



The role of the characteristics of exercise-based cardiac rehabilitation program in the improvement of lipid profile level: A systematic review and meta-analysis

Mohammad Javaherian⁽¹⁾, Narges Dabbaghipour⁽²⁾, Zinat Mohammadpour⁽³⁾, Behrouz Attarbashi Moghadam⁽⁴⁾

Meta-analysis

Abstract

BACKGROUND: The current study aimed to update prior systematic review and meta-analyses (SRMA) in order to determine the effects of supervised exercise-based cardiac rehabilitation (EBCR) and introduce a suitable exercise protocol for management of lipid profile abnormalities in patients with cardiovascular disease (CVD).

METHODS: PubMed, Scopus, and Web of Science databases were searched from 1980 to December 2018. All published, randomized controlled trials (RCTs) reporting the efficacy of supervised EBCR in patients with CVD and measuring at least 1 component of lipid profile were included. The quality of articles was assessed based on the Physiotherapy Evidence Database (PEDro) scale. Random effect model was used to calculate the effect size of post-intervention data.

RESULTS: Initially 774 RCTs were reviewed, 14 of them were included in the study. In comparison with the control group, supervised EBCR was associated with higher serum levels of high-density lipoprotein (HDL) [weight mean difference (WMD): 1.297; 95% confidence interval (CI): -1.620, 4.214] and lower serum level of low-density lipoprotein (LDL) (WMD: -7.797; 95%CI: -14.005, -1.588), total cholesterol (TC) (WMD: -11.029; 95%CI: -20.716, -1.342), and triglyceride (TG) (WMD: -14.602; 95%CI: -28.992, -0.212).

CONCLUSION: It seems that EBCR is correlated with an insignificant increase in HDL serum level and a significant decrease in LDL, TC, and TG serum levels. Considering subgroup analysis results, it is suggested that long duration, moderate exercise volume (EV), and combination of aerobic exercise (AE) and resistance exercise (RE) be used to improve HDL and TG serum levels. Short duration, high EV, and AE+RE seem to significantly reduce LDL serum level. Moreover, moderate EV is associated with a significant reduction in TC level.

Keywords: Cardiac Rehabilitation; Cardiovascular Diseases; Exercise; Lipids; Meta-Analysis

Date of submission: 06 Feb. 2020, Date of acceptance: 10 Apr. 2020

Introduction

Cardiovascular diseases (CVDs) are important causes of increased mortality, morbidity, and physical disability.¹⁻³ Based on the World Health Organization (WHO) reports, 17.7 million people die every year from CVDs 75% of whom are from low-income and middle-income countries.⁴ Moreover, many studies report that unhealthy diet, physical inactivity, and obesity are the major causes of CVDs.⁵ Additionally, economic burden and poor quality of life (QOL) are negative impacts on patients' condition following CVD.^{6,7}

Effective treatments for CVDs include appropriate

pharmacotherapy, percutaneous coronary intervention (PCI), surgical procedures, and cardiac rehabilitation (CR). CR is a multi-disciplinary and comprehensive long-term program for secondary prevention, which comprises medical evaluation, aerobic

How to cite this article: Javaherian M, Dabbaghipour N, Mohammadpour Z, Attarbashi Moghadam B. **The role of the characteristics of exercise-based cardiac rehabilitation program in the improvement of lipid profiles level: A systematic review and meta-analysis.** ARYA Atheroscler 2020; 16(4): 192-207.

1- PhD Candidate, Liver Transplantation Research Center, Imam Khomeini Hospital Complex AND Department of Physiotherapy, School of Rehabilitation, Tehran University of Medical Sciences, Tehran, Iran

2- Department of Physiotherapy, School of Rehabilitation, Tehran University of Medical Sciences, Tehran, Iran

3- Liver Transplantation Research Center, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

4- Associate Professor, Department of Physiotherapy, School of Rehabilitation, Tehran University of Medical Sciences, Tehran, Iran

Address for correspondence: Behrouz Attarbashi Moghadam; Associate Professor, Department of Physiotherapy, School of Rehabilitation, Tehran University of Medical Sciences, Tehran, Iran; Email: attarbashi@tums.ac.ir

exercise (AE), resistance exercise (RE), education, and nutritional and psychological counseling.⁸

It is important that patients with CVD participate in CR due to medical complications, prolonged bed rest, and disability that occur after CVD.⁹ It seems that the most important cardiovascular outcomes of CR are the reduction of morbidity, hospital readmissions, risk of future cardiac events, and cardiac risk factors such as lipid profile and blood pressure.¹⁰⁻¹²

Lipid profile includes serum total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and total triglycerides (TG) factors. It is suggested that HDL serum level, and TC/HDL and TG/HDL ratios are associated with all-cause mortality and risk of hospitalization in patients with CVD.¹³ In addition, some studies indicate that short-term CR can reduce TC, LDL, and TG serum levels in patients with CVD.^{14,15}

The effect of the supervised exercise-based cardiac rehabilitation (EBCR) program has been reviewed in patients with coronary artery disease (CAD) in previous systematic review and meta-analyses (SRMA).^{16,17} Due to the importance of lipid profile as an essential risk factor for CVD and high risk of CVD occurrence in patients without controlled LP, we updated prior SRMAs. Although the CR program is a multi-professional program, the main objective of the current study was to only evaluate the exercises of the CR program. Therefore, the current SRMA aimed to determine and evaluate the effect of EBCR on lipid profile in patients with CVD. The second aim of the study was to determine and recommend the best exercise training characteristics for the improvement of lipid profile in patients with CVD.

Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were employed to perform the current SRMA.

Searching methods

The three online databases of PubMed, Scopus, and Web of Science were systematically searched from 1980 to December 2018 to identify the potentially relevant studies. Moreover, all references cited in the included studies and relevant review articles were checked to find other potential studies.

The inclusion criteria were as follows:

Type of study: All human studies with randomized controlled trial (RCT) design were included. If an article had more than 1 intervention group receiving different types of exercises, we split it into 2 (or more) studies and each intervention group was

separately compared with the control group. Language was not a limitation in the current study.

Type of participants: All studies on patients with CVD were included. All patients must have a stable medical condition to participate in the CR program. Both studies with and without surgical procedure were eligible for the current SRMA.

Type of intervention: Studies using the supervised EBCR with a focus on exercise training (ET) with or without dietary, psychological, or lifestyle counseling were included. Control group was defined as a group that received only medication, usual care, or education about risk factors. Studies with home exercise prescription in the intervention or control group were not included. Furthermore, all studies with a dietary prescription, and psychological or lifestyle counseling in the control group were excluded.

Type of outcome measures: Studies that investigated at least 1 of the lipid profile components were included. Data on general items, characteristics of the CR program, main outcome measures, and predefined criteria were extracted from articles. General items included the name of the first author, publication year, type and phase of CVD, as well as number, age, gender, and body mass index (BMI) of participants in the intervention and control groups. Characteristics of the CR program: included duration, number of sessions per week (frequency), and other received interventions in the experimental and control groups. The main outcome measurements comprised HDL, LDL, TC, and TG serum levels. The predefined criteria included the baseline BMI of participants (BMI < 18 kg/m² as underweight, 18 ≤ BMI < 25 kg/m² as normal weight, 25 ≤ BMI < 30 kg/m² as overweight, and BMI ≥ 30 kg/m² as obese),¹⁸ quality of included articles [Physiotherapy Evidence Database (PEDro) ≤ 3 as low-quality, 4 ≤ PEDro ≤ 6 as medium-quality, and 7 ≤ PEDro ≤ 9 as high-quality], duration of CR (0-8 weeks as short, 9-12 weeks as medium, and 13-24 weeks as long), frequency of CR program (1-2 or 3-4 times per week), and exercise volume (EV) (duration of CR session × frequency) (EV < 120 minute/week as low, 120 ≤ EV < 180 minute/week as moderate, and EV ≥ 180 minute/week as high).

Searching and data extraction procedure: Two independent authors systematically searched the databases and reviewed titles and abstracts. The full texts of all included studies were rechecked. If a full-text paper or its download or purchase link was not available on the website of the database or journal, 3 e-mails during 3 months were sent to the

corresponding author and the full-text article was requested. Data of all included studies were extracted by 2 independent authors. Disagreements between the authors were resolved by a third party. In case of lack of data in the included studies, 2 e-mails requesting data were sent to the corresponding author within a 2-week interval.

Quality assessment: The full texts of all included studies were reviewed and critically appraised by 2 authors using the PEDro scale.¹⁹ Since patient and therapist blinding is not possible in CR interventions, the maximum score of studies was 9.

Data synthesis and statistical analysis: The post-intervention data were employed for analysis in the current meta-analysis. Post-intervention mean \pm SD of lipid profile was extracted from articles. If the confidence interval (CI) was reported in a study, SD was calculated from upper limit, lower limit, and total number of participants in the group. Due to there being more than 1 effect size among studies, the random effect model (Der Simonian-Laird) was employed to calculate the overall effect size. Cochran Q test and I² analysis, with the significance level of < 0.1, were applied to calculate the heterogeneity between studies.²⁰ Moreover,

subgroup analysis was performed based on the predefined criteria to find the potential source of heterogeneity and identify the effect of each criterion. Furthermore, Egger's test was used to assess any potential publication bias and funnel plots were drawn to illustrate it, P-value < 0.050 was considered the level of significance. All of the statistical analyses were performed in Stata software (version 11.2; StataCorp., College Station, TX, USA).

Results

In total, 774 potentially relevant articles were identified through an online search, 725 of which were excluded after scrutiny of titles and abstracts. In addition, 3 articles were found through a manual search. The full text of 4 papers could not be found after searching the scientific databases and websites of related journals. Thus, 3 e-mails were sent to their corresponding authors, but no response was received; therefore, they were excluded from the study.²¹⁻²⁴ Moreover, 3 articles were in languages other than English.²⁵⁻²⁷ These articles were translated into English by native or expert translators. Finally, 12 articles were selected for the current SRMA²⁷⁻³⁸ (Figure 1).

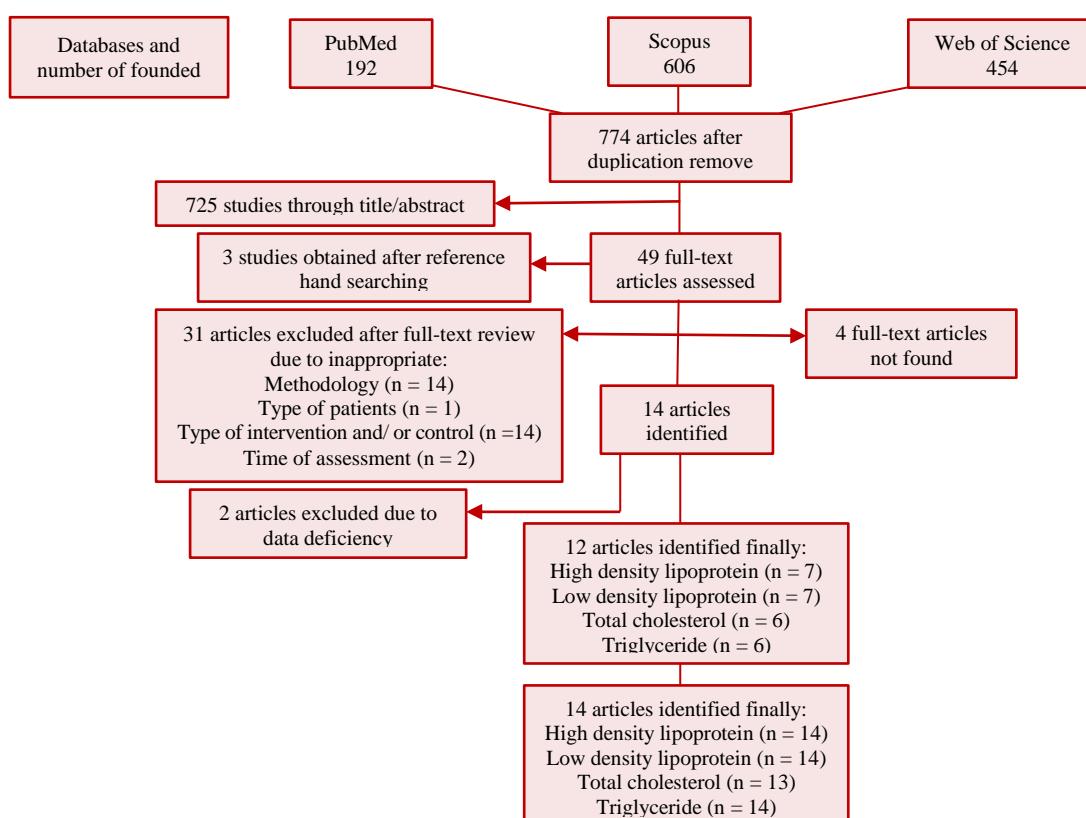


Figure 1. The flow diagram for the identification of the eligible articles evaluating the effect of cardiac rehabilitation on lipid profile
RCT: Randomized controlled trials

Table 1. Summary of characteristics of the included studies

First Author	Type of disease	Sample size		Mean age		BMI		Other intervention	Intervention of cont.	
		Cont.	Int.	Cont.	Int.	Cont.	Cont.			
Wosornu et al. ²⁸	CABG	27	26	56.5	56.6	26.9	27.5	Medication	Medication	
		25		59.2		25.8				
Belardinelli et al. ²⁹	CAD with successful CA	59	59	53	59	24.3	23.9	Medication	Medication and Avoidance of physical training	
Yu et al. ³⁰	AMI or PCI	72	40	62.3	61.2	27.6	27.4	Domiciliary or vocational environment training by occupational therapist	Education about risk factors and disease and benefits of physical activity	
Vona et al. ³¹	Uncomplicated AMI	28	24	56	57	26.5	25.7	Encourage to increase daily physical activity	Avoidance of regular physical activity	
Volaklis et al. ³²	CAD (MI, CABG, CA)	11	10	58	51	NM	NM	NM	Usual daily activities	
Seki et al. ³⁴	AMI, CABG, & PCI	18	16	69	70	23.4	23.5	Medication	Medication & usual outpatient care	
Balen et al. ³³	Post-AMI with PCI	30	30	59	61	28.8	28	Standard care, 30 min supervised walking	Standard care	
Luk et al. ³⁵	CAD treated by medication	32	32	67.7	66.6	24.7	25.1	Education, Counseling, risk factor modification	Education, Counseling, risk factor modification	
Ghroubi et al. ²⁷	MI with coronary stenting CHF (LVEF: 35-55%), CHF with dilated or ischemic cardiomyopathy, CHF with ventricular rhythm	30	38	50	53	27.14	25.5	Education NM	NM NM	
Aksoy et al. ³⁶		19	19	63.7	57.5	28.4	29.1			
		19		59.6		30.1				
Hassan and Nahas ³⁷	PCI	30	30	52.6	53.8	30.3	30.2	Medication & risk factors education	Medication & risk factors education	
Tamburus et al. ³⁸	CAD: MI, PCI, CABG	12	10	56.2	60.4	28.7	28.3	NM	Usual daily activity	

Int.: Intervention; Cont.: Control; CABG: Coronary artery bypass graft; CAD: Coronary artery disease; CA: Coronary angioplasty; AMI: Acute myocardial infarction; PCI: Percutaneous coronary intervention; MI: Myocardial infarction; NM: Not mentioned; min: Minute; CHF: Cardiac heart failure; LVEF: Left ventricular ejection fraction

Cardiac rehabilitation and lipid profiles

Table 2. Details of cardiac rehabilitation program characteristics of the included studies

First Author	Start time of CR program	Type of Exercise(s)	Duration of exercise training	Intensity	Duration of CR (w)	Frequency (s/w)
Wosornu et al. ²⁸	NM	AE: arm circling and raising, step-ups, trunk rotation, bridging, hip abduction, trunk side lying, running, and star jumps RE: bench press, military press, biceps curl, upright row, pull down, push down, pulley row, quadriceps curl, hamstring curl, and sit ups	12-40 min	AE: start with 3*10 and increase over time RE: start with 3*10 and 2-5 kg with increase over time	24	3
Belardinelli et al. ²⁹	NM	Cycle ergometry	Warm-up: 15 min Main program: 30 min Cool-down: 8 min	Moderate aerobic training: 60% of peak O ₂ uptake	24	3
Yu et al. ³⁰	6 w	NM	60 min	Moderate aerobic training: 65 to 85% of maximum aerobic capacity	8	2
Vona et al. ³¹	0-3 w	Cycle ergometry	Warm-up: 10 min Main program: 40 min Cool-down: 10 min	Moderate aerobic training: 75% of maximum HR	12	3
Volaklis et al. ³²	NM	AE: walking, running, cycling, cycle ergometry RE: bench press, seated row, leg extension, pull down, peck-deck, hamstring curl, curl-ups, and back extension	AE (2 sessions): Warm-up: 10 min Main program: 30-40 min (15-20 min running on treadmill and 15-20 min on ergometer) Cool-down: 10 min RE (2 sessions): Warm-up: 10 min Main program: 30-40 min (8 stations) Cool-down: 10 min	Aerobic sessions: 60-80% of maximum HR Resistance sessions: 60% of 1-RM (2 to 3 sets of 12 to 15 repetitions)	24	4

Table 2. Details of cardiac rehabilitation program characteristics of the included studies (continue)

First Author	Start time of CR program	Type of Exercise(s)	Duration of exercise training	Intensity	Duration of CR (w)	Frequency (s/w)
Seki et al. ³⁴	≥ 24 w (Phase III)	Walking, bicycling, jogging, light isotonic exercises	Warm-up: 15 min Main program: 20-60 min Cool-down: 15 min	Moderate aerobic training Borg score: 12-13	24	1
Balen et al. ³³	6-9 d	Cycle ergometry	45 min	Moderate aerobic intensity: 50%-60% of peak O ₂ uptake	3	1
Luk et al. ³⁵	> 24 w	AE: treadmill, cycle ergometry, rowing, steps, arm ergometry RE: dumbbell, weight training	Warm-up: 5 min Main program: 50 min Cool-down: 5 min	AEs: 80% maximum HR (Progressive) RE: 80% maximum HR (Progressive)	8	3
Ghroubi et al. ²⁷	8-12 w	Cycle ergometry	Warm-up: 10 min Main program: 2*10 min (5 min rest) Cool-down: 10 min	70% maximum HR	8	3
Aksoy et al. ³⁶	NM	Ergometry	CAE: Warm-up: 5 min Main program: 25 min (with a certain intensity during the session) Cool-down: 5 min IAE: Warm-up: 5 min Main program: 25 min (60 s with determined intensity and 60 s with low intensity) Cool-down: 5 min	75% of peak O ₂ uptake (Progressive)	10	3
Hassan and Nahas ³⁷	> 48 w	Bicycle ergometry	Warm-up: 5-10 min Main program: 30 min Cool-down: 5-10 min	Mild to moderate intensity exercise: based on 11 to 14 of the Borg scale	24	3
Tamburus et al. ³⁸	MI > 24 w PCI & CABG > 12 w	Cycle ergometry	Warm-up: 10 min Main program: 30-40 min Cool-down: 5-10 min	Moderate intensity exercise: 110% of VAT	16	3

CR: Cardiac rehabilitation; w: Weeks; s/w: Session(s) per week; d: Days; NM: Not mentioned; AE: Aerobic exercise; RE: Resistance exercise; min: Minute; HR: Heart rate; CAE: Continuous aerobic exercise; IAE: Intermittent aerobic exercise; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass surgery; VAT: Ventilatory anaerobic threshold

Table 3. Quality assessment of included studies based on the PEDro scale

Item	Wosornu et al. ²⁸	Belardinelli et al. ²⁹	Yu et al. ³⁰	Vona et al. ³¹	Volaklis et al. ³²	Seki et al. ³⁴	Balen et al. ³³	Luk et al. ³⁵	Ghroubi et al. ²⁷	Aksoy et al. ³⁶	Hassan and Nahas ³⁷	Tamburus et al. ³⁸
Eligibility criteria specification	No	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes
Randomization allocation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Allocation concealment	No	No	No	No	No	No	No	No	No	No	No	Yes
Groups' similarity at baseline	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Subject blinding	No	No	No	No	No	No	No	No	No	No	No	No
Therapist blinding	No	No	No	No	No	No	No	No	No	No	No	No
Assessor blinding	Yes	Yes	No	Yes	No	No	No	Yes	No	No	No	No
Outcome measure obtaining from 85% of subjects initially allocated to groups	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Use of intention to treat analysis	Yes	Yes	No	No	No	No	Yes	Yes	Yes	No	No	No
Reporting between-group statistical comparisons	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Reporting point measures and measures of variability	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Total Quality	7 High	7 High	6 Medium	7 High	5 Medium	5 Medium	6 Medium	7 High	7 High	5 Medium	5 Medium	7 High

Characteristics of the included studies: A summary of the characteristics of the included studies is presented in table 1; 10 out of 12 articles had a two-arm parallel design (CR and control) and 2 articles had a three-arm parallel design. In one study with a control group, the AE+RE were applied to 2 groups.²⁸ In another one, Seki et al. randomly assigned the participants to 3 groups including continuous aerobic exercise (CAE), intermittent aerobic exercise (IAE), and the control group.³⁴ Each of these studies was divided into 2 independent studies. Therefore, 14 studies were analyzed in the current meta-analysis. The language of 11 articles was English, and 1 article was in French.²⁷ In total, 775 participants were included in the current SRMA (412 in the intervention group and 334 in the control group). The mean age of participants in the intervention and control groups was 58.7 ± 5.47 and 58.9 ± 5.46 years, respectively. Table 2 shows details of the CR program of each included study. The CR program started from 6-9 days after acute myocardial infarction (AMI) with PCI to 24 weeks after MI. In the study by Hassan and Nahas, patients were included if they had PCI history of less than 48 weeks. Therefore, the exact duration of PCI to CR program was unclear.³⁷ Moderate intensity was applied to all studies except 1 study that used high intensity exercise (80% of

maximum heart rate) in the intervention group.³⁵ All studies evaluated HDL, LDL, and TC serum levels. The outcome measures of 1 study did not contain serum TC level.²⁷

Results of quality assessment: All the included articles mentioned proper random allocation and baseline similarity of the groups. Assessor blinding was performed in 4 studies; 6 articles had high quality scores, and 6 had medium quality scores. A summary of the PEDro assessment domains of the included articles is provided in table 3.

Data pooling and meta-analysis: Regarding the serum HDL level, 3 studies reported significant difference,^{32,36,37} and 2 studies reported marginal significant difference^{30,31} between the groups after the interventions ($P < 0.050$). The forest plot of HDL analysis showed that the HDL serum level of 4 studies was lower in the intervention group than the control group at the end of the study.^{31,34,36} Significant change was not observed in HDL serum level after the intervention in any of the studies ($n = 14$; weight mean difference (WMD): 1.297; 95% CI: -1.620, 4.214; $P = 0.383$; Figure 2). Subgroup analysis revealed that in studies performed over a long duration with AR+RE and moderate EV, the HDL serum level increased significantly in comparison with the control group ($P < 0.010$; Table 4).

Table 4. Subgroup analysis of high-density lipoprotein based on random effect analysis

Subgroup	Effect size (n)	WMD (95% CIs)	P-within	I ² (%)	Q-test
Overall	14	1.297 (-1.620, 4.214)	0.383	72.6	< 0.001
BMI					
Not detected	1	-	-	-	-
Normal	3	1.759 (-5.270, 8.789)	0.624	60.1	0.081
Overweight	8	0.677 (-2.325, 3.680)	0.658	42.4	0.096
Obese	2	-2.279 (-18.068, 13.510)	0.777	91.8	< 0.001
Study quality					
Medium	7	0.856 (-3.253, 4.964)	0.683	80.1	< 0.001
High	7	1.507 (-2.210, 5.223)	0.427	44.7	0.093
Exercise duration					
Short	4	3.011 (0.331, 5.692)	0.028	0	0.882
Medium	3	-6.080 (-9.640, -2.520)	0.001	0	0.450
Long	7	4.259 (1.284, 7.235)	0.005	46.6	0.085
Exercise type					
AE	11	0.127 (-3.107, 3.360)	0.939	65.4	0.001
RE	1	3.870 (-4.301, 12.041)	0.353	-	-
AE+RE	2	6.804 (4.696, 8.911)	< 0.001	0	0.355
Exercise frequency					
1-2 times per week	3	0.990 (-3.730, 5.709)	0.681	54.2	0.113
3-4 times per week	11	1.411 (-2.262, 5.083)	0.452	76.2	< 0.001
Exercise volume					
Low	6	-1.561 (-6.203, 3.080)	0.510	55.4	0.047
Moderate	5	4.190 (1.811, 6.569)	0.001	0	0.726
High	3	1.906 (-6.591, 10.403)	0.660	91.5	< 0.001

AE: Aerobic exercise; RE: Resistance exercise; WMD: Weighted mean difference (mg/dl); HDL: High-density lipoprotein cholesterol; BMI: Body mass index

I²: Percent variation in WMD attributable to heterogeneity/ Q-test: Test for heterogeneity with significance of < 0.10/ P-Within: Test of WMD of sub-groups by random-effect model with significance of < 0.05

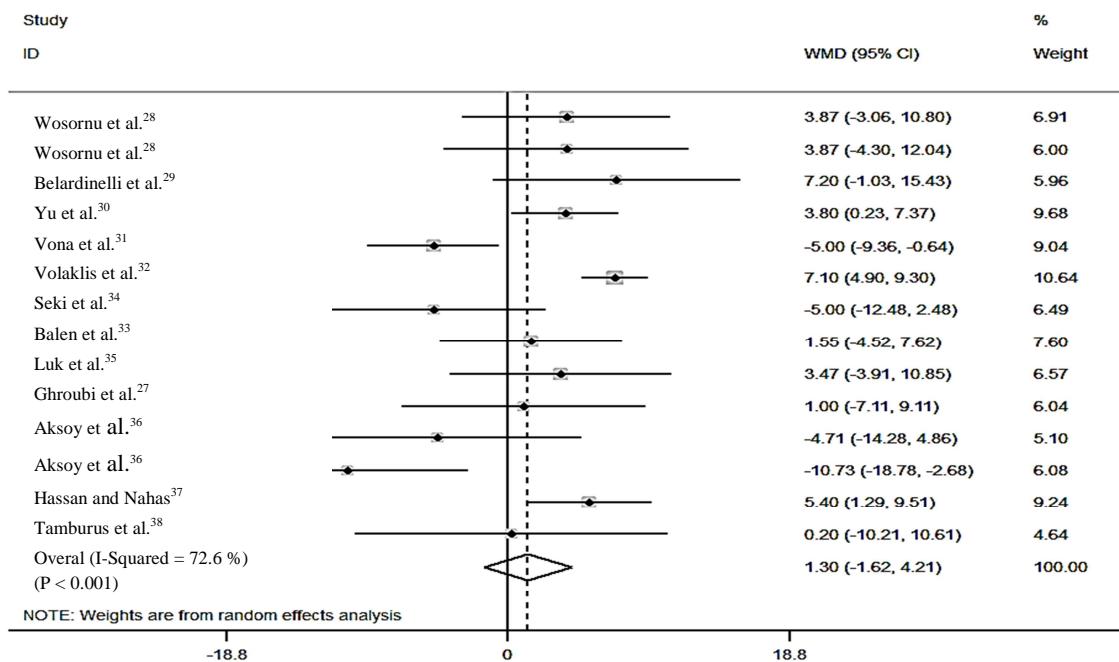


Figure 2. Forest plots of high-density lipoprotein serum level differences between the intervention and control groups after cardiac rehabilitation using random effect analysis
WMD: Weighted mean difference; CI: Confidence interval

In terms of serum LDL level, 4 out of 14 studies reported a significant difference between groups after the interventions ($P < 0.050$).^{29,32,33,37} Furthermore, 3 studies showed higher LDL serum level in the intervention group than the control group, although the difference was not significant.^{28,36,38} Pooling data of all studies showed

a significant difference in the LDL serum level after CR ($n = 14$; WMD = -7.797; 95%CI = -14.005, -1.588; $P = 0.014$; Figure 3). Subgroup analysis indicated that high-quality studies performed over a medium and long duration with AE+RE and low and moderate EV did not significantly change the serum level of LDL ($P > 0.050$; Table 5).

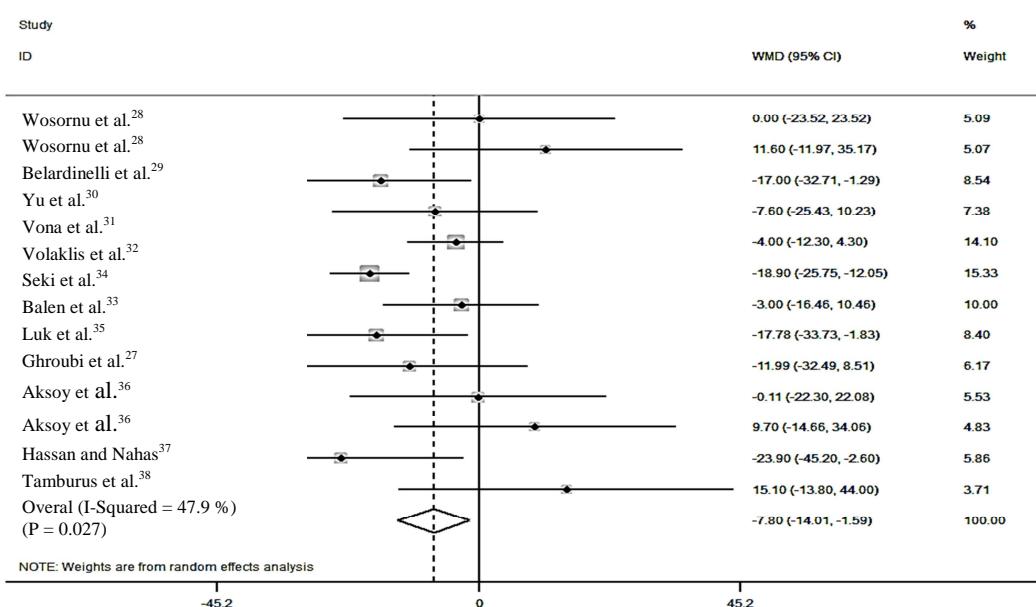


Figure 3. Forest plots of low-density lipoprotein serum level differences between the intervention and control groups after cardiac rehabilitation using random effect analysis
WMD: Weighted mean difference; CI: Confidence interval

Table 5. Subgroup analysis of low-density lipoprotein cholesterol based on random effect analysis

Subgroup	Effect size (n)	WMD (95% CIs)	P-within	I ² (%)	Q-test
Overall	13	-7.797 (-14.005, -1.588)	0.014	47.9	0.027
BMI					
Not detected	1	-	-	-	-
Normal	3	-9.536 (-18.682, -0.391)	0.041	0	0.401
Overweight	7	-3.810 (-10.428, 2.808)	0.259	9.3	0.385
Obese	2	-7.642 (-40.553, 25.268)	0.649	75.9	0.042
Study quality					
Medium	7	-10.846 (-18.946, -2.745)	0.009	46.5	0.082
High	6	-4.164 (-12.387, 4.059)	0.321	24.9	0.247
Exercise duration					
Short	3	-12.937 (-23.219, -2.655)	0.014	0	0.702
Medium	3	-2.300 (-9.707, 5.106)	0.543	0	0.568
Long	7	-8.160 (-18.206, 1.886)	0.111	60.5	0.019
Exercise type					
AE	10	-6.572 (-12.557, -0.587)	0.031	20.2	0.257
RE	1	11.600 (-11.965, 35.165)	0.335	-	-
AE+RE	2	-18.205 (-24.704, -11.706)	< 0.001	0	0.531
Exercise frequency					
1-2 times per week	3	-8.761 (-17.669, 0.148)	0.054	0	0.377
3-4 times per week	10	-6.802 (-14.786, 1.183)	0.095	57.1	0.013
Exercise volume					
Low	6	-2.485 (-11.091, 6.120)	0.571	15.9	0.312
Moderate	4	-10.949 (-24.170, 2.273)	0.105	42.3	0.158
High	3	-11.761 (-23.105, -0.416)	0.042	72.9	0.025

AE: Aerobic exercise; RE: Resistance exercise; WMD: Weighted mean difference (mg/dl); LDL: Low-density lipoprotein cholesterol; BMI: Body mass index

I²: Percent variation in WMD attributable to heterogeneity/ Q-test: Test for heterogeneity with significance of < 0.10/ P-Within: Test of WMD of sub-groups by random-effect model with significance of < 0.05

In terms of serum TC level, 3 of 14 studies^{29,32,34} reported a significant difference and 1 study³⁷ reported a marginal significant difference between the intervention and control groups after the intervention. The forest plot showed that in 2 studies, LDL serum levels were significantly higher in the intervention group than the control group.^{28,31} Pooling data of all

studies revealed significant differences in TC serum level after CR (n = 13; WMD = -11.029; 95% CI: -20.716, -1.342; P = 0.026; Figure 4). Subgroup analysis indicated insignificant differences in the TC serum level between the groups in the high-quality studies with low and high EV on subjects with overweight and obesity (P > 0.500; Table 6).

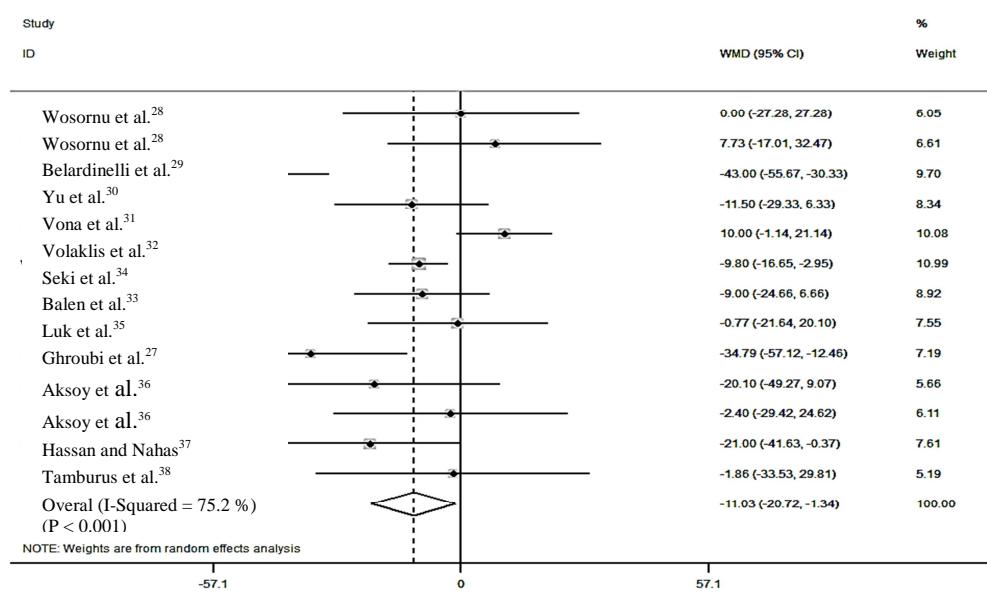


Figure 4. Forest plots of total cholesterol serum level differences between the intervention and control groups after cardiac rehabilitation using random effect analysis
WMD: Weighted mean difference; CI: Confidence interval

Table 6. Subgroup analysis of total cholesterol based on random effect analysis

Subgroup	Effect size (n)	WMD (95% CIs)	P-within	I ² (%)	Q-test
Overall	13	-11.029 (-20.716, -1.342)	0.026	75.2	< 0.001
BMI					
Not detected	1	-	-	-	-
Normal	3	-28.929 (-51.346, -6.512)	0.011	82.0	0.004
Overweight	7	0.768 (-7.330, 8.865)	0.853	10.8	0.347
Obese	2	-13.829 (-31.573, 3.915)	0.127	13.0	0.284
Study quality					
Medium	7	-10.069 (-15.361, -4.778)	< 0.001	0	0.851
High	6	-10.920 (-34.218, 12.377)	0.358	89.0	< 0.001
Exercise duration					
Short	3	-15.156 (-33.558, 3.246)	0.106	59.5	0.084
Medium	3	-0.053 (-17.385, 17.279)	0.995	48.8	0.142
Long	7	-13.050 (-26.423, 0.323)	0.056	77.7	< 0.001
Exercise type					
AE	10	-10.438 (-23.481, 2.605)	0.117	78.4	< 0.001
RE	1	7.730 (-17.014, 32.474)	0.540	-	-
AE+RE	2	-34.790 (-57.121, -12.459)	0.104	77.3	0.036
Exercise frequency					
1-2 times per week	3	-7.841 (18.089, 2.406)	0.134	0	0.732
3-4 times per week	10	-12.133 (-24.723, 0.457)	0.059	81.0	< 0.001
Exercise volume					
Low	6	-4.435 (-13.602, 4.733)	0.343	0	0.761
Moderate	4	-21.711 (-40.825, -2.598)	0.026	74.4	0.008
High	3	-9.296 (-28.526, 9.935)	0.343	87.1	< 0.001

AE: Aerobic exercise; RE: Resistance exercise; WMD: Weighted mean difference (mg/dl); LDL: Low-density lipoprotein cholesterol; BMI: Body mass index

I²: Percent variation in WMD attributable to heterogeneity/ Q-test: Test for heterogeneity with significance of < 0.10/ P-Within: Test of WMD of sub-groups by random-effect model with significance of < 0.05

Regarding the TG serum level, 2 studies reported a significant difference,^{29,32} and 1 study reported a marginal significant difference³⁷ after the interventions ($P < 0.050$). The current analysis showed that 3 studies revealed higher TG serum level in the intervention group than the control group at the end of the intervention.^{31,33,36} The combination of all studies

showed marginal significant differences in serum TG level after CR ($n = 14$; WMD = -14.602; 95% CI: -28.992, -0.212; $P = 0.470$; Figure 5). Subgroup analysis showed that studies performed over a short and medium duration with AE+RE and low and high EV on subjects with overweight did not decrease the serum TG level significantly ($P > 0.050$, Table 7).

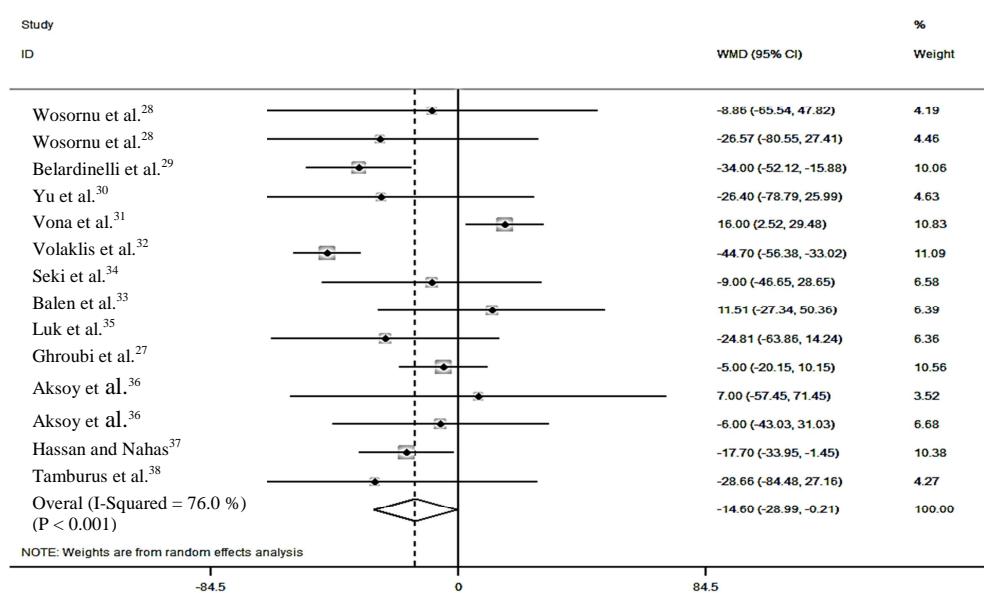


Figure 5. Forest plots of triglyceride serum level differences between the intervention and control groups after cardiac rehabilitation using random effect analysis
WMD: Weighted mean difference; CI: Confidence interval

Table 7. Subgroup analysis of triglyceride based on random effect analysis

Subgroup	Effect size (n)	WMD (95% CIs)	P-within	I ² (%)	Q-test
Overall	14	-14.602 (-28.992, -0.212)	0.047	76.0	< 0.001
BMI					
Not detected	1	-	-	-	-
Normal	3	-28.628 (-43.694, -13.563)	< 0.001	0	0.492
Overweight	8	1.412 (-10.519, 13.344)	0.817	18.5	0.284
Obese	2	-15.81 (-30.689, -0.933)	0.037	0	0.571
Study quality					
Medium	7	-17.349 (-35.685, 0.988)	0.064	64.2	0.010
High	7	-12.642 (-31.775, 6.492)	0.195	72.1	0.002
Exercise duration					
Short	4	-6.632 (-19.500, 6.236)	0.312	0	0.520
Medium	3	13.188 (0.760, 25.615)	0.038	0	0.540
Long	7	-29.622 (-41.756, -17.488)	< 0.001	37.6	0.142
Exercise type					
AE	11	-8.590 (-21.499, 4.319)	0.192	57.6	0.009
RE	1	-26.570 (-80.548, 27.408)	0.335	-	-
AE+RE	2	-43.067 (-54.255, -31.879)	< 0.001	0	< 0.001
Exercise frequency					
1-2 times per week	3	-4.817 (-28.843, 19.208)	0.694	0	0.502
3-4 times per week	11	-16.391 (-32.838, 0.057)	0.051	80.7	< 0.001
Exercise volume					
Low	6	-4.442 (-22.722, 13.838)	0.634	0	0.913
Moderate	5	-18.927 (-31.427, -6.427)	0.003	34.0	0.195
High	3	-17.461 (-63.812, 28.890)	0.460	95.5	< 0.001

AE: Aerobic exercise; RE: Resistance exercise; WMD: Weighted mean difference (mg/dl); LDL: Low-density lipoprotein cholesterol; BMI: Body mass index

I²: Percent variation in WMD attributable to heterogeneity/ Q-test: Test for heterogeneity with significance of < 0.10/ P-Within: Test of WMD of sub-groups by random-effect model with significance of < 0.05

In all analyses, pooled studies were heterogeneous ($P < 0.010$). Subgroup analysis suggested that exercise frequency and volume were potential sources of heterogeneity among all analyses. BMI was suggested as a potential source of heterogeneity in HDL, LDL, and TC serum level analyses. Furthermore, the study quality and type of exercise were potential sources of heterogeneity in HDL, LDL, and TG serum level analyses.

Publication bias: Based on the results of Egger's test and visual inspection of funnel plots, the analysis of HDL ($P = 0.030$) showed publication bias (Figure 6). However, analysis of LDL ($P = 0.081$), TC ($P = 0.955$), and TG ($P = 0.695$) did not present any evidence of publication bias.

Discussion

The present SRMA was conducted to provide evidence about the influence of supervised EBCR on lipid profile changes in patients with CVD. Based on the current study results, supervised EBCR can significantly reduce serum LDL, TC, and TG levels. Moreover, the increase in HDL serum level was not significant.

The current study findings were not consistent with previous SRMAs. In a Cochrane SRMA by

Jolliffe et al., none of the assessed LPs significantly improved after supervised EBCR.¹⁶ This may be explained by the inclusion of a limited number of studies in their study. Moreover, in a SRMA, Chen et al. evaluated the effect of endurance exercise training on patients with CAD and concluded that serum HDL and LDL levels were improved after AE, but TG and TC serum levels was not statistically reduced.¹⁷ They analyzed only 4 articles all of which were included in the current SRMA,^{29-31,34} however, 6 other eligible articles were also included in the current study.^{27,28,33,36-38} These differences between the results can be again due to the inclusion of different articles in the meta-analysis process. There were also 2 SRMAs with different analysis outputs (serum levels of HDL and LDL unchanged, TC and TG decreased significantly).^{39,40} These studies included both center-based and home-based CR programs.

CR is one of the most accepted interventions associated with decreased cardiac mortality, all-cause mortality, risk of re-admission, and infarction.^{41,42} Lowering LP decreases cardiac mortality, all-cause mortality, and vascular event rates.^{43,44}

Based on the results of the subgroup analysis, it is suggested that the level of each component of LP be significantly improved in a specific CR characteristic.

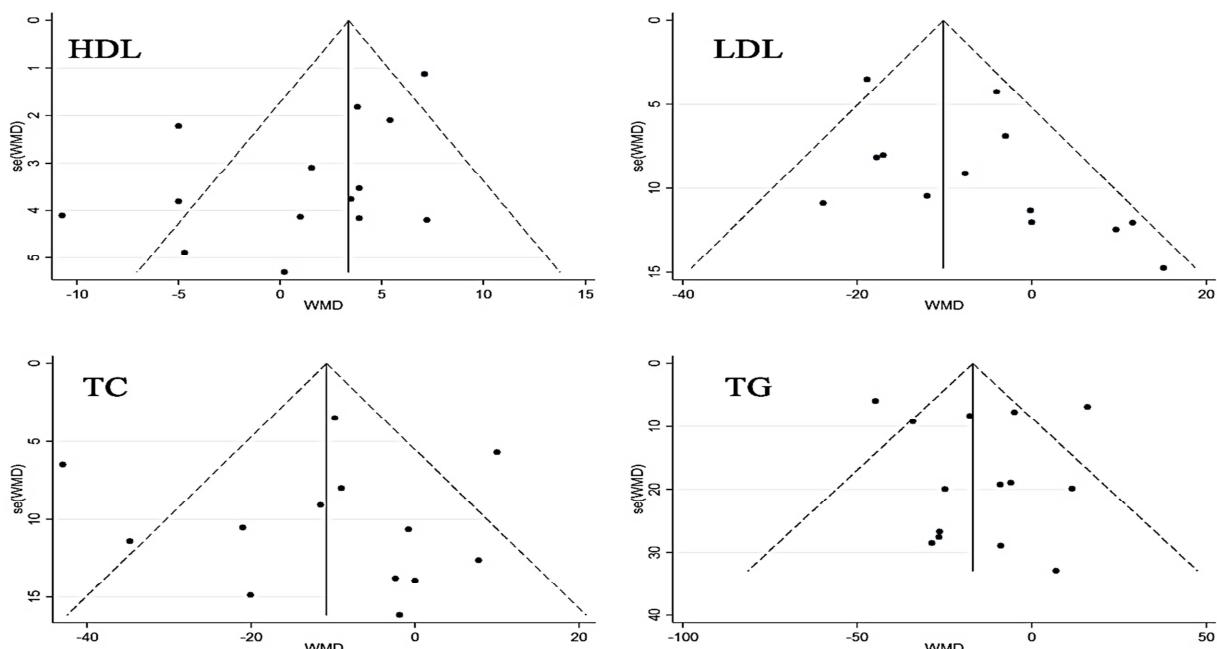


Figure 6. Metafunnel plot of high-density lipoprotein, low-density lipoprotein, total cholesterol, and triglyceride serum level analyses based on Egger's test

*All plots represent pseudo 95% confidence intervals.

WMD: Weighted mean difference; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TC: Total cholesterol; TG: Triglycerides

It seems that supervised EBCR programs performed over a long duration using AE+RE with moderate EV can significantly improve HDL and TG serum levels. Furthermore, supervised EBCR programs performed over a short duration using AE+RE with high EV can significantly decrease LDL serum level. Moreover, moderate EV was the only EBCR property that was associated with significant TC serum level reduction. Although the results of subgroup analysis indicated that frequency of supervised EBCR sessions during a week was not an effective factor on the LP changes, total duration of CR in a week (EV) affected changes in each component of LP.

According to the current study results, AE+RE resulted in more beneficial effects than the implementation of each of them alone. Only 2 studies that used AR+RE were included in the current study; thus, the study findings should be generalized with caution. The current study results were similar to the findings of other studies that compared the effects of AE+RE and AE alone.^{45,46}

The current study findings should be interpreted with the consideration of some limitations. First, only the studies with supervised EBCR were included in this meta-analysis. Many patients cannot participate in regular sessions outside their home due to different reasons. Further SRMAs should be

conducted to compare the effect of center-based and home-based CRs on LP changes in patients with CVD. Second, the study was only aimed at evaluating the effects of supervised EBCR. As mentioned above, CR program is a comprehensive treatment and it seems that the result of comprehensive CR programs differ from EBCR. This should be studied in randomized controlled trials (RCTs) and SRMAs. Third, most RCTs in the current meta-analysis were conducted on middle-aged participants. Therefore, these results should be generalized to older patients with caution. Further RCTs are needed to evaluate the effect of supervised EBCR in elderly patients with CVD. Fourth, all of the studies included in the current review were performed on participants with widely different types of diseases; therefore, the type of disease could not be set as a predefined criterion for subgroup analysis. Moreover, the timespan between disease onset and CR initiation was not reported in 4 of the 12 studies. Accordingly, the CR initiation time criterion and the question about favorable time to start CR phase II remained unanswered. Fifth, 2 categories were defined for frequency in subgroup analysis, 1-2 and 3-4 session(s) per week. There was only 1 study with 1 session per week frequency. Therefore, articles with 2 sessions per week frequency were included more than those with 1

session per week frequency. Finally, all of the reviewed RCTs were performed on patients with a clinically stable condition. Patients with severe CVD or other serious complications were excluded. Consequently, the present findings should not be generalized to patients with severe CVD. No study reported any adverse effects of EBCR during interventions and at the end of the interventions.

Conclusion

The current SRMA analyzed the effect of supervised EBCR on changes in LP in patients with CVD. In total, the subgroup analysis indicated that a supervised EBCR significantly reduced serum LDL, TG, and TC levels. Moreover, it seems that CR programs performed over a long duration using AE+RE with moderate EV can significantly improve the serum level of HDL and TG. Furthermore, the characteristics of short duration, high EV, and AE+RE CR seem to significantly reduce serum LDL level. Finally, moderate EV seems to be associated with significant reduction in TC serum level. The current evidence may help physiotherapists and other disciplines responsible for exercise prescription to achieve better outcomes in CVD patients with dyslipidemia. Further RCTs are necessary to assess the obtained results.

Clinical messages

- Exercise-based cardiac rehabilitation can improve all components of lipid profile.
- The combination of aerobic and resistance exercises improves lipid profile.
- Moderate exercise for a long duration is suggested for the improvement of HDL and TG levels.
- High EV for a short duration is suggested for decreasing LDL serum level.

Acknowledgments

None.

Conflict of Interests

Authors have no conflict of interests.

References

1. Bennett SJ, Sauve MJ. Cognitive deficits in patients with heart failure: A review of the literature. *J Cardiovasc Nurs* 2003; 18(3): 219-42.
2. Roth GA, Huffman MD, Moran AE, Feigin V, Mensah GA, Naghavi M, et al. Global and regional patterns in cardiovascular mortality from 1990 to 2013. *Circulation* 2015; 132(17): 1667-78.
3. Ades PA. Cardiac rehabilitation and secondary prevention of coronary heart disease. *N Engl J Med* 2001; 345(12): 892-902.
4. World Health Organization. *Obesity: Preventing and managing the global epidemic*. Geneva, Switzerland: WHO; 2000.
5. Thompson DR, Jenkinson C, Roebuck A, Lewin RJ, Boyle RM, Chandola T. Development and validation of a short measure of health status for individuals with acute myocardial infarction: The myocardial infarction dimensional assessment scale (MIDAS). *Qual Life Res* 2002; 11(6): 535-43.
6. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Executive summary: Heart disease and stroke statistics-2012 update: A report from the American Heart Association. *Circulation* 2012; 125(1): 188-97.
7. Yeates K, Lohfeld L, Sleeth J, Morales F, Rajkotia Y, Ogedegbe O. A global perspective on cardiovascular disease in vulnerable populations. *Can J Cardiol* 2015; 31(9): 1081-93.
8. Ades PA, Coello CE. Effects of exercise and cardiac rehabilitation on cardiovascular outcomes. *Med Clin North Am* 2000; 84(1): 251-xi.
9. Leon AS, Franklin BA, Costa F, Balady GJ, Berra KA, Stewart KJ, et al. Cardiac rehabilitation and secondary prevention of coronary heart disease: An American Heart Association scientific statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity), in collaboration with the American association of Cardiovascular and Pulmonary Rehabilitation. *Circulation* 2005; 111(3): 369-76.
10. Chen JT, Lin TH, Voon WC, Lai WT, Huang MH, Sheu SH, et al. Beneficial effects of home-based cardiac rehabilitation on metabolic profiles in coronary heart-disease patients. *Kaohsiung J Med Sci* 2016; 32(5): 267-75.
11. Heran BS, Chen JM, Ebrahim S, Moxham T, Oldridge N, Rees K, et al. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2011; (7): CD001800.
12. Clark AM, Hartling L, Vandermeer B, McAlister FA. Meta-analysis: Secondary prevention programs for patients with coronary artery disease. *Ann Intern Med* 2005; 143(9): 659-72.
13. Orozco-Beltran D, Gil-Guillen VF, Redon J, Martin-Moreno JM, Pallares-Carratala V, Navarro-Perez J, et al. Lipid profile, cardiovascular disease and mortality in a Mediterranean high-risk population: The ESCARVAL-RISK study. *PLoS One* 2017; 12(10): e0186196.
14. Redfern J, Briffa T, Ellis E, Freedman SB. Patient-centered modular secondary prevention following

- acute coronary syndrome: A randomized controlled trial. *J Cardiopulm Rehabil Prev* 2008; 28(2): 107-15.
15. Yates BC, Rowland S, Mancuso K, Kupzyk KA, Norman JF, Shurmur S, et al. Reducing cardiovascular risk in spouses of cardiac patients: A randomized controlled trial. *West J Nurs Res* 2015; 37(1): 85-102.
 16. Jolliffe JA, Rees K, Taylor RS, Thompson D, Oldridge N, Ebrahim S. Exercise-based rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2001; (1): CD001800.
 17. Chen YC, Tsai JC, Liou YM, Chan P. Effectiveness of endurance exercise training in patients with coronary artery disease: A meta-analysis of randomised controlled trials. *Eur J Cardiovasc Nurs* 2017; 16(5): 397-408.
 18. Lysen LK, Israel DA. Nutrition in weight management. In: Mahan LK, Escott-Stump S, Raymond JL, Krause MV, Editors. *Krause's food & the nutrition care process*. Philadelphia, PA: Elsevier Health Sciences; 2012. p. 462-88.
 19. Furuyama F, Koba S, Yokota Y, Tsunoda F, Shoji M, Kobayashi Y. Effects of Cardiac Rehabilitation on High-Density Lipoprotein-mediated Cholesterol Efflux Capacity and Paraoxonase-1 Activity in Patients with Acute Coronary Syndrome. *J Atheroscler Thromb* 2018; 25(2): 153-69.
 20. Higgins JP, Green S. *Cochrane handbook for systematic reviews of interventions*. Hoboken, NJ: John Wiley & Sons; 2011.
 21. Berg A. Influence of physical exercise therapy (heart groups) on cardiovascular and metabolic functions in patients after myocardial infarction. *Herz Kreislauf* 1985; 17(10): 522-8.
 22. Bigi R, Corradetti C, Gemma S, Occhi G, Partesana N, Curti PN. Short-term effect of a cardiac rehabilitation program on high-density lipoprotein-cholesterol of male survivors of myocardial infarction. *Minerva Cardioangiologica* 1985; 33(3): 127-34.
 23. Li S, Wu X, Sun Q, He ZS, Ru LS, Yang L, et al. Effects of a two-week, hospitalized cardiac rehabilitation program on serum lipid profiles, quality of life and psychological status in patients with acute myocardial infarction. *Chinese Journal of Rehabilitation Medicine* 2006; 21(8): 696.
 24. Aronov DM, Krasnitskii VB, Bubnova MG, Posdniakov I, Ioseliani DV, Shchegol'kov AN, et al. Exercise in outpatient complex rehabilitation and secondary prophylaxis in patients with ischemic heart disease after acute coronary events (a cooperative trial in Russia). *Ter Arkh* 2006; 78(9): 33-8.
 25. Aronov DM, Krasnitskii VB, Bubnova MG, Pozdniakov I, Ioseliani DG, Shchegol'kov AN, et al. Physical training at ambulatory-polyclinical stage in complex rehabilitation and secondary prevention of patients with ischemic heart disease after acute incidents. Effect on physical working capacity, hemodynamics, blood lipids, clinical course and prognosis (Russian cooperative study). *Kardiologiiia* 2009; 49(3): 49-56.
 26. Korzeniowska-Kubacka I, Piotrowicz R. Influence of exercise training on physical capacity, lipid profile and return to work of women after myocardial infarction. *Folia Cardiol* 2004; 10: 719-25.
 27. Ghroubi S, Elleuch W, Abid L, Kammoun S, Elleuch MH. Cardiac rehabilitation, coronary stenting and myocardial infarction. *J Readapt Med* 2014; 34(4): 173-81. [In French].
 28. Wosornu D, Bedford D, Ballantyne D. A comparison of the effects of strength and aerobic exercise training on exercise capacity and lipids after coronary artery bypass surgery. *Eur Heart J* 1996; 17(6): 854-63.
 29. Belardinelli R, Paolini I, Cianci G, Piva R, Georgiou D, Purcaro A. Exercise training intervention after coronary angioplasty: the ETICA trial. *J Am Coll Cardiol* 2001; 37(7): 1891-900.
 30. Yu CM, Li LS, Ho HH, Lau CP. 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(3): 321-5.
 31. Vona M, Rossi A, Capodaglio P, Rizzo S, Servi P, De Marchi M, et al. Impact of physical training and detraining on endothelium-dependent vasodilation in patients with recent acute myocardial infarction. *Am Heart J* 2004; 147(6): 1039-46.
 32. Volaklis KA, Spassis AT, Tokmakidis SP. Land versus water exercise in patients with coronary artery disease: Effects on body composition, blood lipids, and physical fitness. *Am Heart J* 2007; 154(3): 560-6.
 33. Balen S, Vukelic-Damijani N, Persic V, Ruzic A, Miletic B, Samardija M, et al. Anti-inflammatory effects of exercise training in the early period after myocardial infarction. *Coll Antropol* 2008; 32(1): 285-91.
 34. Seki E, Watanabe Y, Shimada K, Sunayama S, Onishi T, Kawakami 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(8): 1230-4.
 35. Luk TH, Dai YL, Siu CW, Yiu KH, Chan HT, Lee SW, et al. Effect of exercise training on vascular endothelial function in patients with stable coronary artery disease: A randomized controlled trial. *Eur J Prev Cardiol* 2012; 19(4): 830-9.
 36. Aksoy S, Findikoglu G, Ardic F, Rota S, Dursunoglu D. Effect of 10-week supervised moderate-intensity intermittent vs. continuous aerobic exercise programs on vascular adhesion

- molecules in patients with heart failure. *Am J Phys Med Rehabil* 2015; 94(10 Suppl 1): 898-911.
37. Hassan AM, El Nahas NG. Efficacy of cardiac rehabilitation after percutaneous coronary intervention. *Int J PharmTech Res* 2016; 9: 134-41.
 38. Tamburus NY, Kunz VC, Salviati MR, Castello S, Catai AM, Da SE. Interval training based on ventilatory anaerobic threshold improves aerobic functional capacity and metabolic profile: a randomized controlled trial in coronary artery disease patients. *Eur J Phys Rehabil Med* 2016; 52(1): 1-11.
 39. Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K, 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(10): 682-92.
 40. Oldridge N. Exercise-based cardiac rehabilitation in patients with coronary heart disease: Meta-analysis outcomes revisited. *Future Cardiol* 2012; 8(5): 729-51.
 41. Lawler PR, Filion KB, 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(4): 571-84.
 42. Anderson L, Oldridge N, Thompson DR, Zwisler AD, Rees K, Martin N, et al. Exercise-based cardiac rehabilitation for coronary heart disease: Cochrane systematic review and meta-analysis. *J Am Coll Cardiol* 2016; 67(1): 1-12.
 43. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; 342(3): 145-53.
 44. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: Randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003; 362(9386): 782-8.
 45. Dor-Haim H, Barak S, Horowitz M, Yaakobi E, Katzung S, Swissa M, et al. Improvement in cardiac dysfunction with a novel circuit training method combining simultaneous aerobic-resistance exercises. A randomized trial. *PLoS One* 2018; 13(1): e0188551.
 46. Pierson LM, Herbert WG, Norton HJ, Kiebzak GM, Griffith P, Fedor JM, et al. Effects of combined aerobic and resistance training versus aerobic training alone in cardiac rehabilitation. *J Cardiopulm Rehabil* 2001; 21(2): 101-10.