European Journal of
Cardiovascular
Nursing
EUROPEAN SOCIETY OF CARDIOLOGY®

Original Article

European Journal of Cardiovascular Nursing
1–12

DOI: 10.1177/1474515116684407
cnu.sagepub.com
SAGE

Effectiveness of endurance exercise training in patients with coronary artery disease: A meta-analysis of randomised controlled trials

Yu-Chi Chen[1], Jen-Chen Tsai[2], Yiing-Mei Liou[3] and Paul Chan[4]

Abstract

Background: Exercise interventions apparently reduce the risks of and prevent coronary artery disease (CAD). Developing an exercise intervention for patients with CAD is a rapidly expanding focus worldwide. The results of previous studies are inconsistent and difficult to interpret across various types of exercise programme.

Aim: This study aimed to update prior systemic reviews and meta-analyses in order to determine the overall effects of endurance exercise training on patients with CAD.

Methods: The databases (PubMed, Medline, CINAHL, EMBASE and Cochrane Library) were searched for the interventions published between January 1, 2000, and May 31, 2015. Comprehensive meta-analysis software was used to evaluate the heterogeneity of the selected studies and to calculate mean differences (MDs) while considering effect size.

Results: A total of 18 studies with 1286 participants were included. Endurance exercise interventions at a moderate to high training intensity significantly reduced resting systolic blood pressure (MD: −3.8 mmHg, p = 0.01) and low-density lipoprotein cholesterol (MD: −5.5 mg/dL, $p = 0.02$), and increased high-density lipoprotein cholesterol (MD: 3.8 mg/dL, $p < 0.001$). There were also significant positive changes in peak oxygen consumption (MD: 3.47 mL/kg/min, $p < 0.001$) and left ventricular ejection fraction (MD: 2.6%, $p = 0.03$) after the interventions. Subgroup analysis results revealed that exercise interventions of 60–90 minutes per week with a programme duration of >12 weeks had beneficial effects on functional capacity, cardiac function and a number of cardiovascular risk factors.

Conclusions: Endurance exercise training has a positive effect on major modifiable cardiovascular risk factors and functional capacity. Nurses can develop endurance exercise recommendations for incorporation into care plans of clinically stable CAD patients following an acute cardiac event or revascularisation procedure.

Keywords

Coronary artery disease, blood pressure, endurance exercise, blood lipid, functional capacity

Date received: 10 August 2016; revised: 3 November 2016; accepted: 25 November 2016

Introduction

Coronary artery disease (CAD) is the most prevalent form of cardiovascular disease. The prevalence of CAD is increasing in the middle-aged and elderly populations. It has remained one of the leading causes of mortality in the past decade and has led to high medical expenditure in many countries.[1,2] CAD is a significant health concern. In 2013, the total CAD prevalence for Americans aged ⩾20 years was 6.2%, and the prevalence was 3.3% among Asians aged ⩾18 years.[1] Projections show that by 2030,

[1]Institute of Clinical Nursing, National Yang-Ming University, Taipei, Taiwan
[2]School of Nursing, National Yang-Ming University, Taipei, Taiwan
[3]Institute of Community Care, Director of School Health Research Center, National Yang-Ming University, Taipei, Taiwan
[4]Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan

Corresponding author:
Jen-Chen Tsai, School of Nursing, National Yang-Ming University, No. 155, Sec. 2, Li-Nong Street, Taipei, 112 Taiwan (ROC).
Email: jenchent@ym.edu.tw

CAD prevalence will increase to 18% in American adults.[1,3] Moreover, the overall CAD-caused death rate was 20% in Europe; the death rates per 100,000 were 102.6 for the USA,140.8 for Austria, 90.3 for the UK and 111.2 for Germany in 2013.[3,4] CAD causes significant morbidity and mortality and significantly contributes to disabilities in developed countries.[5] With advanced treatments, more people are able to live longer with symptomatic CAD. The effectiveness and accessibility of health care for people with CAD is crucial for preventing re-infarction and maintaining physical function.[6,7]

Chronic elevation of blood pressure (BP), blood lipid disorders, physical inactivity and a decline in functional capacity remain the major modifiable risk factors for CAD. Exercise-based rehabilitation programmes are some of the most widely recommended strategies for reducing these risks, thereby facilitating secondary prevention.[6–9] Secondary prevention interventions include exercise as an integral component of nursing care. In such programmes, nurses support the management of patients in the vulnerable period following hospital discharge.[10] Considering the inadequate provisions of cardiac rehabilitation services in many countries and the present emphasis on cost containment, further analysis is warranted in order to examine the relative efficacy of exercise programmes for patients with CAD. In 2004, a systemic review and meta-analysis revealed that exercise-based cardiac rehabilitation reduced cardiac mortality and improved triglyceride (TG) levels and systolic BP (SBP), but no significant changes were found in high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels and diastolic BP (DBP) in CAD patients.[11] More recently, two meta-analyses focusing on the effect of exercise-based cardiac rehabilitation for CAD on cardiovascular mortality discovered inconsistent results in re-infarction and all-cause mortality rates.[7,8]

From a nurse's perspective, the effects of exercise programmes on cardiovascular risk factors and functional capacity among CAD patients are concerning issues.[6,10] Furthermore, the effects of exercise training vary with exercise modality; thus, the exercise dose that would optimise benefits for patients with CAD remains unclear.[12,13] Other factors affecting the assessment of exercise training are the differences in the measured outcome variables. Exercise recommendations are likely to vary according to these differences. Therefore, it is important to update prior systemic reviews and meta-analysis results in order to examine the training modality of endurance exercise programmes (type, volume, and duration of exercise training intervention programme), as well as to investigate the overall effectiveness of exercise training programmes on cardiovascular risk factors and functional capacity for CAD patients.

Aims

This study (a) conducted a systemic review and meta-analysis of current randomised controlled trials (RCTs) in order to update and assess the effects of endurance exercise training on patients with CAD by considering the magnitude of changes in major cardiovascular risk factors, functional capacity and cardiac functioning, and (b) examined whether the magnitudes of change in these measured variables were related to the characteristics of the exercise programme. Our findings would help to establish a scientific basis for the provision of specific exercise guidance for patients with CAD.

Methods

This review was conducted in accordance with the guidelines of the Preferred Reporting Items for Systemic Reviews and Meta-Analyses[14] and recommendations from the Cochrane Collaboration.

Search strategy

The electronic databases PubMed, Medline, CINAHL, EMBASE and the Cochrane Library were searched using search strategies focusing on aerobic endurance exercise interventions conducted with patients diagnosed with CAD. The searches were limited to RCTs published in English between January 1, 2000, and May 31, 2015. The literature search was conducted using search terms categorising aerobic exercise intervention, cardiovascular risk factors, functional capacity, cardiac function and CAD. Furthermore, the references of the included studies and any relevant reviews and meta-analyses were manually searched. Two reviewers (Y-CC and J-CT) independently screened the titles and abstracts of each identified article and read potentially eligible articles in full to determine whether they met the inclusion criteria. Disagreements were reviewed by a third reviewer (Y-ML), and then all the reviewers discussed them item by item together according to the inclusion criteria until consensus was reached.

Inclusion and exclusion criteria

Studies were considered as eligible if they were RCTs and included patients who had experienced a myocardial infarction (MI), coronary artery bypass graft or percutaneous coronary intervention, or had CAD diagnosed through angiography (⩾70% stenosis of at least one major coronary artery). Considering the effective duration of exercises, we included RCTs that had an intervention duration of 8–24 weeks, an exercise frequency of ⩾3 times/week and an individual exercise session duration of ⩾20 minutes of at least moderate intensity. These criteria were in concordance with previous guidelines.[15,16] Additional inclusion criteria for the present analysis were as follows: (a) study participants aged ⩾20 years; (b) RCTs that investigated the effects of dynamic endurance exercise; and (c) RCTs that compared an aerobic exercise programme with usual care or no endurance exercise intervention. In this review, we excluded studies involving patients who had other medical conditions, such as severe chronic heart failure.

Measured outcomes

For inclusion, RCTs had to assess one of the major cardiovascular risk factors (the primary outcomes), namely resting BP, plasma HDL-C, LDL-C or total cholesterol levels or TC levels. Functional capacity, as directly measured by peak oxygen consumption (peak VO_2) on the basis of exercise testing, and the left ventricular ejection fraction (LVEF), determined by echocardiography studies, were defined as the secondary outcomes.

Study quality assessment

The Physiotherapy Evidence Database (PEDro) scale was used to assess the methodological quality of each study.[17–19] The score ranged from 0 to 10, with a higher score indicating higher quality. The quality appraisal and data extraction results of each selected study were independently recorded by two reviewers. Disagreements were resolved by discussion or a third reviewer.

Data extraction and statistical analysis

Comprehensive meta-analysis V2 software (Biostat, NJ, USA) was used to analyse the extracted data and calculate the mean difference of the effect size and 95% confidence intervals (CIs). Variances were calculated from the pooled standard deviation of the change scores between the intervention and control groups. Heterogeneity between study results was assessed and quantified using the Cochrane Q and I^2 statistic tests.[20,21] Data from each trial were pooled using a fixed-effects model. When substantial heterogeneity existed according to the I^2 statistic, a random effects model was used.[22] Subgroup analysis was conducted in order to investigate the relationships between the magnitudes of change in outcome variables and the dose of intervention. In addition, the present analysis calculated the fail-safe n,[22] and a funnel plot was drawn for each outcome variable in order to assess the risk of publication bias.[23–25]

Results

Literature search results

Figure 1 shows the literature search flowchart and the study inclusion results. In total, 1077 potentially relevant RCTs were initially identified after a comprehensive electronic database literature search. A total of 1010 articles were screened out based on the abstracts and titles. The main reasons for exclusions included: inappropriate population, such as patients with chronic heart failure, inadequate duration length of exercise programme, and lacking statistical information. A total of 18 RCTs[12,26–42] that met all of the inclusion criteria were selected.

Methodological quality of the studies

The PEDro scores of the 18 RCTs ranged from 5 to 8. These RCTs fulfilled the eligibility criteria, involved randomised allocation and had an appropriately matched intervention group at baseline. Of the 18 RCTs, one (5.5%) blinded the participants,[39] one (5.5%) blinded the therapists[42] and five (27.8%) blinded the assessors.[26–29,39] Funnel plots were used to detect the potential publication bias of the included RCTs. There was no significant publication bias as evidenced by funnel plot asymmetry. Therefore, publication bias is unlikely to have affected the results of the present meta-analysis.

Participant characteristics

The participants, applied exercise programmes and outcomes of the selected RCTs are presented in Table 1. These studies were conducted in the USA and different countries in Asia and Europe. Thirteen RCTs (72.2%)[26–30,32–34,37,38,40–42] included both men and women participants, and five RCTs (27.8%)[12,31,35,36,39] included only men. The sample sizes of the studies ranged from 25 to 269 participants. A total of 712 participants completed their exercise interventions, and 571 were in control groups. Seven RCTs (38.88%)[26,32–34,37,38,42] reported the attrition rates of the study participants, ranging from 4.2% to 20%, and the average dropout rate was 11.2%. The overall mean age of the study participants was 57 years (SD = 10.8).

Exercise interventions

Among the selected RCTs, one[39] comprised home-based and cardiac rehabilitation exercise groups, three[28,29,33] included exercise-based rehabilitation programmes, eight[12,26,27,30,31,34,38,42] had hospital-based or supervised outpatient exercise programmes, three[32,40,41] involved home-based exercise programmes and three[35–37] included combined outpatient and home-based exercise programmes. The intensity of aerobic training was determined according to the maximal heart rate (HRmax; $n = 4$; 60–85%), heart rate reserve (HRR; $n = 5$; 40–85%), functional capacity ($n = 6$; 55–70% peak VO_2) or anaerobic threshold by exercise testing ($n = 3$). The exercise frequency of the selected RCTs ranged from three to seven times per week, and the duration of each exercise session was 20–60 minutes. Five RCTs[26,27,29,34,42] reported their adherence rates for the exercise sessions, ranging from 75% to 94%.

Effects of exercise on primary outcome in cardiovascular risk factors

Figure 2 shows the forest plot of the changes in BP. Seven RCTs[12,26,30–34] compared resting SBP between the exercise ($n = 204$) and control ($n = 203$) groups. Endurance training resulted in a mean difference (MD) in SBP decrease of 3.8 mmHg ($p = 0.01$). The effect of exercise training on DBP was assessed in four studies,[12,32–34] with 105 participants in

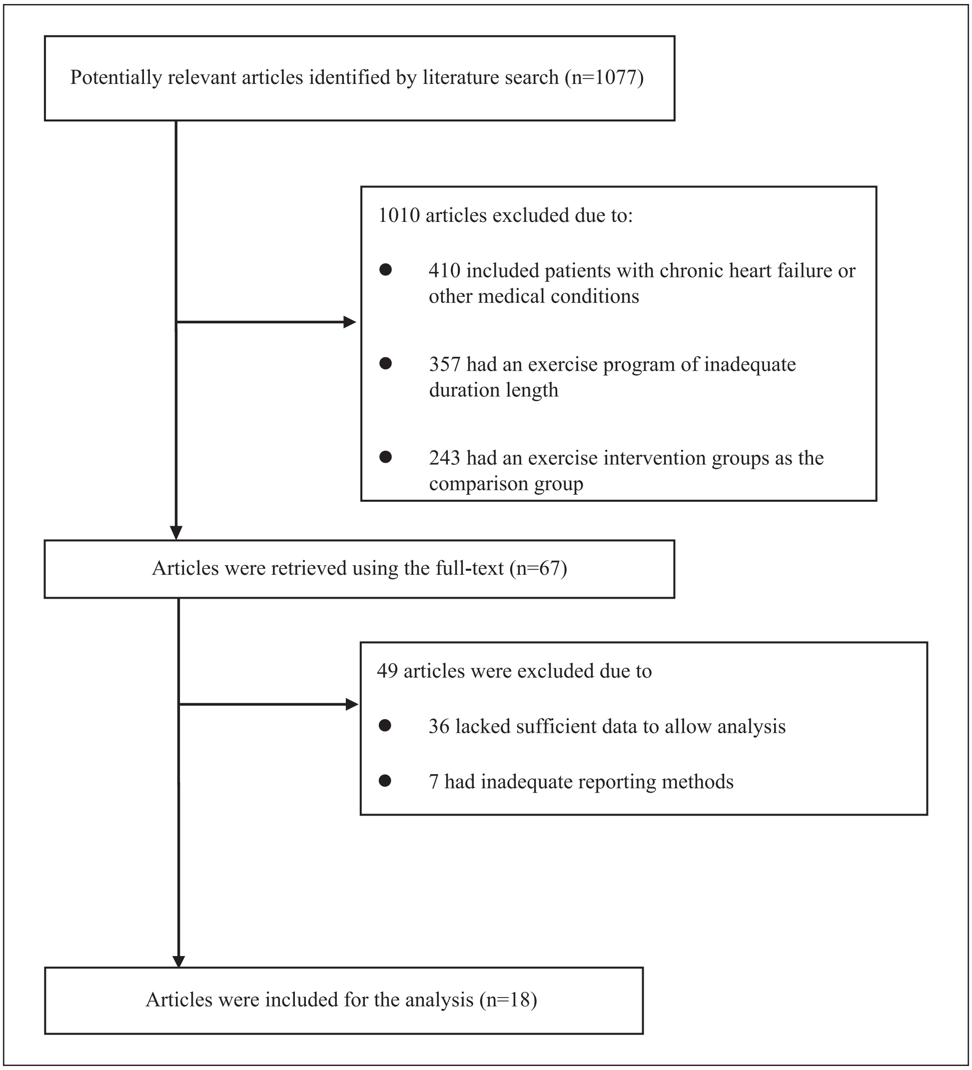


Figure 1. Flow chart of the literature search.

each group, and there was no statistically significant effect of exercise training on DBP (MD: −1.4 mmHg, $p = 0.25$).

Figure 3 shows the forest plot of the overall changes in the blood lipid profile. Data were analysed from four RCTs,[26,35,38,41] with 177 and 139 participants in the training and control groups, respectively. The meta-analysis results revealed a significant exercise training effect on LDL-C (MD: −5.5 mg/dL, $p = 0.02$) and HDL-C (MD: 3.8 mg/dL, $p < 0.001$) concentrations. Changes in TG (MD: −4.8 mg/dL, $p = 0.37$) and total cholesterol (MD: −13.2 mg/dL, $p = 0.28$) levels were not statistically significant.

Effects of secondary outcomes in exercise on peak VO_2 and LVEF

Figure 4 illustrates the changes in peak VO_2 and LVEF after the interventions. The effect of exercise training on peak VO_2 was reported in 14 RCTs,[12,26–31,33–37,39,42] which collectively had 405 and 390 participants in the training and control groups, respectively. One RCTs[39] compared home-based and cardiac rehabilitation exercise groups to a control group and was separated into two analyses. The results of this meta-analysis revealed a significant positive effect of exercise training on peak VO_2 (MD: 3.47 mL/kg/min, $p < 0.001$). Seven RCTs[26,28–31,40,42] with 369 and 275 participants in the training and control groups, respectively, were used in order to investigate the effect of dynamic exercise training on LVEF. LVEF values significantly improved among the participants in the training groups (MD: 2.6%, $p = 0.03$).

Subgroup analyses

Duration of exercise intervention. Among the selected RCTs[12,30–34,37–39] with an intervention duration of ⩽12 weeks (8–12 weeks), endurance exercise training significantly reduced SBP (MD: −3.3 mmHg, $p = 0.03$) and peak VO_2 (MD: 3.6 mL/kg/min, $p < 0.001$) compared with usual

Table 1. Study participants, programme characteristics and outcomes of the selected 18 trials.

First author (year)	Participants and country	Group (*n*) pre/post	Intervention (FITT)	Outcomes	PEDro score
Belardinelli[26] (2001)	CAD after PCI Mean age: 57 y 84.6% male USA	E: 67/59 C: 63/59	E: 3/week, 60% peak VO_2, hospital based (cycle ergometer), 30 min/session, total 24 weeks C: sedentary, do not exercise regularly	SBP (p = 0.02) peak VO_2 (p < 0.001) LVEF (p = 0.02) TC (p < 0.001) LDL-C (p < 0.001) HDL-C (p = 0.02) TG (p = 0.02)	6
Blumenthal[27] (2005)	Stable CAD (MI, CABG, angioplasty) Mean age: 63 y 69% male USA	E: 48/48 C: 42/42	E: 3/week, 70–85% HRR, supervised exercise training (walking, jogging), 35 min/session, total 16 weeks C: usual care	Peak VO_2 (p = 0.02)	8
Giallauria[30] (2006)	AMI at hospital discharge Age ⩾65 y 82.5% male Italy	E: 20/20 C: 20/20	E: 3/week, 60% peak VO_2, supervised outpatient (cycling), 30 min/session, total 12 weeks C: instruction of correct lifestyle	SBP (NS) Peak VO_2 (p < 0.001) LVEF (NS)	6
Giallauria[29] (2011)	2–4 weeks after MI (first event) Mean age: 60 y 80% male Italy	E: 37/37 C: 38/38	E: 3/week, 60–70% peak VO_2, exercise-based CRP (bicycle), 30 min/session, total 24 weeks C: usual care	Peak VO_2 (p < 0.001) LVEF (p < 0.001)	7
Giallauria[28] (2013)	Acute STEMI Mean age: 54 y 87% male Italy	E: 25/25 C: 21/21	E: 3/week, 60–70% peak VO_2, exercise-based CRP (bicycle), 30 min/session, total 24 weeks C: usual care	Peak VO_2 (p < 0.05) LVEF (p < 0.05)	7
Lee[31] (2008)	MI >3 months, Age ⩽65 y 100% male Taiwan	E: 20/20 C: 19/19	E: 3/week, 55–70% peak VO_2, RPE: 12–13, supervised outpatient (cycling), 20 min/session, total 12 weeks C: no training	SBP (NS) Peak VO_2 (p < 0.05) LVEF (NS)	6
Lee[32] (2013)	ACS with PCI Age: 18–80 y 80% male Korea	E: 30/26 C: 30/29	E: 4–5/week, 40–80% HRR, wireless home-based rehabilitation, 30 min/session, total 12 weeks C: usual care	SBP (NS) DBP (NS)	5
Myers[12] (2000)	Recent MI Mean age: 56 y 100% male Switzerland	E: 12/12 C: 13/13	E: 4/week, 60–70% peak VO_2, supervised exercise (cycling), 45 min/session, total 8 weeks C: usual clinical follow-up	SBP (NS) DBP (NS) Peak VO_2 (p < 0.05)	6
Oliveira[33] (2014)	Recent MI Mean age: 56 y 83.7% male Portugal	E: 49/47 C: 47/45	E: 3/week, 70–85% HR maximum, supervised exercise-based CRP (cycle ergometer or treadmill), 30 min/session, total 8 weeks C: usual care	SBP (p < 0.05) DBP (NS) Peak VO_2 (p < 0.05)	6
Ribeiro[34] (2012)	CAD patients 81.6% male Portugal	E: 24/20 C: 23/18	E: 3/week, 65–75% HR maximum, supervised outpatient exercise programme, 35 min/session, total 8 weeks C: usual care	Peak VO_2 (p < 0.05) SBP (NS) DBP (NS)	6
Seki[36] (2003)	Stable CAD (AMI, PCI, CABG >6 months) Age ⩾65 y 100% male Japan	E: 20/20 C: 18/18	E: 1/week (outpatient) + 2/week (home based), at anaerobic threshold level (walking or bicycling), 20–30 min/session, total 24 weeks C: standard care	Peak VO_2 (NS)	6

(Continued)

Table 1. (Continued)

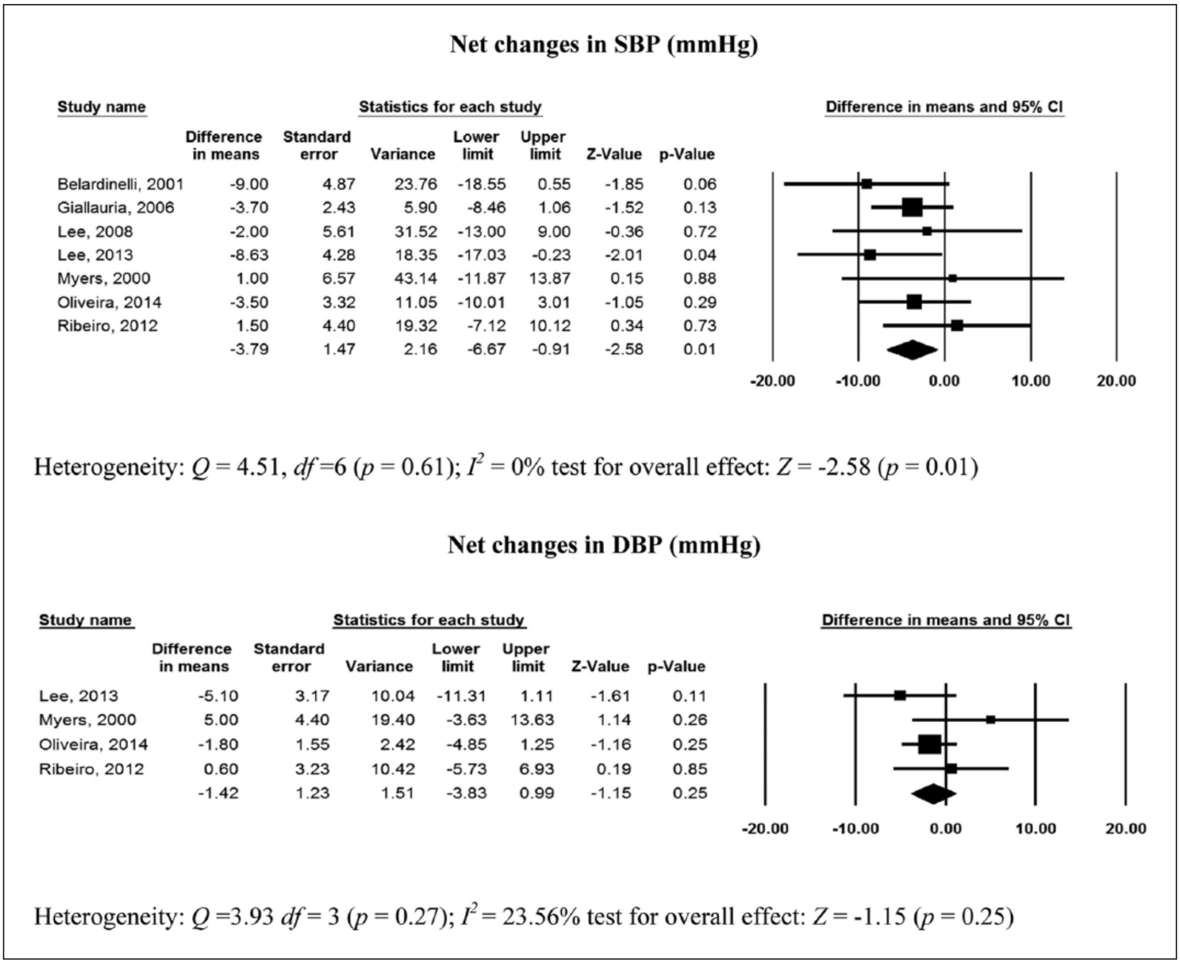
First author (year)	Participants and country	Group (n) pre/post	Intervention (FITT)	Outcomes	PEDro score
Seki[35] (2008)	CAD (AMI, PCI, CABG ⩾6 months) Age: ⩾65 y 100% male Japan	E: 20/18 C: 19/16	E: 1/week (outpatient, 20–60 min/session) + 2/week (home based, ⩾30 min/session), at anaerobic threshold or RPE: 12–13 (walking, bicycle), total 24 weeks C: usual outpatient care	Peak VO_2 (NS) TC (p < 0.05) TG (NS) HDL (p < 0.05) LDL (NS)	5
Tsai[37] (2006)	1 month after PTCA Age ⩽75 y 82.1% male Taiwan	E: 42/34 C: 42/33	E: 1–3/week, 60–85% HRR, supervised outpatient (cycle ergometer) combined 1–3 /week with home exercise, 40 min/session (average: 3.2± 1.1/week), total 8 weeks C: usual daily activities	Peak VO_2 (p < 0.001)	6
Vona[38] (2004)	Uncomplicated AMI ⩽3 weeks Age: <70 y 76.9% male Italy	E: 28/28 C: 24/24	E: 3/week, 75% HR maximum, supervised aerobic training (cycling), 40 min/session, total 12 weeks C: usual care	TC (NS) TG (NS) HDL (p < 0.05) LDL (NS)	7
Wu[39] (2006)	Pectoris angina with CABG Mean age: 62 y 100% male Taiwan	E: 18/18 C: 18/18	E: 3/week, 60–85% peak HR, A: CRP (bicycle, treadmill), B: home based, 30–60 min/session, total 12 weeks C: usual care	Peak VO_2 (p < 0.05) A, B	7
Yu[41] (2003)	CAD (AMI, PCI) Mean age: 61 y 79.5% male Hong Kong	E: 72/72 C: 40/40	E: 7/week, 65–85% HRR, home exercise, 60 min/session, total 24 weeks C: conventional therapy	TC (NS) LDL (p < 0.05) HDL (p < 0.05) TG (NS)	5
Yu[40] (2004)	CAD (AMI, PCI within 6 weeks) Mean age: 63 y 75% male Hong Kong	E: 181/181 C: 88/88	E: 7/week, 65–85% HRR or resting HR + 30, home exercise, 60 min/session, total 24 weeks C: conventional therapy	LVEF (NS)	5
Zheng[42] (2008)	AMI (3–7 days post-primary PCI) China	E: 30/27 C: 30/30	E: 3/week, at anaerobic threshold levels, supervised outpatient (cycling), 30 min/session, total 24 weeks C: routine therapy	LVEF (p < 0.01) Peak VO_2 (p < 0.01)	6

Participants: AMI: acute myocardial infarction; CAD: coronary artery disease; PCI: percutaneous coronary intervention; HF: heart failure; PTCA: percutaneous transluminal coronary angioplasty; CABG: coronary artery bypass grafting; STEMI: ST segment elevation myocardial infarction; ACS: acute coronary syndrome; y: years.
Group: E: exercise group; C: control group.
Intervention: FITT: frequency, intensity, type, time; HR: heart rate; HRR: heart rate reserve; CRP: cardiac rehabilitation programme; RPE: rating of perceived exertion; A and B represent the CRP and home-based exercise groups, respectively.
Outcome: Peak VO_2: peak oxygen consumption; DBP: diastolic blood pressure; SBP: systolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride; LVEF: left ventricular ejection fraction; TC: total cholesterol.

care. Among the RCTs[26–29,35,36,40–42] with an intervention duration of >12 weeks, exercise training had significant positive effects on HDL-C (MD: 4.50 mg/dL, p = 0.01), LDL-C (MD: −8.92 mg/dL, p = 0.04), TG (MD: −29.0 mg/dL, p < 0.001), peak VO_2 (MD: 3.1 mL/kg/min, p < 0.001) and LVEF (MD: 4.2%, p < 0.001).

Type of exercise programme. The studies that implemented exercise-based cardiac rehabilitation programmes[28,29,33] or supervised exercise programmes[12,26,27,30,31,33,34,42] showed significant training effects on SBP (MD: −3.2 mmHg, p = 0.04), HDL-C (MD: 2.0 mg/dL, p < 0.001), LDL-C (MD: −5.7 mg/dL, p = 0.04), peak VO_2 (MD: 3.6 mL/kg/min, p < 0.001) and LVEF (MD: 3.4%, p = 0.01) compared with control groups. The studies that mainly implemented home-based exercise programmes[35–37,39] showed significant effects on SBP (MD = −8.63 mmHg, p = 0.04) and peak VO_2 (MD: 2.3 mL/kg/min, p = 0.01).

Volume of exercise training. We conducted a subgroup analysis in order to compare the exercise effects of training programmes with a weekly exercise volume of 60–90 minutes



Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Belardinelli, 2001	-9.00	4.87	23.76	-18.55	0.55	-1.85	0.06
Giallauria, 2006	-3.70	2.43	5.90	-8.46	1.06	-1.52	0.13
Lee, 2008	-2.00	5.61	31.52	-13.00	9.00	-0.36	0.72
Lee, 2013	-8.63	4.28	18.35	-17.03	-0.23	-2.01	0.04
Myers, 2000	1.00	6.57	43.14	-11.87	13.87	0.15	0.88
Oliveira, 2014	-3.50	3.32	11.05	-10.01	3.01	-1.05	0.29
Ribeiro, 2012	1.50	4.40	19.32	-7.12	10.12	0.34	0.73
	-3.79	1.47	2.16	-6.67	-0.91	-2.58	0.01

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Lee, 2013	-5.10	3.17	10.04	-11.31	1.11	-1.61	0.11
Myers, 2000	5.00	4.40	19.40	-3.63	13.63	1.14	0.26
Oliveira, 2014	-1.80	1.55	2.42	-4.85	1.25	-1.16	0.25
Ribeiro, 2012	0.60	3.23	10.42	-5.73	6.93	0.19	0.85
	-1.42	1.23	1.51	-3.83	0.99	-1.15	0.25

Figure 2. Average net changes and 95% confidence intervals (CIs) for systolic blood pressure (SBP) and diastolic blood pressure (DBP) after exercise interventions.
df: degrees of freedom.

to weekly exercise training for longer than 90 minutes. The participants of the study programmes with a weekly exercise volume (represented by the frequency of exercise sessions/week × the duration of each session) of 60–90 minutes showed significant improvements in SBP (MD: −4.2 mmHg, $p = 0.02$), HDL-C (MD: 3.5 mg/dL, $p = 0.03$), TG level (MD: −29.4 mg/dL, $p < 0.001$), peak VO_2 (MD = 4.1 mL/kg/min, $p < 0.001$) and LVEF (MD: 3.4%, $p = 0.01$). The subgroup analysis also revealed no additional significant effects on the study outcomes in exercise interventions with a weekly training volume of longer than 90 minutes in comparison with the control groups.

Discussion

The PEDro scores of the 18 selected studies ranged from 5 to 8 out of 10 points, representing adequate quality. Although no clear cut-off point and unequivocal threshold score existed regarding acceptable methodological quality, according to the evidence and validation studies, Sherrington et al.[43] reported median PEDro scores of 4 and 5 based on 615 sports physiotherapy trials. Moreover, de Morton also presented the mean of total PEDro scores to be 4.8 from 1966–2009 publications.[19] The most common limitations in study design included lack of blinding. However, such blinding is often not possible in RCTs that involve exercise interventions.

The results demonstrate that endurance exercise training has a positive effect on the primary outcomes of the modifiable cardiovascular risk factors of SBP, HDL-C and LDL-C. Our findings are consistent with previous studies, and also demonstrate a significant improvement in secondary outcomes (peak VO_2 and LVEF). Notably, there were significant effects for exercise programmes with exercise durations ranging from 60 to 90 minutes weekly. A total of 20–30 minutes/day and 3–5 days/week of moderate- to vigorous-intensity exercise is recommended for most adults in order to obtain health/fitness benefits,[16,44] so the minimum dose selected was 60–90 minutes per week. This study revealed a significant reduction of 3.8 mmHg in SBP among CAD patients following dynamic endurance training. The lack of significant effect of exercise training on

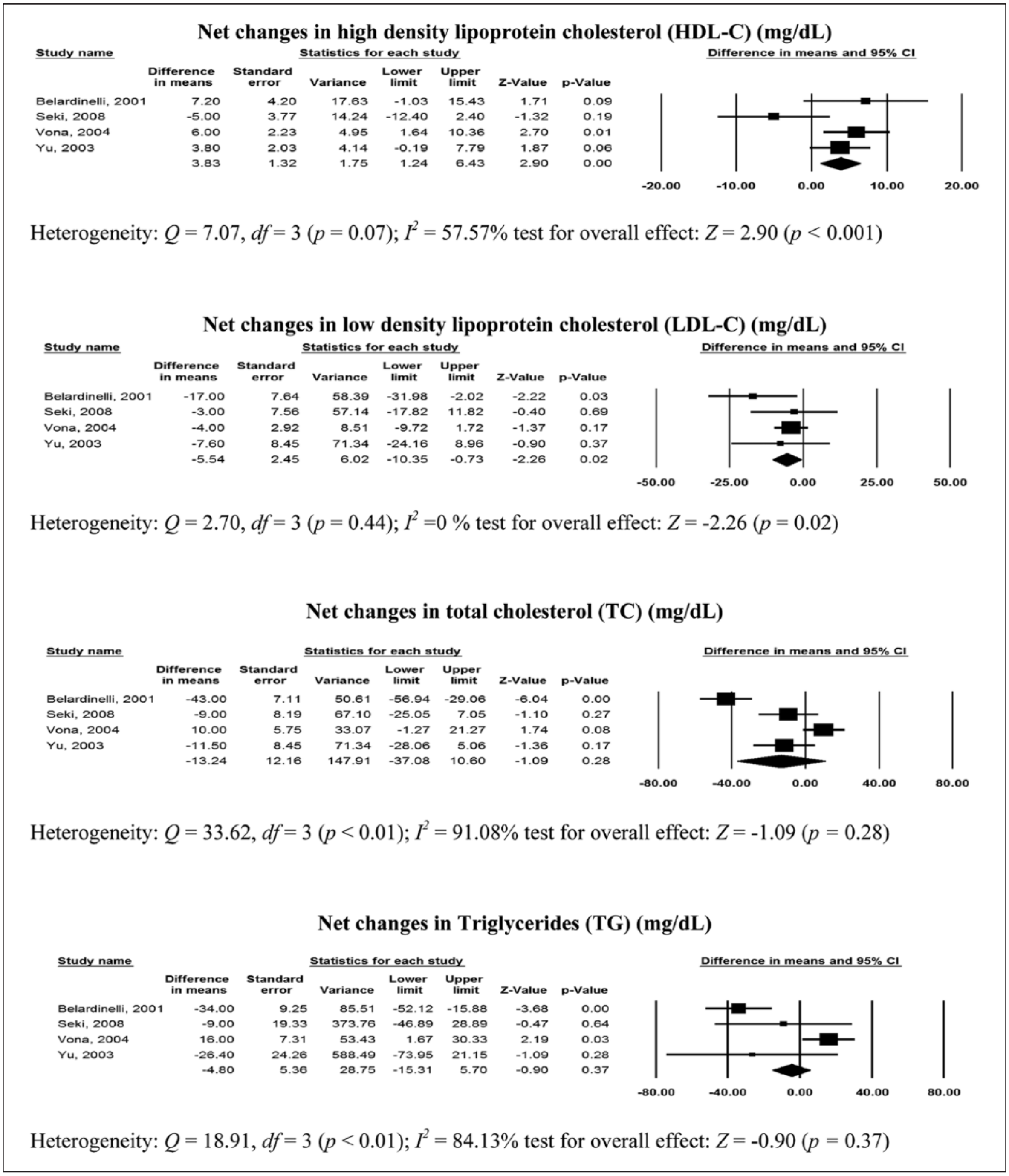


Figure 3. Average net changes and 95% confidence intervals (CIs) for blood lipid profiles after exercise interventions.
df: degrees of freedom.

DBP reductions in this meta-analysis might be partly because this analysis included the RCTs that were conducted with intervention durations of 8–12 weeks. The exercise guidelines provided by the American College of Cardiology (ACC)[16] and the American Heart Association (AHA) suggest that for an exercise to be effective at reducing cardiovascular risks, the exercise duration needs to last for, on average, 12 weeks.[44] The duration of exercise training intervention in the included studies (8–12 weeks) would not be long enough to make a significant change. Furthermore, the mean baseline DBP value of the study participants was classified as either pre-hypertensive (80–89 mmHg) or normal (<80 mmHg), so it was not easy to reduce DBP significantly. The factors discussed above might have contributed to the failure to detect a significant change in DBP.

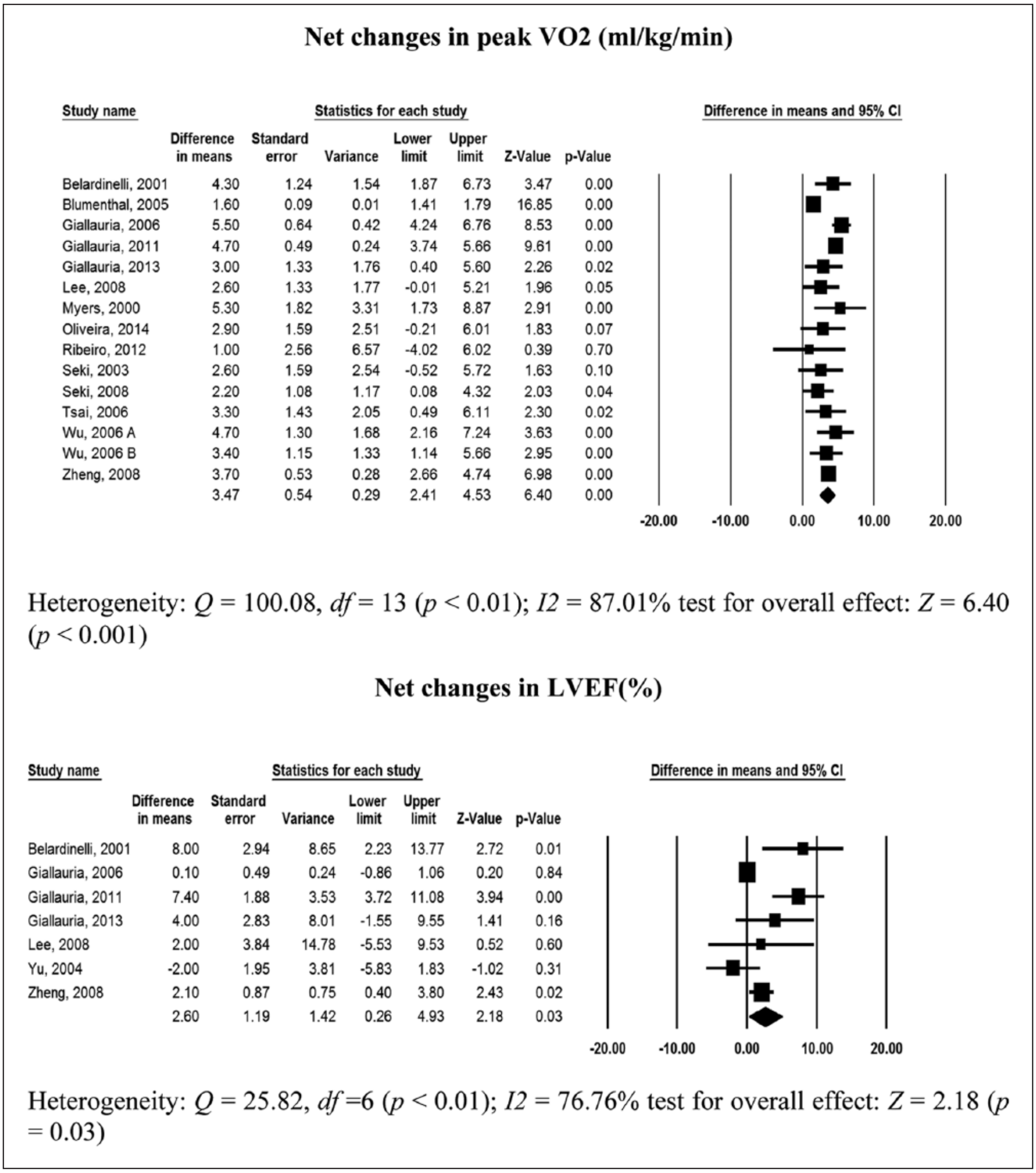


Figure 4. Average net changes and 95% confidence intervals (CIs) for peak oxygen consumption (peak VO_2) and left ventricular ejection fraction (LVEF) after exercise interventions.
Wu, 2006 A and Wu, 2006 B represents cardiac rehabilitation programme and home-based exercise groups respectively.
df: degrees of freedom.

HDL-C levels were significantly increased among the exercise participants when compared with their counterparts in the control groups. We also found a significant effect of exercise training on LDL-C, namely a reduction of 5.5 mg/dL. This is a crucial finding because a 1% reduction in LDL-C has been shown to reduce the risk of major coronary events by approximately 2%.[45] TG levels were not significantly reduced in our analysis. In our subgroup analyses, TG levels significantly decreased among the study participants who engaged in exercise training for >12 weeks (MD: −29.0 mg/dL, $p < 0.001$). This analysis included 50% of the RCTs that were implemented with exercise training durations of 8–12 weeks only. However, a previous study found that it should take at least 12 weeks in order to observe a clinically significant change in TG.[9] This means greater levels of more regular exercise could reduce the level of TG.[6,9] In addition, the exercise adherence and attrition rates were reported incompletely, so we could not investigate and infer the possibility of effectiveness. In future studies, exercise interventions should be implemented for >12 weeks in order to show the correlative effect for reducing TG levels.

Low functional capacity was reported to be a stronger predictor of cardiovascular diseases and mortality than other established risk factors.[46] In our meta-analysis, 14 RCTs reported an effect of endurance training on peak VO_2, with a significant mean increase of 3.5 mL/kg/min. Similar findings were reported in a meta-analysis involving 18 studies on CAD (net change of peak VO_2: 2.3 mL/kg/min) with training programme durations of 2–24 weeks.[47] An increase of one metabolic equivalent (equivalent to 3.5 mL/kg/min) in functional capacity was associated with a risk ratio for all-cause death of 0.84.[48] Our subgroup analysis results revealed that endurance exercise interventions significantly affected peak VO_2, regardless of the programme type (supervised or home based), training duration (8–12 weeks or >12 weeks) and weekly exercise volume (60–90 minutes or >90 minutes) when the intervention groups were compared with the usual care control groups.

LVEF was found to be a significant clinical parameter for assessing the prognosis of cardiovascular disease,[49,50] and it is currently widely used as such. For every 1% decrease in the LVEF value, the odds of death increased by a factor of 1.04.[51] The improvement in LVEF was probably due to revascularisation procedures or a resumption of cardiac function in patients with CAD recovering from their cardiac events. Despite the aforementioned factors, we found significant improvements in LVEF values among exercise participants compared with controls. This result is partly in agreement with previous systemic reviews that have reported a significant effect of endurance exercise on LVEF in patients with heart failure (MD: 2.59%, $p < 0.001$).[52] Our subgroup analysis results suggest that LVEF is evidently improved if the exercise programme lasts 12 weeks. Additional high-quality RCTs are warranted in order to confirm the effects of aerobic exercise training on LVEF among patients with CAD.

The present findings should be interpreted with consideration of the following limitations. First, we could not analyse numerous potentially confounding factors that may have affected the outcome variables, such as diet changes, body weight and comorbidities, due to a lack of original study report data. Second, five of the 18 selected RCTs included only men. While the remaining 13 RCTs included both men and women, there still remained a very large proportion of men among the study participants. This study's findings should not be generalised to women. Further investigation is required in order to adequately address this. Third, only five of the selected RCTs mentioned the attendance rate of the exercise participants. Considering the inadequate reporting of exercise adherence in the selected RCTs, we could not investigate the effect of compliance on the study outcomes; therefore, we suggest including this factor in future studies. Finally, the reviewed RCTs enrolled clinically stable patients with CAD. Patients with significant CAD-related complications were excluded from this analysis. Consequently, the present findings should not be generalised to patients with severe CAD complications. More randomized control studies are necessary to determine the safety and optimal duration of endurance exercise training for patients with CAD, particularly women patients and patients with comorbidities.

Conclusion

In this study, we analysed the effectiveness and magnitudes of change of cardiac outcomes in CAD patients on endurance exercise interventions. Our meta-analysis displayed novelty results to confirm that exercise training modalities conducted for 60–90 minutes per week at moderate to vigorous exercise intensity (approximately 60–85% HRR) for 12 weeks or longer show beneficial effects in CAD patients, including improved functional capacity, better cardiac function and reduced cardiovascular risk factors. Among those, a supervised exercise programme demonstrated positive effects on LVEF and peak VO_2 and reduced most cardiovascular risk factors, such as SBP, LDL-C and HDL-C, among clinically stable patients with CAD following cardiac events. This evidence may help advanced practice nurses when counselling cardiac patients in order to engage them in regular exercise aimed at achieving desired levels of physical activity and improving quality of life.

Implication for clinical practice

- It is evident that endurance exercise training provides important physiological benefits and continues to be a major approach to treating clinically stable CAD patients. It is found that, when training at moderate to high intensity, levels of SBP and LDL-C are reduced; the level of HDL-C and the values of LVEF and peak VO_2 are improved in CAD patients.
- Programme duration and amount of exercise are important factors in making exercise training programmes successful for CAD patients. Endurance exercise training with a programme duration of >12 weeks at 60–90 minutes/week favourably modifies most cardiovascular risk factors (SBP, LDL-C, HDL-C and TG) and improves LVEF and peak VO_2.
- Due to the fact that different types of exercise programme lead to different clinical effects, practicing nurses need to consider CAD patients' individual needs when planning exercise programmes. Supervised exercise programmes have significant effects on SBP, LDL-C, HDL-C, LVEF and peak VO_2, while a home-based exercise training programme can improve SBP and peak VO_2.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding

This research was financially supported by the Ministry of Science and Technology, Taiwan (NSC 101-2314-B-010-063-MY3).

References

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Executive summary: Heart disease and stroke statistics – 2016 update: A report from the American Heart Association. *Circulation* 2016; 133: 447–454.
2. World Health Organization (WHO). *Global Health Observatory (GHO) Data – The Top 10 Causes of Death*. 2014. Available at: http://www.who.int/mediacentre/factsheets/fs310/en/
3. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics – 2016 update: A report from the American Heart Association. *Circulation* 2016; 133: e38–e360.
4. Townsend N, Nichols M, Scarborough P, et al. Cardiovascular disease in Europe – Epidemiological update 2015. *Eur Heart J* 2015; 36: 2696–2705.
5. Racca V, Spezzaferri R, Modica M, et al. Functioning and disability in ischaemic heart disease. *Disabil Rehabil* 2010; 32: S42–S49.
6. Piepoli MF, Corra U, Benzer W, et al. Secondary prevention through cardiac rehabilitation: From knowledge to implementation. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev Rehabil* 2010; 17: 1–17.
7. Anderson L, Oldridge N, Thompson DR, et al. Exercise-based cardiac rehabilitation for coronary heart disease: Cochrane systematic review and meta-analysis. *J Am Coll Cardiol* 2016; 67: 1–12.
8. Lawler PR, Filion KB and Eisenberg MJ. Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: A systematic review and meta-analysis of randomized controlled trials. *Am Heart J* 2011; 162: 571–584.e2.
9. Menezes AR, Lavie CJ, Milani RV, et al. Cardiac rehabilitation in the United States. *Prog Cardiovasc Dis* 2014; 56: 522–529.
10. Riley JP, Astin F, Crespo-Leiro MG, et al. Heart failure association of the European Society of Cardiology heart failure nurse curriculum. *Eur J Heart Fail* 2016; 18: 736–743.
11. Taylor RS, Brown A, Ebrahim S, et al. Exercise-based rehabilitation for patients with coronary heart disease: Systematic review and meta-analysis of randomized controlled trials. *Am J Med* 2004; 116: 682–692.
12. Myers J, Goebbels U, Dzeikan G, et al. Exercise training and myocardial remodeling in patients with reduced ventricular function: One-year follow-up with magnetic resonance imaging. *Am Heart J* 2000; 139: 252–261.
13. Naughton J, Dorn J, Oberman A, et al. Maximal exercise systolic pressure, exercise training, and mortality in myocardial infarction patients. *Am J Cardiol* 2000; 85: 416–420.
14. Moher D, Liberati A, Tetzlaff J, et al.; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Ann Intern Med*. 2010; 8: 336–341.
15. Corra U, Mendes M, Piepoli M, et al. Future perspectives in cardiac rehabilitation: A new European Association for Cardiovascular Prevention and Rehabilitation Position Paper on 'secondary prevention through cardiac rehabilitation'. *Eur J Cardiovasc Prev Rehabil* 2007; 14: 723–725.
16. American College of Sports Medicine (ACSM). *ACSM's Guidelines for Exercise Testing and Prescription*. Baltimore, MD: Lippincott Williams & Wilkins, 2014.
17. Maher CG, Sherrington C, Herbert RD, et al. Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phys Ther* 2003; 83: 713–721.
18. Moseley AM, Herbert RD, Sherrington C, et al. Evidence for physiotherapy practice: A survey of the physiotherapy evidence database (PEDro). *Aust J Physiothe* 2002; 48: 43–49.
19. de Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: A demographic study. *Aust J Physiother* 2009; 55: 129–133.
20. Borenstein M, Hedges LV, Higgins JPT, et al. *Introduction to Meta-Analysis*. West Sussex, UK: John Wiley & Sons, 2009.
21. Lipsey M and Wilson D. *Applied Social Research Methods Series: Vol. 49. Practical Meta-Analysis*. London: SAGE Publications, 2001.
22. Cooper H, Hedges LV and Valentine JC. *The Handbook of Research Synthesis and Meta-Analysis*. New York: Russell Sage Foundation, 2009.
23. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629–634.
24. Rosenberg MS. The file-drawer problem revisited: A general weighted method for calculating fail-safe numbers in meta-analysis. *Evolution* 2005; 59: 464–468.
25. Song F, Khan KS, Dinnes J, et al. Asymmetric funnel plots and publication bias in meta-analyses of diagnostic accuracy. *Int J Epidemiol* 2002; 31: 88–95.
26. Belardinelli R, Paolini I, Cianci G, et al. Exercise training intervention after coronary angioplasty: The ETICA trial. *J Am Coll Cardiol* 2001; 37: 1891–1900.
27. Blumenthal JA, Sherwood A, Babyak MA, et al. Effects of exercise and stress management training on markers of cardiovascular risk in patients with ischemic heart disease: A randomized controlled trial. *JAMA* 2005; 293: 1626–1634.
28. Giallauria F, Acampa W, Ricci F, et al. Exercise training early after acute myocardial infarction reduces stress-induced hypoperfusion and improves left ventricular function. *Eur J Nucl Med Mol Imaging* 2013; 40: 315–324.
29. Giallauria F, Cirillo P, D'Agostino M, et al. Effects of exercise training on high-mobility group box-1 levels after acute myocardial infarction. *J Card Fail* 2011; 17: 108–114.
30. Giallauria F, Lucci R, De Lorenzo A, et al. Favourable effects of exercise training on N-terminal pro-brain natriuretic peptide plasma levels in elderly patients after acute myocardial infarction. *Age Ageing* 2006; 35: 601–607.
31. Lee BC, Chen SY, Hsu HC, et al. Effect of cardiac rehabilitation on myocardial perfusion reserve in postinfarction patients. *Am J Cardiol* 2008; 101: 1395–1402
32. Lee YH, Hur SH, Sohn J, et al. Impact of home-based exercise training with wireless monitoring on patients with acute coronary syndrome undergoing percutaneous coronary intervention. *J Korean Med Sci* 2013; 28: 564–568.

33. Oliveira NL, Ribeiro F, Teixeira M, et al. Effect of 8-week exercise-based cardiac rehabilitation on cardiac autonomic function: A randomized controlled trial in myocardial infarction patients. *Am Heart J* 2014; 167: 753–761.e3.
34. Ribeiro F, Alves AJ, Teixeira M, et al. Exercise training enhances autonomic function after acute myocardial infarction: A randomized controlled study. *Rev Port Cardiol* 2012; 31: 135–141.
35. Seki E, Watanabe Y, Shimada K, et al. Effects of a phase III cardiac rehabilitation program on physical status and lipid profiles in elderly patients with coronary artery disease: Juntendo Cardiac Rehabilitation Program (J-CARP). *Circ J* 2008; 72: 1230–1234.
36. Seki E, Watanabe Y, Sunayama S, et al. Effects of phase III cardiac rehabilitation programs on health-related quality of life in elderly patients with coronary artery disease: Juntendo Cardiac Rehabilitation Program (J-CARP). *Circ J* 2003; 67: 73–77.
37. Tsai MW, Chie WC, Kuo TB, et al. Effects of exercise training on heart rate variability after coronary angioplasty. *Phys Ther* 2006; 86: 626–635.
38. Vona M, Rossi A, Capodaglio P, et al. Impact of physical training and detraining on endothelium-dependent vasodilation in patients with recent acute myocardial infarction. *Am Heart J* 2004; 147: 1039–104639.
39. Wu SK, Lin YW, Chen CL, et al. Cardiac rehabilitation vs. home exercise after coronary artery bypass graft surgery: A comparison of heart rate recovery. *Am J Phys Med Rehabil* 2006; 85: 711–717.
40. Yu CM, Li LS, Lam MF, et al. Effect of a cardiac rehabilitation program on left ventricular diastolic function and its relationship to exercise capacity in patients with coronary heart disease: Experience from a randomized, controlled study. *Am Heart J* 2004; 147: 11–18.
41. Yu C-M, Li LS-W, Ho H, et al. Long-term changes in exercise capacity, quality of life, body anthropometry, and lipid profiles after a cardiac rehabilitation program in obese patients with coronary heart disease. *Am J Cardiol* 2003; 91: 321–325.
42. Zheng H, Luo M, Shen Y, et al. Effects of 6 months exercise training on ventricular remodelling and autonomic tone in patients with acute myocardial infarction and percutaneous coronary intervention. *J Rehabil Med* 2008; 40: 776–779.
43. Sherrington C, Moseley AM, Herbert RD, et al. Ten years of evidence to guide physiotherapy interventions: Physiotherapy Evidence Database (PEDro). *Br J Sports Med* 2010; 44: 836–837.
44. Riebe D, Franklin BA, Thompson PD, et al. Updating ACSM's recommendations for exercise preparticipation health screening. *Med Sci Sports Exerc* 2015; 47: 2473–2479.
45. Pedersen TR, Olsson AG, Færgeman O, et al. Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). *Circ* 1998; 97: 1453–1460.
46. Lee DC, Artero EG, Sui X, et al. Mortality trends in the general population: The importance of cardiorespiratory fitness. *J Psychopharmacol* 2010; 24: 27–35.
47. Valkeinen H, Aaltonen S and Kujala UM. Effects of exercise training on oxygen uptake in coronary heart disease: A systematic review and meta-analysis. *Scand J Med Sci Sports* 2010; 20: 545–55.
48. Laukkanen JA, Rauramaa R, Salonen JT, et al. The predictive value of cardiorespiratory fitness combined with coronary risk evaluation and the risk of cardiovascular and all-cause death. *J Intern Med* 2007; 262: 263–272.
49. Clavel M-A, Ennezat PV, Maréchaux S, et al. Stress echocardiography to assess stenosis severity and predict outcome in patients with paradoxical low-flow, low-gradient aortic stenosis and preserved LVEF. *JACC Cardiovas Imaging*. 2013; 6: 175–183.
50. Dayan V, Vignolo G, Magne J, et al. Outcome and impact of aortic valve replacement in patients with preserved LVEF and low-gradient aortic stenosis. *J Am Coll Cardiol* 2015; 66: 2594–2603.
51. Bosch X and Theroux P. Left ventricular ejection fraction to predict early mortality in patients with non-ST-segment elevation acute coronary syndromes. *Am Heart J* 2005; 150: 215–220.
52. Haykowsky MJ, Liang Y, Pechter D, et al. A meta-analysis of the effect of exercise training on left ventricular remodeling in heart failure patients: The benefit depends on the type of training performed. *J Am Coll Cardiol* 2007; 49: 2329–2336.