1}min^{-1}) at anaerobic threshold. **CONT** moderate intensity continuous training; **INT** Interval training; **WMD** weighted mean difference; **95% CI** 95% confidence intervals.

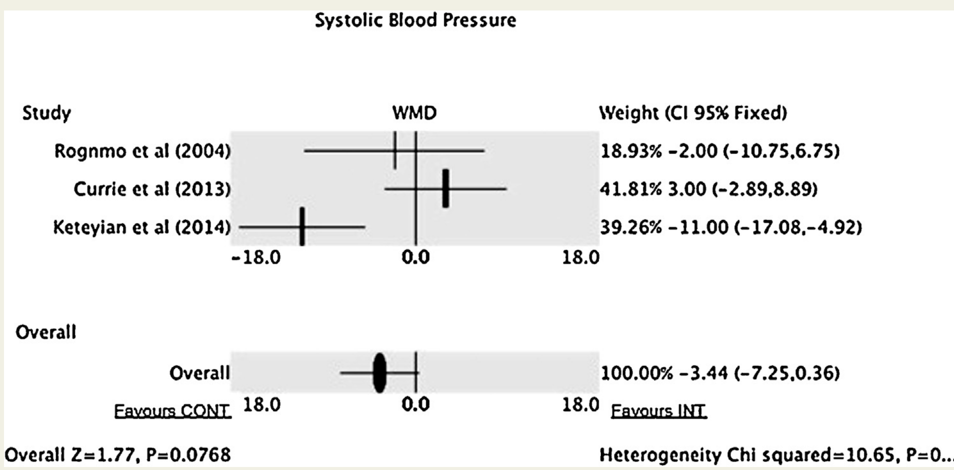

Figure 4 Effect of interval versus continuous exercise training on systolic blood pressure (mmHg) **CONT** moderate intensity continuous training; **INT** Interval training; **WMD** weighted mean difference; **95% CI** 95% confidence intervals.

significant increase being reported in the study by Moholdt et al. [22] following INTERVAL and a trend for increased HDL following INTERVAL in the study by Moholdt et al. [14]. The absence of any change in HDL number following exercise training has been reported previously in hypercholesterolaemic men [30], although meta-analysis of the HDL response to exercise indicates that modest improvements in HDL with exercise may only be apparent with weekly exercise durations in excess of 120 minutes, with little effect of exercise intensity [31]. Additionally, the total length of the exercise program may be an important factor with changes in HDL being previously demonstrated after two years of aerobic exercise training, but not one [32]. A larger effect may have eluded the studies reporting HDL number possibly due to the short exercise program employed by Moholdt et al (2009) [14] or the total weekly exercise duration of less than 120 minutes in the study by Moholdt et al (2012) [22].

Prescribing high-intensity exercise to patients with CAD warrants careful consideration. Vigorous exercise can acutely and transiently increase the risk of sudden cardiac arrest or myocardial infarction in susceptible patients [33]. During traditional exercise-based cardiac rehabilitation, the risk of a fatal event is approximately one event per every 750,000 training hours. The estimated risks for cardiac arrest and myocardial infarction are one in 116,000 and one in 219,000 training hours, respectively. A recent multicentre analysis of cardiovascular risk in CAD patients performing INT, reports only two non-fatal cardiac arrests across a total of 46,000 training hours [13]. Given the benefits of INTERVAL exercise in patients with CAD, it appears that the overall risk of INTERVAL is low although possibly higher than that seen in traditional cardiac rehabilitation. However, caution should be taken when interpreting this data given the limited dataset in which this analysis was performed. Further

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evaluation of the safety of INTERVAL is a critical requirement for future large, multicentre studies.

Despite the evidence presented here and elsewhere [10] favouring INTERVAL compared to CONTINUOUS in patients with heart disease, in the course of conducting this meta analysis, no study was identified that evaluated the long-term benefits on cardiovascular morbidity and/or mortality. Systematic reviews confirm the widely held view that exercise is highly beneficial to patients with CAD [1], thus making it likely that INTERVAL may offer similar advantages. However, whether INTERVAL is more effective than CONTINUOUS in this regard remains to be answered. Future studies should aim to evaluate not only the short-term physiological adaptations with INTERVAL but also the longer-term health benefits that this form of training may offer. Furthermore, future studies should assess the effect of INTERVAL on cardiovascular risk factor profiles so that exercise can be individualised to cardiovascular risk scores.

Study Limitations

The conclusions regarding the benefits of INTERVAL are constrained by the quality of the trials reported, which typically include small sample sizes. Few trials adequately reported the randomisation procedure in sufficient detail to determine whether selection bias may have influenced the study outcomes. Blinding of the assessors to treatment allocation was also absent or unclear in a number of studies, raising the possibility of performance bias. Finally, intention to treat analysis was not performed in any of the studies reported, where data from withdrawn patients was not included, which may have resulted in attrition bias. Future studies investigating the effectiveness of INTERVAL versus other treatment options should address these matters in their study design.

Conclusions

When compared to traditional aerobic training, high-intensity INTERVAL appears to be a more effective option than CONTINUOUS for increasing aerobic capacity in patients with stable CAD in the absence of any disclosed heart failure, despite minimal or no effect on other cardiovascular risk factors. For this form of exercise rehabilitation to become commonplace in clinical practice, high-quality randomised controlled trials are required to elucidate whether INTERVAL confers any additional benefit on cardiovascular morbidity and mortality in this population.

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