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Effect of combined aerobic and resistance training on peak oxygen consumption, muscle strength and health-related quality of life in patients with heart failure with reduced left ventricular ejection fraction: a systematic review and meta-analysis

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ABSTRACT

Objective: The aim of this study was to investigate the effects of combined aerobic and resistance training on peak oxygen consumption (peak VO_2), minute ventilation/carbon dioxide production (VE/VCO_2 slope), muscle strength and health-related quality of life (HRQoL) in heart failure patients with reduced left ventricular ejection fraction (HFrEF).
Methods: We searched Cochrane, Pubmed, and PEDro (from the earliest date available to September 2018) for RCTs that evaluated the effects of combined aerobic and resistance training in HFrEF patients. Weighted mean differences (WMD), standardized mean difference (SMD), and 95% confidence interval (CI) were calculated.
Results: 39 studies met the study criteria, including 2008 patients, 14 compared combined aerobic and resistance training versus aerobic training, and 25 compared combined aerobic and resistance training versus control. Compared to aerobic training, combined aerobic and resistance training resulted in improvement in muscle strength SMD 0.7 (95% CI: 0.3 to 1.0 $N = 167$) and, HRQoL WMD –2.6 (95% CI: −5.0 to −0.1 $N = 138$). A nonsignificant difference in peak VO_2 and VE/VCO_2 slope was found for participants in the combined aerobic and resistance training group compared with aerobic training group. Compared to control, combined aerobic and resistance training resulted in improvement in peak VO_2 WMD 2.9 (95% CI: 1.6 to 4.4 $N = 638$), muscle strength SMD 0.64 (95% CI: 0.4 to 0.9 $N = 315$) and, HRQoL WMD –9.8 (95% CI: −15.2 to −4.5 $N = 524$).
Conclusions: Combined aerobic and resistance training improves peak VO_2, muscle strength and HRQoL and should be considered as a component of care of HFrEF patients.

1. Background

Heart failure (HF) is a major health care burden in the world [1]. Patients with HF experience numerous symptoms that affect their quality of life and activities of daily living, such as dyspnea, fatigue, poor exercise tolerance and fluid retention. Patients with HF also have increased risk of hospital readmission and mortality [2,3].

Recently Cattadori et al., presented update to review the evolution of the interaction between HF and exercise. They reported that exercise is a tool of primary prevention and therapy for HF patients [4]. Studies consistently reported that exercise training is a safe and effective intervention to improve exercise tolerance and quality of life in HF patients with reduced left ventricular ejection fraction (HFrEF) [5,6]. Continuous aerobic exercise training, which is endorsed by current guidelines [7,8], is very important to improve

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peak oxygen consumption (peak VO_2) and health-related quality of life (HRQoL). Peak VO_2 and HRQoL are associated with prognosis in HFrEF [9]. On the other hand, meta-analyses have shown that resistance exercise training increases muscle strength, HRQoL and peak VO2 (even in a small magnitude) [10,11]. However, the effects of combining aerobic and resistance training to potentiate the outcomes in HFrEF is controversial, and the optimal exercise training protocol is still under discussion [12].

Cornelis et al., assessed the effectiveness of different exercises modalities on prognostic cardiopulmonary exercise test parameters, quality of life and left ventricular remodeling. One of key findings was that, an increase in exercise capacity, was not significantly favored by a specific training modality. They concluded that regarding cardiopulmonary exercise test parameters and quality of life, it is not clear which training modality is the best [13].

As far as we know, there is no published meta-analysis of randomized controlled trials (RCTs) examining the effects of combined aerobic and resistance training versus aerobic training alone in HFrEF patients. Thus, the aim of this systematic review and meta-analysis was to analyze the published RCTs that investigated the effects of combined aerobic and resistance training on peak VO_2, minute ventilation/carbon dioxide production (VE/VCO_2 slope), muscle strength and HRQoL in HFrEF patients.

2. Methods

This systematic review was completed in accordance with Cochrane Collaboration recommendations and PRISMA guidelines [14].

2.1. Eligibility criteria

The review included RCTs that studied the effects of combined aerobic and resistance training compared to aerobic training alone or control (no exercise) in HFrEF patients (defined as left ventricular ejection fraction ≤45%) [15].

Studies were eligible for this systematic review if they met the following criteria: a) included adult patients (aged ≥18 years) with HFrEF (≤45%) b) a randomized controlled clinical trial design; c) combined aerobic and resistance training controlled by aerobic training alone or control (no exercise). Studies that enrolled patients with other cardiac or respiratory diseases were excluded. The outcomes of interest were peak VO_2 (mL/Kg/min), VE/VCO_2 slope, muscle strength (isometric, dynamic or isokinetic muscle strength evaluated by repetition maximum assessment test, hand-held or isokinetic dynamometer) and HRQoL (any standardized and validated scales or questionnaires).

2.2. Search methods for identification of studies

We searched for references on MEDLINE, Physiotherapy Evidence Database (PEDro), Scientific Electronic Library Online (SciELO) and the Cochrane Central Register of Controlled Trials (CENTRAL Cochrane) up to September 2018 without language restrictions or publication status restrictions. We used a standard protocol for this search and, whenever possible, a controlled vocabulary (Mesh term for MEDLINE and Cochrane). In search strategy, we used three groups of keywords and their synonymous: study design, participants, and interventions.

The strategy developed by Higgins and Green [16] was used for the identification of RCTs in PUBMED. The search strategy for MEDLINE via PUBMED is presented in Table E1 (Supplementary Material 1). To identify the RCTs in other database we adopted a search strategy using similar terms. We checked the references of the articles included in this meta-analysis to identify other potentially eligible studies. For ongoing studies, confirmation of any data or getting additional information, authors were contacted by e-mail.

2.3. Data collection and analysis

The list of titles and abstracts from each data source were independently evaluated by two reviewers. If at least one of the reviewers considered one reference eligible, the full text was obtained for complete assessment. Then, two reviewers independently assessed the full text of selected articles to verify if they met the criteria for inclusion or exclusion. We also checked each selected article's reference list to identify other potentially eligible studies. Two authors independently extracted data from the published reports using standard data extraction forms adapted from Cochrane Collaboration [16]. Aspects of the study population, intervention performed, follow-up period and rates of missing data, outcome measures, and results were reviewed.

2.4. Quality of meta-analysis evidence

The quality of studies included was scored by two authors using the PEDro scale, which is based on important criteria, such as concealed allocation, intention-to-treat analysis, and the adequacy of follow-up [17]. These characteristics make the PEDro scale a useful tool for assessing the quality of rehabilitation RCTs [17–19]. Any disagreements in the rating of the studies were resolved by a third reviewer.

2.5. Summary of findings table

The quality of evidence for the outcomes peak VO2, VE/VCO2 slope, muscle strength and HRQoL was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to interpret result findings and used GRADEpro GDT 2015 to import data from Review Manager to create a 'Summary of findings table'. The assessment involved five items: risk of bias, imprecision, inconsistency, indirectness, and publication bias [16]. Decisions to downgrade the quality of studies were justified using footnotes and made comments to aid readers' understanding of the review where necessary.

2.6. Statistical assessment

Pooled-effect estimates were obtained by comparing the least square mean change from baseline to endpoint for each group and were expressed as the weighted mean difference between groups. For continuous variables results were expressed as the mean difference in the change in the variable between randomized groups. Conversion of nonparametric data to means and standard deviation (SD) was based on recently established methods [20]. When the SD of change was not available, but confidence interval was available, we converted to SD as guidance by Higgins and Green [16]. Calculations were done using a fixed-effects and random-effects model. If the trial was a multiple-arm RCT, all relevant experimental intervention groups (combined aerobic and resistance training versus aerobic training or combined aerobic and resistance training versus control) had data extracted. In follow-up reports with multiple end points, only data closest to the end of the exercise program were included. In cross-over trials, size effects were only extracted at the first cross-over point.

Means and standard deviations of muscle strength were extracted for the purpose of calculating differences between groups. In studies reporting absolute values of muscle strength (N or Nm), explosive muscle strength (N/s or Nm/s), and these values were subsequently normalized to the body mass reported by the respective studies. If body mass was not reported, the corresponding author of the study was contacted to obtain the data.

Two comparisons were made: [1] combined aerobic and resistance training versus aerobic training alone and [2] combined aerobic and resistance training versus controls (no exercise). Weighted mean differences (WMD), standardized mean difference (SMD), and 95% confidence interval (CI) were calculated. An α value <0.05 was considered statistically significant. Heterogeneity among studies was examined with Cochran's Q and I^2 statistic, in which values >40% were considered indicative of high heterogeneity [21] and random-effects model was chosen. Analyses were performed with Review Manager (Version 5.3) [22].

3. Results

3.1. Description of selected studies

The initial search led to the identification of 3912 abstracts, from which 51 were considered as potentially relevant. Of these, 41 studies [23–63] were retrieved for detailed analysis. Of these, two studies were duplicates (studies that considered the same participants). The study by Andersen et al. [62] used the same participants as the study by Jonsdottir et al. [51]. The study by Gary et al. [63] used the same participants as the study by Gary et al. [44]. Finally, thirty-nine studies [23–61] met the eligibility criteria. Supplementary Material 2 shows the PRISMA flow diagram of studies in this review (Fig. 1). All studies were scored using the PEDro scale methodology by both authors. PEDro scores are presented individually in Table E2 and E3 (Supplementary Materials 3 and 4). The reference list of excluded studies after full-text checking can be found in Supplementary File 5 (Table E4).

3.2. Study characteristics

The number of participants in RCTs included in this meta-analysis ranged from 16 [35] to 181 [58]. The mean age of participants ranged from 47.4 [32] to 75.5 [37] years old. The characteristics of the studies compared combined aerobic and resistance training versus aerobic training and control have been reported in most studies Sample size, outcomes and results of included studies are summarized in Tables 1 and 2.

3.3. Effects of the combined aerobic and resistance training versus aerobic training (14 studies)

3.3.1. Peak VO_2

Eleven studies [24–32,34] assessed peak VO_2 as outcome. The total number of patients in the combined aerobic and resistance training group was 159, whereas 160 patients were included in the aerobic training group. The meta-analyses showed (Fig. 2a) a nonsignificant difference in peak VO_2 of 0.5 $mL \cdot kg^{-1} \cdot min^{-1}$ (95% CI: CI: −0.2 to 1.3 $N =$ 319) for participants in the combined aerobic and resistance training group compared with aerobic training group.

3.3.2. VE/VCO_2 slope

Six studies [24–27,30,31] assessed VE/VCO_2 slope as outcome. The total number of patients in the combined aerobic and resistance training group was 93, whereas 94 patients were included in the aerobic training group. The meta-analyses showed (Fig. 2b) a nonsignificant difference in VE/VCO_2 Slope of - 0.2 (95% CI: CI: −1.7 to 1.3 $N = 187$) for participants in the combined aerobic and resistance training group compared with aerobic training group.

3.3.3. Muscle strength

Six studies [27–30] assessed isometric Muscle Strength of Knee extensors as outcome. The total number of patients in the combined aerobic and resistance training group was 84, whereas 83 patients were included in the aerobic training group. Considering the different instruments used in the assessment of muscle strength, we performed a meta-analysis with standardized mean difference. The meta-analyses showed (Fig. 2c) a significant difference in Knee extension muscle strength of 0.7 (95% CI: CI: 0.3 to 1.0 $N = 167$) for participants in the combined aerobic and resistance training group compared with aerobic training group.

3.3.4. Health-related quality of life

Five of the trials [26,27,30,32] reported validated measures of HRQoL by disease-specific instruments as the Minnesota Living With Heart Failure Questionnaire The total number of patients in the combined aerobic and resistance training group was 68, whereas 70 patients were included in the aerobic training group. The meta-analyses showed (Fig. 2b) a significant improvement in HRQoL of −2.6 (95% CI: CI: −5.0 to −0.1 $N = 138$) for participants in the

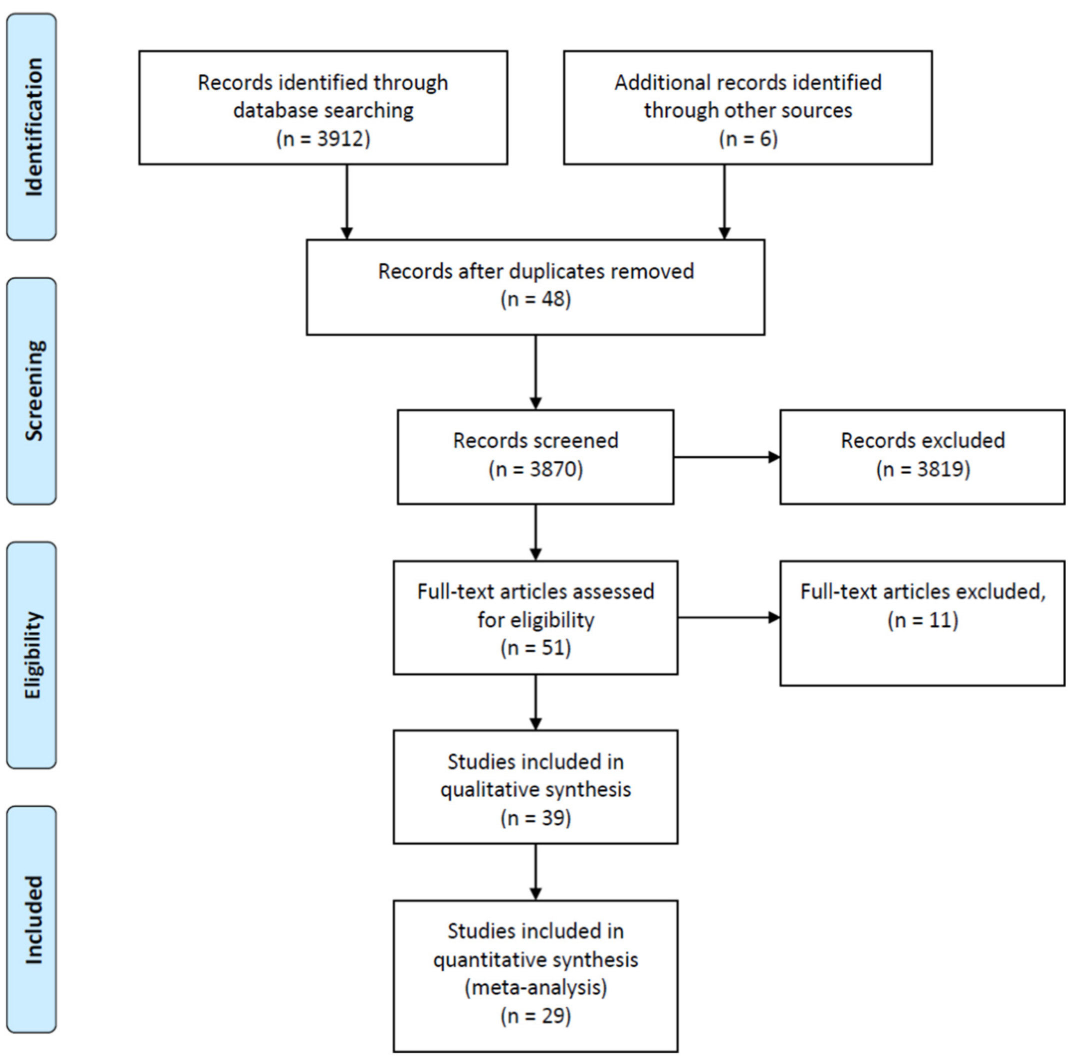

Fig. 1. Flow diagram showing the reference screening and study selection.

Table 1
Characteristics of the included studies (combined aerobic and resistance training versus aerobic training).

Study	Patients (N analyzed, age, gender)	Outcome measures			Key findings
		Aerobic capacity	Muscle strength	HRQoL	
	$N = 29$, 47–69 years, 100% male.	Treadmill Stress Test	1-Repetition maximum	SF-12	SCT may yield greater benefits to the left ventricle mechanical function as well as to the patient's aerobic fitness and physical QoL. Moreover, the SCT program was found to be feasible as well as safe.
Abolahrari-Shirazi et al. 2017	$N = 75$, 57 years, 74,6% males	Treadmill Stress Test	1-Repetition maximum	NR	CT was as effective as ARE in reducing NT-pro BNP level and improving functional capacity in heart failure patients.
Tzanis et al. 2017	$N = 13$, 51 years	CPET cycle ergometer	1-Repetition maximum	NR	HIIT reverses skeletal myopathy of HF patients with the adaptive responses of the IGF-1 bioregulation system possibly contributing to these effects. ARE program seemed to be superior to CT to induce muscle hypertrophy.
Georgantas et al. 2014	$N = 42$, 54 years, 83,3% males.	CPET cycle ergometer	2-Repetition maximum	NR	The addition of strength training to AIT induces significant beneficial effects in terms of ventilatory and metabolic recovery kinetics than AIT alone in CHF patients
Laoutaris et al. 2013	$N = 27$, 58 years, 70% male.	Treadmill Stress Test	Peak quadriceps muscle torque, 1-MR, PImax	MLHFQ	Combined aerobic training was safe and resulted in incremental benefits in both peripheral and respiratory mus- cle weakness, cardiopulmonary function and QoL.
Feiereisen et al. 2013	$N = 45$, 43.5 years, 100% male	CPET upright bicycle	1-Repetition maximum	NR	Exercise training has no effects on circulating IGF-1 and GH.
Robert McIntosh et al. 2013	$N = 20$, 70,5 years, 70% male	CPET cycle ergometer	NR	MLHFQ	Both groups showed significant improvements in ventilatory threshold and in quality of life
Servantes et al. 2012	$N = 45$, 51 years, 52% male	CPET treadmill	1-Repetition maximum	MLHFQ	Training groups showed improvement in all outcomes evaluated: CPET, isokinect strength, QoL. Untrained Group demonstrated significant decrease or no change on measurements after three months without training.
Anagnostakou et al. 2011	$N = 45$, 53 years, 77,7% male	CPTE cyclergometer	2-Repetition maximum	NR	A significant improvement in FMD was observed in the combined training group, in contrast to the interval training alone group; the improvement was significantly greater in the combined training than in the interval training alone group
Bouchla et al. 2011	$N = 20$, 53,6 years	CPTE cyclergometer	2-Repetition maximum	NR	Combined aerobic interval and strength training induces a greater benefit than interval training alone on muscle strength in CHF patients
Mandic et al., 2009	$N = 42$, 60 years	Treadmill Stress Test	1-Repetition maximum	NR	Strength and VO_2 max improved in CARE group compared to No exercise ($p = 0.05$)
Beckers et al., 2008	$N = 58$, 59 years, 72.5% male	CPTE treadmill	1-Repetition maximum	The Health Complaints Scale (HCS)	Combined had a more pronounced effect on submaximal exercise capacity, muscle strength, and quality of life.
Feiereisen et al., 2007	$N = 60$, 60.6 years	CPTE cyclergometer upright bicycle	1-Repetition maximum	MLHFQ	Independently of the training modality, intensive exercise training is efficient in increasing cardiac function, exercise capacity, peripheral muscle function, and QoL in CHF patients
Delagardelle et al., 2002	$N = 20$, 60.4 years	CPTE cyclergometer	1-Repetition maximum	NR	Combined endurance/strength training was superior to endurance training alone concerning improvement of LV function, peak VO2, and strength parameters. ($p = 0.05$)
Barnard et al., 2000	$N = 21$, 60.3 years, —	Estimated bruce protocol	1-Repetition maximum	NR	significantly improved strength in comparison with the aerobic exercise group, with an average increase of 26%

Cardiopulmonary exercise test (CPTE); Health related quality of life (HRQol); Combined training (CT); Aerobic interval training (AIT); Quality of life (QoL); Short form 12 (SF-12) Aerobic exercise (ARE); Minnesota living with heart failure questionnaire (MLHFQ); Not reported (NR).

combined aerobic and resistance training group compared with aerobic training group.

3.4. Combined aerobic and resistance training versus control (no exercise, 25 studies)

3.4.1. Peak VO_2

Seventeen studies [24,30,31,33,37–40,42,49–51,53,55–57,60] assessed peak VO_2 as outcome. The total number of patients in the combined aerobic and resistance training group was 318, whereas 320 patients were included in the control group. The mean peak VO_2 in the analyzed studies was 17.1 mL kg^{-1} min^{-1} at baseline, and it increased to 19.7 mL kg^{-1} min^{-1} at the end of the intervention. The meta-analyses showed (Fig. 3a) a significant improvement in peak VO_2 of 2.94 mL kg^{-1} min^{-1} (95% CI: 1.6, 4.4, $N = 638$) for participants in the combined aerobic and resistance training group compared with control group without exercise.

3.4.2. VE/VCO_2 slope

Four studies [24,30,31,37] assessed VE/VCO_2 slope as outcome. The total number of patients in the combined aerobic and resistance training group was 71, whereas 82 patients were included in the control group. The meta-analyses showed (Fig. 3b) a nonsignificant difference in VE/VCO_2 slope of - 2.6 (95% CI: CI: −5.5 to 0.2 $N = 153$) for participants in the combined aerobic and resistance training group compared with control group without exercise.

3.4.3. Muscle strength

Seven studies [31,33,39,44,52,54,59] assessed isometric muscle strength of knee extensors as outcome. The total number of patients in the combined aerobic and resistance training group was 157, whereas 158 patients were included in the control group without exercise. Considering the different instruments used in the assessment of muscle strength, we performed a meta-analysis with standardized mean difference. The meta-analyses showed (Fig. 3c) a significant improvement in knee extension muscle strength of 0.6 (95% CI: CI: 0.4 to 0.9 $N = 315$) for participants in the combined aerobic and resistance training group compared with control group without exercise.

3.4.4. Health-related quality of life

Eight [31,33,37,44,49,50,55,58] of the trials reported validated measures of HRQoL by disease-specific instruments as the Minnesota Living

Table 2
Characteristics of the included studies (combined aerobic and resistance training versus control (no exercise).

Study	Patients (N analyzed, age, gender)	Outcome measures			Key findings
		Aerobic capacity	Muscle strength	HRQoL	
Oka et al., 2000	$N = 40$, 60.3 years, 77.5% male	CPET treadmill	1-Repetition maximum	The chronic Heart Failure Questionnaire	The exercise intervention improved fatigue ($p < 0.02$), emotional function ($p < 0.01$), and mastery ($p < 0.04$).
Silva et al., 2002	$N = 24$, 52 years, 75% male	CPET treadmill	NR	NR	Exercise training programs in patients with heart failure can bring about an improvement in physical capacity
McKelvie et al., 2002	$N = 181$, 63 years, 80% male	CPET cyclergometer	1-Repetition maximum	MLHFQ	There was a significant increase in 6-minute walk distance at 3 and 12 months but no between-group differences. Incremental peak oxygen uptake increased in the exercise group compared with the control group at 3 and 12 months
Roveda et al., 2003	$N = 16$, 53 years, 68.7% male	CPET cyclergometer	NR	NR	In heart failure patients, peak VO2 and forearm blood flow, but not left ventricular ejection fraction, increased after training.
Koukouvou et al., 2004	$N = 26$, 52 years	CPET treadmill	NR	MLHFQ	After training VO2 peak increased by 36% and exercise time by 35%, $p < 0.05$. A significant decrease in anxiety and depression was also observed. Moreover, trained patients demonstrated a significant improvement in quality of life
Sabelis et al., 2004	$N = 29$, 56,9 years	CPET cycle ergometer	NR	NR	Physical training positively affected maximal workload. Plasma levels of endothelial markers were not affected by physical training and not related to exercise tolerance. After training, stimulated (maximal exercise) plasma von Willebrand Factor (vWF) release was present, whereas at baseline this release was absent.
Senden et al., 2005	$N = 61$, 59.8 years, 64.4% male	CPET cycle ergometer	Isokinect and isometric strength	NR	In CHF patients, home-based training in conjunction with a supervised strength and endurance training program is safe, feasible and effective and does not require complex training equipment
Austin et al., 2005	$N = 200$, 71 years, 44% male	6MWT	NR	MLHFQ/EuroQol	There were significant improvements in MLHF and EuroQol scores, NYHA classification and 6-min walking distance (meters) at 24 weeks between the groups ($p < 0.001$).
Witham et al., 2005	$N = 82$, 81 years, 54,8% male	6MWT	NR	Guyatt chronic heart failure questionnaire and HADS	Six-minute walk distance and quality of life did not change between groups, but daily activity as measured by accelerometry increased in the exercise group relative to the control group.
Andersen et al., 2006	$N = 43$, 69 years, 79% male	CPET cyclergometer/6MWT	1-Repetition maximum	T-score (Iceland questionnaire)	Significant improvement was found between groups in the six minute walk test ($p = 0.01$), work load on the bicycle exercise test ($p = 0.03$), time on the bicycle exercise test ($p = 0.02$). Quality of life factors that reflect exercise tolerance and general health, improved significantly in the training group compared to the control group.
De Mello Franco et al., 2006	$N = 29$, 56 years, 75% male.	CPET cyclergometer	NR	MLHFQ	After the initial 4 months of training patients in the exercise group showed a significant increase in peak VO2 and reduction in MSNA, compared to the untrained group, but this was not maintained during 4 months of home-based training.
Jónsdóttir et al., 2006	$N = 43$, 69 years, 79% male	CPET upright cyclergometer/6MWT	1-Repetition maximum	Heilsutengd lı'fsgæði (Valid Iceland quality of life questionnaire).	Significant improvement was found between groups in the 6MWT ($p = 0.01$), work load on the bicycle exercise test ($p = 0.03$) and quadriceps muscle strength test. Quality of life factors that reflect exercise tolerance and general health, improved significantly in the training group compared to the control group.
Dracup et al., 2007	$N = 173$, 54 years, 71.7% male	CPET cyclergometer/6MWT	1-Repetition maximum	MLHFQ	There was no significant difference between experimental and control groups in the combined clinical end point at 12 months and in functional status, quality of life, or psychological states over 6 months.
Bocalini et al., 2008	$N = 42$, 61 years, 88% male	Ability to walk 800 m	NR	WHOQOL questionnaire	Improvement in the trained group was identified in all components of functional capacity when compared to the untrained group ($p < 0.001$).
Pozehl et al., 2008	$N = 21$, 66 years, 86,7% male	NR	NR	NR	Exercise group significantly decreased sensory fatigue (Piper Fatigue Scale) over time ($\chi2 = 6.49$, $p = 0.04$) while the control group did not change ($\chi2 = 0.93$, $p = 0.63$). Dyspnea showed a non-significant decrease over time for the exercise group ($\chi2 = 4.16$, $p = 0.13$) while the control group showed a decrease from baseline to 12 weeks but an increase to above baseline values by week 24 ($\chi2 = 0.18$, $p = 0.91$).
Jolly et al., 2009	$N = 169$, 70 years, 64% males	ISWT	NR	MLHFQ/HADS	There was no statistically significant difference between groups in the MLwHFQ at 6 month (mean, 95% CI) (22.53, 27.87 to 2.80) and 12 month (20.55, 25.87 to 4.76) follow-up or secondary outcomes with the exception of a higher EQ-5D score (0.11, 0.04 to 0.18) at 6 months and lower Hospital Anxiety and Depression Scale score (21.07, 22.00 to 20.14) at 12 months, in favor of the exercise group.
Santos et al., 2010	$N = 23$, 55 years, 56,5%	CPET cyclergometer	NR	NR	Peak oxygen consumption increased by 13.8% after 4 months of exercise training and decreased by 1.9% in the control group.
Gary et al., 2011	$N = 24$, 60 years, 50% male	6MWT	NR	MLHFQ	Patients with stable HF who participate in a moderate-intensity combined aerobic and resistance exercise program may improve performance of routine physical activities of daily living by using a home-based exercise approach
Witham et al., 2012	$N = 107$, 80 years, 67% male	6MWT	NR	MLHFQ	This exercise intervention did not improve exercise capacity or quality of life in older patients with heart failure and was not cost saving to the National Health Service.

(continued on next page)

Table 2 (*continued*)

Study	Patients (N analyzed, age, gender)	Outcome measures			Key findings
		Aerobic capacity	Muscle strength	HRQoL	
Gary et al., 2012	$N = 24$, 60 years, 50% male	6MWT	Handgrip strength	KCCQ	The Kansas City Cardiomyopathy Questionnaire overall summary score was significantly improved (P G 0.001) at T2 in the exercise intervention group compared with the ACWL group.
Norman et al., 2012	$N = 40$, 59 years, 57.5% male	CPET treadmill/6MWT	NR	KCCQ	A clinically significant increase in 6MWT was demonstrated by the EX but not the control group. The exercise group achieved a clinically significant change on the KCCQ at 12 weeks, with further improvement by 24 weeks
Antunes-Correa et al., 2014	$N = 33$, 56 years, 84% male	CPET cyclergometer	NR	NR	Exercise training improves muscle metaboreflex and mechanoreflex control of MSNA in humans with HF.
Meirelles et al., 2014	$N = 30$, 55 years, 46.6% male	CPET cyclergometer	NR	NR	Peak VO2 increased after exercise training (18.0 ± 2.2 vs. 23.8 ± 0.5 mlO2/kg/min; $p < 0.05$).
Groehs et al., 2015	$N = 26$, 53 years, 84.6% male	CPET cyclergometer	NR	NR	Exercise training prevents the deterioration of Arterial baroreflex control of muscle sympathetic nerve activity in CHF patients
Chrysohoou et al., 2015	$N = 72$, 59.5 years, 85% male	CPET cyclergometer	1-Repetition maximum	MLHFQ	Interval high-intensity aerobic training, combined with strength exercise, seems to benefit aortic dilatation capacity and augmented systolic pressure in parallel with improvement in left ventricular diastolic function
Stevens et al., 2015	$N = 22$, 66 years, 72.2% male	CPET cyclergometer	1-Repetition maximum	EQ5D	Exercise training resulted in improved oxygen uptake at the second ventilatory threshold ($p < 0.05$) and isokinetic strength endurance of the upper leg.

Cardiopulmonary exercise test (CPTE); health related quality of life (HRQol); six-minute walk test distance (6MWT); muscle sympathetic nerve activity (MSNA) Minnesota living with heart failure questionnaire (MLHFQ); Kansas city cardiomyopathy questionnaire (KCCQ); hospital anxiety and depression scale (HADS); World Health Organization Quality of Life instrument (WHOQOL); EuroQoL questionnaire (EQ5D); Not reported (NR).

With Heart Failure Questionnaire (MLHF-Q). The total number of patients in the combined aerobic and resistance training group was 263, whereas 261 patients were included in the control group. The meta-analyses showed (Fig. 3d) a significant difference in HRQoL of −9.8 (95% CI: CI: −15.2 to −4.5 $N = 524$) for participants in the combined aerobic and resistance training group compared with control group without exercise.

3.4.5. GRADE assessments

The GRADE assessments are presented in Summary of Findings Tables E5 and E6 (Supplementary Materials 6 and 7). Compared to aerobic training (Table E5), the quality of evidence for peak VO_2, VE/VCO_2 slope, muscle strength and HRQoL was assessed as being moderate. When compared to control (Table E6), the quality of evidence for muscle strength was assessed as being moderate. The quality of evidence for peak VO_2, VE/VCO_2 slope, and HRQoL was assessed as being low.

4. Discussion

Our study showed that combined aerobic and resistance training was more efficient than aerobic training on muscle strength and HRQoL gain in HFrEF patients. We detected no significant difference between groups in Peak VO2 and VE/VCO2 slope. When compared to controls without exercise, combined aerobic and resistance training resulted in improvement in peak VO2, muscle strength and HRQoL.

The quality of evidence for the analyzed outcomes was determined to be moderate to low, due to the inclusion studies without allocation concealment, random allocation, and/or sample size calculation. A high statistical significance heterogeneity was identified between the included studies in meta-analysis. In general, the studies presented moderate to low methodological quality. Subjects and experimenters were not blinded in most of the included studies. In addition, most included studies failed to report the method for concealed allocation and Intention-to-treat analysis.

The aim of the present study was to compare the effects of combined aerobic and resistance training vs aerobic training and vs control without exercise. Moreover, we included peak VO_2, VE/VCO_2 slope, muscle strength, and HRQoL, important outcomes associated with prognosis in HFrEF [10,64–67]. The peak VO_2, VE/VCO_2 slope were recently included in a new risk score for systolic HF patients, the MECKI score (metabolic exercise test data combined with cardiac and kidney indexes) [4]. The MECKI score, that include six variables (haemoglobin, sodium, kidney function, left ventricle ejection fraction, peak VO2, and VE/VCO2 slope), is a long-term prognostic score with the highest area under the curve [68].

Aerobic exercise training is well established as an important non pharmacological therapy in adult with HFrEF, which is endorsed by the main guidelines around the world [9,15]. In the European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic HF [15] and for the management of stable coronary artery disease [69] for example, there is a recommendation to encourage patients with heart conditions to join 30 min of aerobic exercise training at least 3 times a week. However, guidelines lack on recommendation of resistance exercises.

Our results show the importance of combined aerobic and resistance training to potentiate the effects on muscle strength and HRQoL. This potentialize effect was expected in our meta-analysis. It is known that there is no better modality between aerobic and resistance training. It depends on rehabilitation aim with the patient. Following the principle of specificity of exercise training, if the patients perform aerobic exercise we expect to gain more aerobic performance than strength. On the other hand, if patients perform strength training, we expect to gain more muscle strength than aerobic performance. In general, the combined aerobic and resistance training provides the patient the benefits on muscular strength and on exercise capacity.

Peak VO_2 is well established as a prognostic variable in HFrEF [70]. Is known that an increase in Peak $VO_2 > 10\%$ after a cardiac rehabilitation program is satisfactory and represents a good prognosis in patients with HF [70]. The magnitude of improvement with combined aerobic and resistance training (mean change: $+2.8\ mL \cdot kg^{-1} \cdot min^{-1}$) is superior to the difference observed following no exercise (mean change: $-0.2\ mL \cdot kg^{-1} \cdot min^{-1}$). This magnitude of improvement was higher than 15%.

Muscle strength has been linked to life expectancy [71]. In HF patients, survival rate is significantly lower in the low muscle strength group [65,71]. A previous published systematic review with meta-

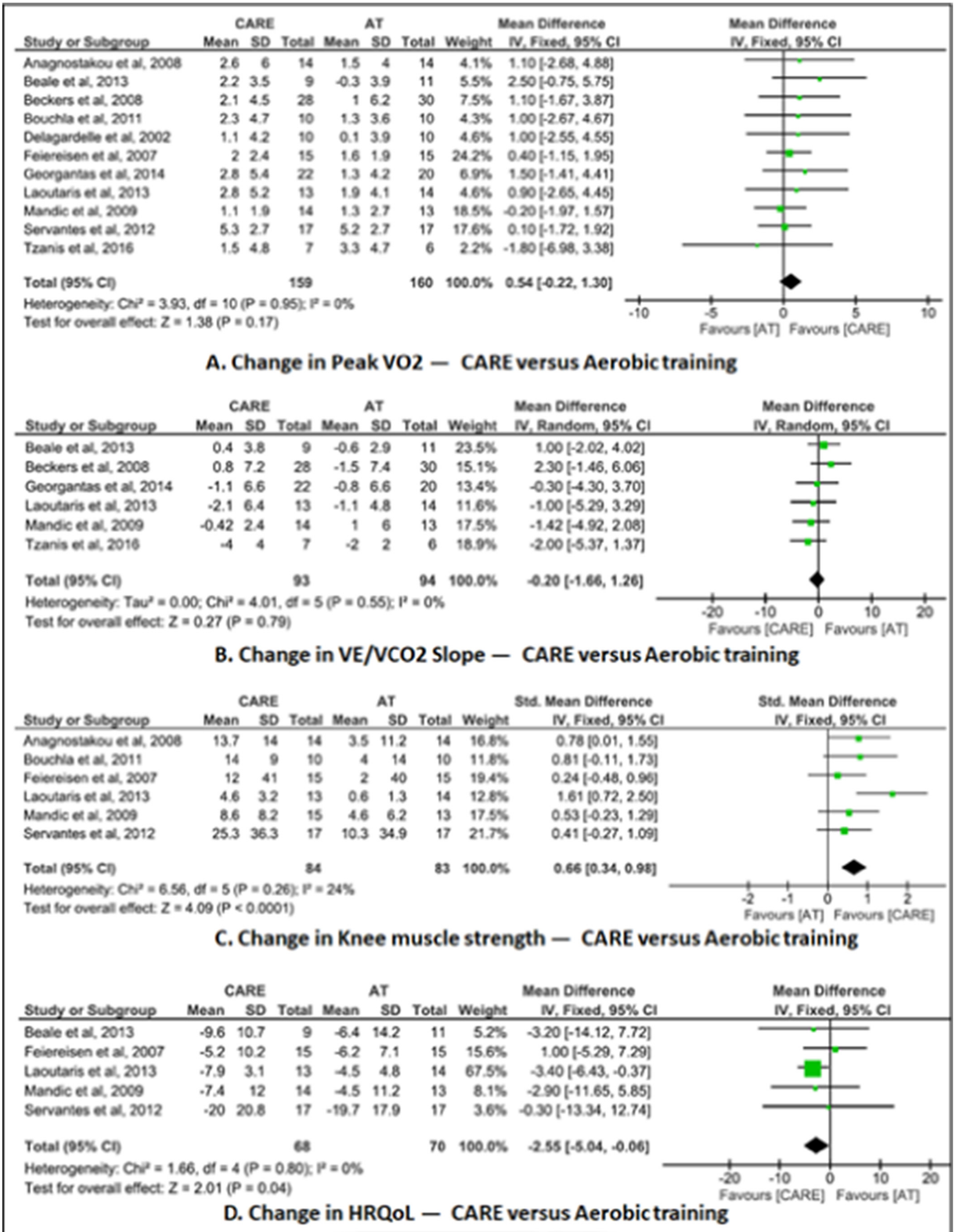

Fig. 2. Combined aerobic and resistance training versus aerobic training. Review Manager (RevMan). Version 5.3 The Cochrane Collaboration, 2013.

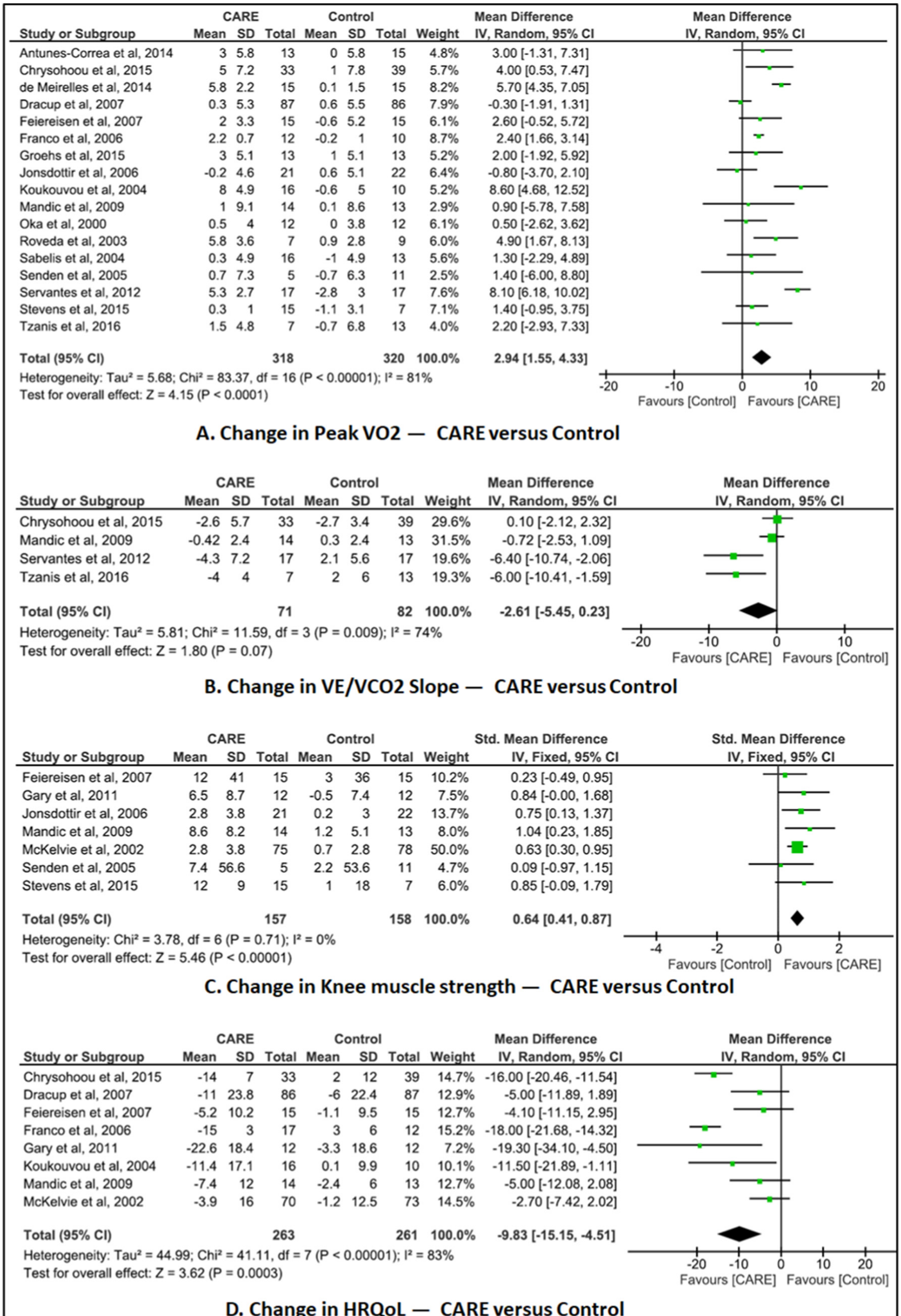

Fig. 3. Combined aerobic and resistance training versus control (no exercise). Review Manager (RevMan). Version 5.3 The Cochrane Collaboration, 2013.

analysis [11] examined the effects of resistance training on muscle strength, aerobic capacity and HRQoL. The authors reported that resistance training, as a single intervention, can increase muscle strength, aerobic capacity and HRQoL in patients with HF [11]. The assessment of the HRQoL is also an essential issue in HFrEF. Moreover, HRQoL is an essential component in an exercise rehabilitation program and is well known to be related to exercise capacity and improves meaningfully when the patients with HF are engaged in an exercise rehabilitation program [72]. In addition, our results are in agreement with the study of Cornelis et al., that investigated the effectiveness of different exercise modalities on prognostic cardiopulmonary exercise test parameters and quality of life. The meta-analysis showed that combined continuous-strength training significantly improve quality of life compared to continuous training alone [13]. In addition they advise to include resistance training in combination with another form of training, to improve exercise capacity and prognosis [13].

Our results showed that there is a nonsignificant difference in VE/VCO2 slope for participants in the combined aerobic and resistance training group compared both with control group without exercise and to aerobic training group. In comparison with the Peak VO_2 we observed that only a few studies have used VE/VCO2 slope as an outcome. It is important that further studies include the VE/VCO2 slope as an outcome because the VE/VCO2 slope has recently demonstrated prognostic significance in patients with HF [73,74]. In addition, high VE/VCO2 slope (typically > 34) are at a greater risk of a cardiovascular event [30,74,75].

Despite the benefits and recommendations in favor of exercise training, there is a lack of utilization of exercise and cardiac rehabilitation in HF patients. Studies indicate that between 40% and 91% of patients with heart failure do not engage in any regular exercise [76]. Recently Deka et al. [77], summarized exercise recommendations for patients with HF, and analyzed the exercise prescription methodologies used in studies that have reported exercise adherence. Most studies did not indicate program adherence as a primary outcome measure. In relation to the combination of aerobic and resistance training, Deka et al., reported that studies of exercise programs that included resistance exercise along with aerobic exercise reported adherence of 75–99% to the resistance exercises [77].

The result of this systematic review is limited by the lack of high-quality, and multicenter studies. So, we are not able to make judgments about the best protocol of combined aerobic and resistance training for HFrEF patients. A notable limitation of the included studies is the small sample sizes in most the studies. However, the criteria for methodological quality and the presence of 2 independent reviewers, a wide search in multiple databases without language or time restrictions, and the use of specific tools for the analyses were carried out to minimize the biases involved in this systematic review.

This review highlights the paucity of high-quality research addressing combined aerobic and resistance training in HFrEF patients. Further investigations into the prescription of the aerobic and resistance training variables (e.g. intensity, volume, frequency, duration, etc.) are recommended to enhance our understanding of the real positive effects of combined aerobic and resistance training in HFrEF patients.

5. Conclusion

Combined aerobic and resistance training was more efficient than aerobic training on muscle strength and HRQoL improvement in HFrEF patients. When compared to controls without exercise, combined aerobic and resistance training was efficient in improvement in peak VO_2, muscle strength and HRQoL. Thus, taking in account the available studies, this meta-analysis showed that the combination of aerobic and resistance training is an effective modality in the cardiac rehabilitation and should be considered as a component of care of HFrEF patients.

Declaration of Competing Interest

There is no conflict of interest

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.02.050.

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