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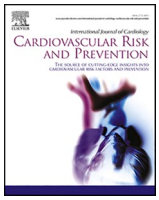

Cardiac rehabilitation for participants with implantable cardiac devices: A systematic review and meta-analysis

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ABSTRACT

Aim: The aim is to discuss efficacy and safety of exercise-based cardiac rehabilitation (CR) programmes in participants with implantable cardiac devices compared with usual care.
Methods: MEDLINE, EMBASE and Cochrane databases were searched from inspection till July 15, 2022. Randomized controlled trials were included if they enrolled adult participants with implantable cardiac devices and tested exercise-based CR interventions in comparison with any control. Risk of bias was assessed, and endpoints data were pooled using random-effects model.
Results: Sixteen randomized trials enrolling 2053 participants were included. Study interventions differed between studies in terms of programme components, setting, exercise intensity, and follow-up. All studies included physical exercise component. In both implantable cardioverter defibrillators (ICD) and cardiac resynchronization therapy (CRT) groups, exercise training in CR programmes improved peak oxygen uptake (VO_2) [(mean difference (MD) 2.08 ml/kg/min; 95 % CI: 1.44–2.728, $p < 0.0001$; $I^2 = 99$ %) and (MD 2.24 ml/kg/min; 95 % CI: 1.43–3.04, $p < 0.0001$; $I^2 = 96$ %), respectively] and 6-min walk test in ICD group (MD 41.51 m; 95 % CI: 15.19–67.82 m, $p = 0.002$; $I^2 = 95$ %) compared with usual care. In CRT group, there was no statistically significant improvement in left ventricular ejection fraction change between comparison groups. The results were consistent in subgroup analysis according to high or low-to-moderate exercise intensity for change in peak VO_2 and ejection fraction in CRT group. There was no difference in number of ICD shocks between the comparators.
Conclusion: Exercise-based CR programmes appear to be safe when enrolling participants with implantable cardiac devices and leading to favourable functional outcomes.

1. Introduction

The use of implantable cardiac devices has significantly increased over the past three decades. These devices, including pacemakers, implantable cardioverter defibrillators (ICD), cardiac resynchronization therapy (CRT) devices, and CRT devices with ICD (CRT-D), are indicated for the treatment of arrhythmias, such as bradycardia or ventricular arrhythmias, and for preventing sudden cardiac arrest in heart failure patients [1]. The benefits of these devices extend beyond improved mortality and safety [1,2], with improvement in quality of life (QoL) also observed. For instance, pacemaker implantation for bradycardia has been associated with improved health-related QoL in both the short- and long-term (7.5 years) [1]. Despite these benefits, implantable cardiac devices can also result in complications (e.g., bleeding, infection, lead dysfunction, inappropriate shocks) [3], as well as psychological problems such as anxiety and depression [1,4]. These emotional sequelae can negatively impact QoL, increase rehospitalization rates, reduce productivity and earnings, and increase the risk of morbidity and mortality [4]. However, it has been observed that improvements in cardiac symptoms and rehabilitation have been found to reduce anxiety

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levels at six-month follow-up [5]. Early identification and management of adverse emotional responses may also prevent the development of depression [1].

Comprehensive cardiac rehabilitation (CR) that includes education, exercise training, psychosocial management, and behaviour modification is beneficial in improving physical and emotional health for individuals with heart diseases [4]. Consequently, CR reduced mortality, rehospitalization, healthcare-related costs, and improved QoL and exercise capacity in patients with history of myocardial infarction and heart failure [4,6,7]. Despite the known benefits of CR in improving physical and emotional outcomes for heart disease patients, there is limited and inconsistent evidence regarding its effectiveness in individuals with cardiac devices. Evidence on CR for patients after cardiac device implantation is limited and inconsistent. Furthermore, there is a lack of international guidelines with universal recommendations or protocols for CR in this patient population [4]. This systematic review aims to discuss and evaluate the efficacy and safety of exercise-based CR programmes in participants with implantable cardiac devices, namely ICD and CRT ± ICD, compared with the usual care.

2. Methods

This systematic review and meta-analysis was performed according to the 'Cochrane Handbook for Systematic Reviews [8]. The reporting of the study was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [9,10] and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42022342316.

2.1. Search strategy

An electronic literature search was conducted by two authors (D.A. and R.K.) using MEDLINE, EMBASE, and CENTRALE (Cochrane library) from inspection till July 15, 2022. The electronic databases were searched for articles containing the following terms "Pacemaker, Artificial", "Cardiac Resynchronization Therapy Devices" and "Defibrillators, Implantable" which were combined with "Cardiac Rehabilitation" and "Exercise", each using Boolean operators (i.e., "OR" and "AND"). The following search threads, for example, were created: (("Pacemaker, Artificial"[Mesh] OR "Cardiac Resynchronization Therapy Devices"[Mesh]) AND "Exercise"[Mesh], ("Pacemaker, Artificial"[Mesh] OR "Cardiac Resynchronization Therapy Devices"[Mesh]) AND "Cardiac Rehabilitation"[Mesh], ("Defibrillators, Implantable"[Mesh]) AND "Cardiac Rehabilitation"[Mesh], and ("Defibrillators, Implantable"[Mesh]) AND "Exercise"[Mesh]. The search was limited to "Clinical Trial" and "English" language. Another electronic literature search to explore the ongoing registered clinical studies on the United States National Institutes of Health Registry (http://clinicaltrials.gov/) was conducted on June 19, 2022, using similar terms combinations. Manual screening by checking of the references of the identified studies was also undertaken to identify other relevant trials. Contacting study authors for clarifications or missing data was not needed for additional data. The detailed search strategy is presented in Table S1.

2.2. Eligibility criteria

This systematic review included randomized controlled trials (RCTs) that enrolled adult participants treated with any type of implantable cardiac device and compared the efficacy and safety of exercise-based cardiac rehabilitation (CR) programs against any control group. Excluded from this review were studies that enrolled non-adult participants, retrospective studies, case reports or series, conference posters, and proceedings.

2.3. Study selection and data extraction

The literature search records were reviewed at both the title and abstract levels. The potential abstracts were then retrieved in full text. The selected studies were tabulated, and data was extracted for the study design, year of publication, recruitment period, main country for multicentre studies, device indication, selected demographics and comorbidities, setting, intervention, risk of bias, and outcomes. Data extraction was performed by one author (R.K.) to ensure consistency and verified by another author (H.T.). The primary outcome was exercise capacity, which included the peak oxygen uptake (VO_2) and the 6-min walk test (6-MWT). Other outcomes evaluated included QoL, improvement in left ventricular ejection fraction (LVEF) for patients with a CRT device, incidence of ICD shocks, mortality, and hospitalization. High-intensity training was defined as peak VO_2 of 85% or more or peak heart rate at 90% or more of the target heart rate [11].

2.4. Risk of bias and quality assessment

The revised Cochrane risk-of-bias (RoB-2) tool for randomized trials was used to assess the methodological quality of each included study. The tool consists of five core domains: randomisation process (i.e., generation of random sequence and allocation concealment), deviation from intended treatment (e.g., blinding of participants and personnel), missing data (i.e., incomplete outcome data), outcome assessment, and selective outcome reporting. Each domain and the overall study were judged as for low, some, or high risk of bias [12]. The risk of bias assessment for all outcomes was performed by two authors (D.A., R.K.) and the agreement between them was quantified using Cohen's kappa coefficient [13]. Disagreement was solved by involving a third author (H.T.).

2.5. Statistical analysis

The odds ratio (OR) of clinical endpoint proportion and mean difference (MD) of the improvement in the functional endpoint between experimental and control groups was calculated with 95% confidence interval (CI), and a minimum of two studies were meta-analysed for each endpoint. The standard error of the improvement was calculated using the following formula: $= SD\sqrt{\frac{2}{N}}$, where SE is the standard error of the improvement, SD is the average standard deviation of the pre- and post-intervention groups, N is the sample size of the group. An aggregate data approach was used with a random-effects model. The inconsistency between the trials was assessed by visual inspection of forest plots, CI, Q statistics, and inconsistency factor. Sensitivity analysis was performed to assess the robustness of findings for the shortest follow-up period, and subgroup analysis was performed based on exercise intensity. Reporting or publication bias was evaluated using a visual inspection of the funnel plot [14–16]. The analysis was carried out using R Software (R-4.2.3), and SPSS version 29 (Armonk, NY: IBM Corp.) was used to identify the level of agreement between the authors by measuring Cohen's kappa coefficient.

3. Results

3.1. Search results

A total of 1161 search records were screened based on titles and abstracts. Of these, 48 studies were retrieved in full text and assessed for eligibility for inclusion. After excluding 32 studies for various reasons (Tables S2 and S3), 16 eligible randomized trials published between 2003 and 2021 were identified [17–32]. The PRISMA flow diagram shows the process of selecting and excluding literature search records (Fig. 1). A search of the United States National Institutes of Health Registry (ClinicalTrials.gov) resulted in three ongoing studies, after

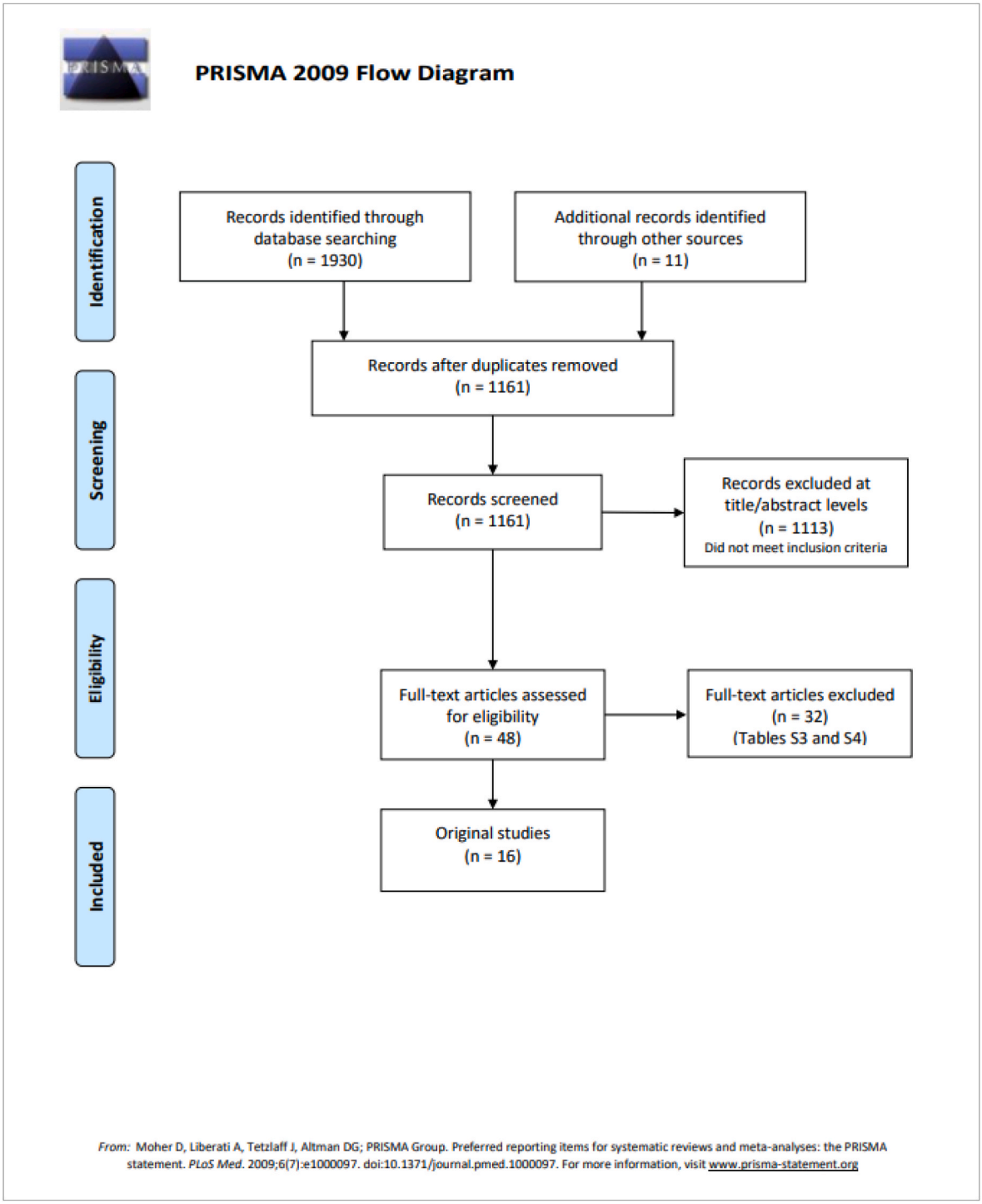

Fig. 1. Literature search flow diagram.

duplicates were removed (Tables S1 and S4). One included study was a subgroup from a big study [24].

3.2. Study characteristics

The 16 RCTs [17–32] included 2053 participants and from 11 European countries [18,20,22,23,25–27,29–32], the United States [21,24], Iran [19], Brazil [28] and Republic of Korea [17]. One large study (N = 1053) accounted for over half of the total population (51.3%) [24], while the other studies enrolled participants in ranges from 16 to 196. Three studies enrolled participants using any device (ICD or CRT) were not included in the analysis [17–19], except for one of them reporting results of both ICD and CRT groups separately which were analysed with their respective groups not as combined [18]. Seven studies enrolled patients with an ICD [20–26]. However, one study had approximately 60% of its participants with an ICD [25], and another one included 12% of participants with an CRT (Table 1) [20]. The remaining six studies enrolled patients with CRT [27–32]. The recruitment periods were not reported in all the studies. Of the total participants, 1076 were randomized to exercise interventions and 997 to control. The general study characteristics of the included studies are presented in Table 1.

Table 1
Study general characteristics.

Study	Year of publication	Recruitment period	Main country	Sample size	Intervention/ Comparator size	Study design	Setting	Comments
Any device								
Ahn et al., 2021 [17]	2021	–	Republic of Korea	27	12/15	Single centre, pilot RCT	Hospital	New pacemaker
Belardinelli et al., 2006 [18]	2006	8 months	Italy	52	30/22	Longitudinal RCT	Hospital	ICD/CRT-D Primary and secondary prevention ICD in last 3 months CRT: 25/52 (48%)
Rakhshan et al., 2017 [19]	2017	September 2018 to February 2019	Iran	100	50/50	RCT	Hospital and home	ICD: 26/50 (52%) CRT: 24/50 (48%) Any device duration of use was allowed
Implantable cardioverter defibrillator								
Berg et al., 2015 (COPE-ICD) [20]	2015	October 2007 to November 2009	Denmark	196	99/97	RCT	Hospital and home	First time ICD implant. Primary and secondary prevention. Randomisation 3 months after ICD implantation. CRT: 23/196 (12%)
Dougherty et al., 2015 [21]	2015	2007–2012	US	160	84/76	Single-blind randomized control	Community and home	Primary or secondary prevention
Fitchet et al., 2003 [22]	2003	–	UK	16	8/8	RCT	Hospital	Any duration of device use was allowed
Frizelle et al., 2004 [23]	2004	–	UK	22	12/10	RCT	Hospital	Any duration of device use was allowed
Piccini et al., 2013 (HF-ACTION) [24]	2013	–	US	1053	546/507	Multicentre, international RCT	Hospital and home	–
Piotrowicz et al., 2015 [25]	2015	December 2009 to June 2012	Poland	107	75/32[a]	Single-centre, prospective, parallel-group, RCT	Home-based telemonitoring	–
Smolis-Bąk et al., 2017 [26]	2017	January 2008 to December 2011	Poland	84	41/43	Single centre RCT	In-patient and out-patient	Primary prevention
Cardiac resynchronization therapy ± ICD								
Conraads et al., 2007 [27]	2007	–	Belgium	17	8/9	Single centre Pilot RCT	Ambulatory	Patients had 1 month of relative rest before starting exercise programme to allow recovery and prevent lead dislocation
Nobre et al., 2016 [28]	2016	–	Brazil	30	14/16[b]	Randomised	Hospital	–
Patwala et al., 2009 [29]	2009	July 2004 to June 2006	UK	50	25/25	Randomised	Non-clinical (university)	–
Santa-Clara et al., 2019 [30]	2019	2012 to 2015	Portugal	63 Completed study: 37 (PP)	34/29 Completed study: 20/17	Single centre, randomised	Hospital	–
Smolis-Bąk et al., 2015 [31]	2015	2008–2012	Poland	52	26/26	Single centre RCT	Hospital and telemonitoring	–
Spee et al., 2020 [32]	2020	February 2011 to April 2014	Netherlands	24	12/12	Multicentre, RCT	Hospital	–

Abbreviations: BV, biventricular; CRT, cardiac resynchronization therapy; HF, heart failure; ICD, Implantablecardioverter defibrillator; LBBB, left bundle branch block; PP, per-protocol; RCT, randomised controlled trial; US, The United States of America.

[a] Patients with ICD: 56/75 (74.7%) vs 16/32 (50%), P = 0.0128.

[b] 15 participants dropped out; not intention-to-treat analysis and results reported for 9/6 participants.

3.3. Patient characteristics

The age of the study population ranged from 40 to 69 years old, with the majority (ranging from 25 to 96%) being men. The most frequent cardiac condition among participants in the ICD group was of cardiomyopathy of an ischemic aetiology, while most participants with CRT had cardiomyopathy of a non-ischemic aetiology. The prevalence of hypertension ranged from 18% to 66%. Most of the patients were overweight and had reduced LVEF. Table 2 presents selected baseline patient characteristics.

3.4. Study intervention

The study interventions differed in terms of programme components, setting, intensity, and follow-up. All the studies included physical exercise components, with two studies including exercise and psychoeducation [19,20], and three studies included a three-component intervention (i.e., education, physical training, and

Table 2
Patient baseline characteristics.

Study	Age (year)	Male sex n/N (%)	BMI (kg/m^2)	HTN n/N (%)	Smoking n (%)	AF n/N (%)	ICM n/N (%)	NICM n/N (%)	LVEF (%)	NYHA I/II n/N (%)	Peak VO_2 (ml/kg/min)
Any device Intervention vs Control											
Ahn et al., 2021 [17]	67.8 vs 62.9	3/12 (25) vs 5/15 (33.3)	24.8 vs 24.8	7/12 (58.3) vs 6/15 (40)	–	–	–	–	60 vs 60	–	15.6 vs 16
Belardinelli et al., 2006 [18]	55 vs 53	30/30 (100) vs 22/22 (100)	–	–	–	–	–	–	30.2 vs 33.6	NYHA II: 17/30 (56.6) vs 12/22 (54.5)	14.8 vs 14.7
Rakhshan et al., 2017 [19]	Age >40: 42/50 (84%) vs 41/50 (82%)	20/50 (40) vs 21/50 (42)	–	13/50 (26) vs 16/50 (32)	–	2/50 (4) vs 2/50 (4)	–	–	–	–	–
Implantable cardioverter defibrillator Intervention vs Control											
Berg et al., 2015 (COPE-ICD) [20]	57.6 vs 56.7	79/99 (80) vs 76/97 (78)	BMI≥30: 24/99 (24) vs 19/97 (20)	18/99 (18) vs 23/97 (24)	–	27/99 (27) vs 21/97 (22)	–	–	32.2 vs 32.7	72/99 (72.7) vs 62/97 (63.9)	20.9 vs 20.8 (At randomisation)
Dougherty et al., 2015 [21]	56.1 ± 12.1 vs 53.6 ± 12.2	67/84 (79.8) vs 57/76 (75.0)	29.3 ± 5.2 vs 29.9 ± 5.4	–	–	–	37 (44.0) vs 32 (42.1)	27 (32.1) vs 21 (27.6)	38.7 ± 14.8 vs 42.6 ± 16.5	–	24.6 ± 5.7 vs 23.5 ± 5.8
Fitchet et al., 2003 [22]	All patients: 58	All patient: 14/16 (88)	–	–	–	All patients: 1/16 (6.25)	–	All patients: 2/16 (12.5)	All patients: 38	–	–
Frizelle et al., 2004 [23]	60.4 vs 62.8	–	–	–	–	–	–	–	–	–	–
Piccini et al., 2013 (HF-ACTION) [24]	61 vs 60	433/546 (79) vs 398/507 (79)	30 vs 29	314/546 (58) vs 274/507 (54)	–	155/546 (28) vs 140/507 (28)	331/546 (61) vs 313/507 (62)	–	24 vs 24	NYHA II: 312/546 (57) vs 291/507 (57)	14.1 vs 14.1
Piotrowicz et al., 2015 [25]	54.4 vs 62.1 P = 0.0029	64/75 (85) vs 31/32 (97)	28 vs 28	–	–	9/75 (12) vs 5/32 (15.6)	50/75 (66.7) vs 27/32 (84.4) P = 0.0318	25/75 (33.3) vs 4/32 (15.6) P = 0.0318	30 vs 34 P = 0.0227	NYHA II: 51/75 (68) vs 23/32 (72)	16.1 vs 17.4
Smolis-Bąk et al., 2017 [26]	63.7 vs 61.1	36/41 (87.8) vs 40/43 (93)	28.3 vs 28.2	27/41 (65.9) vs 24/43 (55.8)	–	14/41 (34.1) 23/43 (53.4)	36/41 (87.8) vs 30/43 (69.8)	5/41 (12.2) vs 13/43 (30.2)	–	–	13 vs 12.5
Cardiac resynchronization therapy ± ICD Intervention vs Control											
Conraads et al., 2007 [27]	57 ± 2 vs 61 ± 4	3/8 (37.5) vs 5/9 (55.5)	–	–	–	–	1/8 (12.5) vs 3/9 (33.3)	7/8 (87.5) vs 6/9 (66.6)	27 ± 5 vs 28 ± 5	–	13.8 ± 1.0 vs 11.9 ± 0.9
Nobre et al., 2016 [28]	54 vs 55	7/14 (50) vs 9/16 (56.2)	25.2 vs 26.9	–	–	0	2/14 (14.3) vs 1/16 (6.2)	15/16 (93.7) vs 12/14 (85.7)	28 vs 27	13/14 (92.8) vs 12/16 (75)	17.9 vs 19.2
Patwala et al., 2009 [29]	64.4	All patients: 46/50 (92%)	–	–	–	All patients: 17/50 (34%)	–	–	All patients: 23.6	–	Before CRT: 16.12 At randomisation: 18.41

(*continued on next page*)

Table 2 (*continued*)

Study	Age (year)	Male sex n/N (%)	BMI (kg/m^2)	HTN n/N (%)	Smoking n (%)	AF n/N (%)	ICM n/N (%)	NICM n/N (%)	LVEF (%)	NYHA I/II n/N (%)	Peak VO_2 (ml/kg/min)
Santa-Clara et al., 2019 [30]	68 vs 67	15/20 (76.5) vs 13/17 (75)	26.3 vs 28.7	–	–	–	8/20 (41.9) vs 6/17 (35.7)	11/20 (58) vs 11/17 (64.3)	ITT: 16.9 vs 24.9 PP: 27 vs 25.5	–	ITT: 13.8 vs 16.4 PP: 14 vs 17.4
Smolis-Bąk et al., 2015 [31]	60 vs 65 P = 0.0192	25/26 (96.1) vs 22/26 (84.8)	29.3 vs 27.4	12/26 (46.1) vs 10/26 (38.5)	–	17/26 (65.4) vs 15/26 (57.7)	11/26 (42.6) vs 13/26 (50)	15/26 (57.6) vs 13/26 (50)	25.3 vs 24.9	–	13 vs 10.7
Spee et al., 2020 [32]	68.9 vs 68.8	12/12 (100%) vs 7/12 (58.3)	–	–	–	3/12 (25) vs 2/12 (16.6)	8/12 (66.6) vs 4/12 (33.3)	4/12 (33.3) vs 8/12 (66.6)	26.9 vs 30.2 All patient at randomisation: 35.7	NYHA II: 5/12 (41.6) vs 1/12 (8.3) 3 months before randomisation	All patient at randomisation: 18.7

Abbreviations: AF, atrial fibrillation; AV, atrioventricular; BMI, body mass index; CRT, cardiac resynchronization therapy; HTN, hypertension; ICD, Implantablecardioverter defibrillator; ICM, ischemic cardiomyopathy; ITT, intention-to-treat; LVEF, left ventricular ejection fraction; NICM, non-ischemic cardiomyopathy; PP, per-protocol; SSS, sick sinus syndrome.

psychological/behavioural intervention) [19,22,23]. Three studies in the CRT group investigated high intensity training [29,30,32]. Most of the programmes were delivered in a hospital setting (i.e., inpatient and/or outpatient) or a combination of hospital and home setting. Berg et al. delivered their intervention according to participant's preference, either in hospital or at home [20]. Piotrowicz and colleagues performed home-based sessions [25]. The frequency of the intervention ranged from one to five times per week and the duration of each session and training programme ranged from 40 to 60 min, and four to 24 weeks, respectively. Three studies started exercise training after one [28] or three [29,32] months of CRT implantation to allow recovery and prevent lead dislocation. The follow-up duration ranged from four weeks to two years. Table S5 outlines the interventions for each included study, while Tables S6–S8 define and detail the exercise testing, QoL assessment, and the 6-MWT performed in the studies, respectively.

3.5. Risk-of-Bias assessment

The overall risk of bias assessment was "high" in 10 and had "some concerns" in six studies, according to the revised RoB-2 tool (Table S9). The kappa agreement between the two authors (D.A., R.K.) ranged between −0.08 and 1.00 (i.e., no and perfect agreement, respectively) as presented in Table S10.

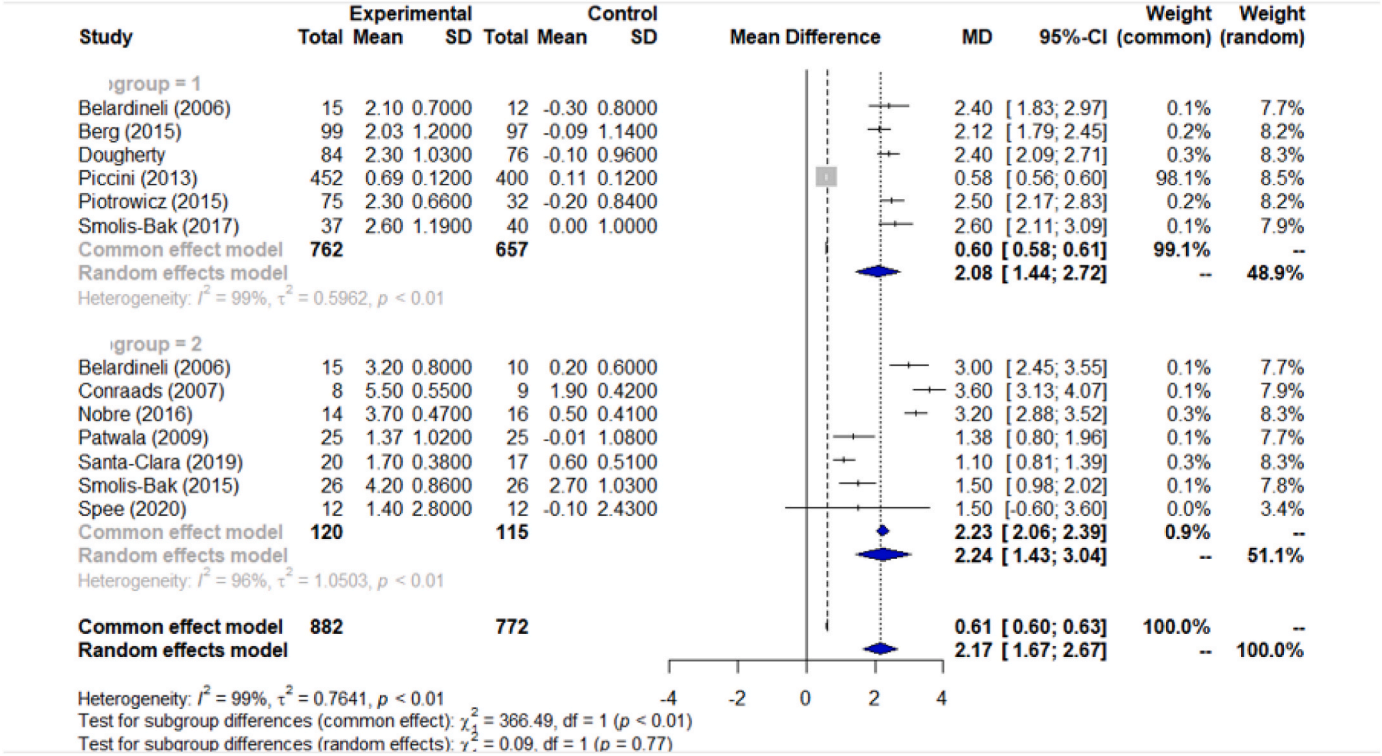

Fig. 2. Change in peak oxygen uptake Group 1 represents ICD and Group2 represents CRT studies.

3.6. Outcome measurements

3.6.1. Exercise capacity in maximal exercise test

Exercise capacity was the most reported endpoint in all studies except three [19,22,23]. In both ICD and CRT groups, exercise training in CR programmes improved peak VO_2 compared with control groups [(MD 2.08 ml/kg/min; 95% CI: 1.44–2.728, p < 0.0001; I^2 = 99%) and (MD 2.24 ml/kg/min; 95% CI: 1.43–3.04, p < 0.0001; I^2 = 96%), respectively] with significant heterogeneity. Sensitivity analysis after removing the studies with the shortest follow-up assessment (i.e., 8 weeks), resulted in similar results (Figs. S1 and S2). When the ICD and CRT groups were combined, the CR programme continues to show greater improvement in the peak VO_2 compared with control groups (MD 2.17 ml/kg/min; 95% CI: 1.67–2.67 ml/kg/min, p < 0.0001; I^2 = 99%) (Fig. 2). Table S11 summarizes the reported functional outcomes.

3.6.2. Exercise capacity in sub-maximal exercise test

Three studies in the ICD group reported results on 6-MWT distance [20,25,26], and patients under CR programmes showed greater improvement in 6-MWT distance than those in control groups (MD 41.51 m; 95% CI: 15.19–67.82 m, p = 0.002; I^2 = 95%) (Fig. 3).

3.6.3. Cardiac function

All studies on patients with CRT reported LVEF at baseline and at the end of follow-up period [18,27–32]. Baseline LVEF ranged from 25% to 35%. There was no statistically significant improvement in the LVEF change between the comparison groups (Fig. 4).

3.6.4. Other endpoints

Only five studies reported death; two of them reported no death [18,21] and the others reported non-significant death rates between the comparison groups [24,26,31]. One study reported death as composite with ICD shocks [24]. The pooled data of the remaining two trials of different devices did not show significant difference (OR 0.66; 95% CI: 0.22–2.0, p = 0.46; I^2 = 0%) (Fig. S3) [26,31]. Three studies reported non-significant all-cause hospitalization difference between comparators [21,26,31], whereas, one found a significantly higher hospitalization rate in the device group (67% vs 45.4%, p < 0.0001) regardless of the device type [18]. However, when data from the two studies in the ICD group were combined (OR 1.18; 95% CI: 0.62–2.25, p = 0.62; I^2 = 0%) [21,26] or when the other two studies [18,31] with different device type were added to them (OR 1.27; 95% CI: 0.77–2.09, p = 0.35; I^2 = 0%), there was no difference in hospitalization endpoint (Figs. S4 and S5). There was no difference in the number of ICD shocks between the comparators in the studies that reported this endpoint (Table S12) [18,21,22,24,26,31].

3.7. Subgroup analysis

Subgroup analysis was conducted to assess the changes in peak VO_2 and LVEF according to the exercise intensity in the CRT group. Three studies adopted high intensity [29,30,32] and four adopted low-to-moderate intensity exercise training [18,27,28,31]. The change in peak VO_2 significantly improved in both subgroups regardless of the exercise intensity [(MD 1.16 ml/kg/min; 95% CI: 0.09–1.42, p = 0.0006; I^2 = 0%) and (MD 2.70 ml/kg/min; 95% CI: 1.86–3.54, p = 0.0006; I^2 = 90%), respectively (Fig. 5)]. Whereas the change in LVEF was not affected in either group (Fig. 6).

3.8. Publication bias

Funnel plots of the peak VO_2 endpoint for the combined groups (ICD and CRT) indicated publication bias in the ICD group (Figs. S6 and S7). The funnel plots for change in 6-MWT distance in ICD group and change in LVEF in CRT group indicated publication bias (Figs. S8 and S9). The funnel plots for death and hospitalization endpoints indicated close symmetry (Figs. S10–S12).

4. Discussion

This systematic review and meta-analysis evaluated the effect of exercise-based CR on patients with ICD, CRT or CRT-D. Sixteen RCTs were included, enrolling 2053 participants from 11 European countries, the United States, Iran, Brazil, and South Korea. The majority of the interventions included physical exercise, with some including additional psychoeducation or psychological interventions. The CR programs were delivered in hospital settings, at home, or a combination of both, and the exercise sessions were different in terms of intensity, frequency, and duration. The results showed a significant improvement in peak VO_2 and the 6-MWT, but there was no clear conclusion about the improvement in clinical or safety outcomes given the limited number of studies that reported them. The overall risk of bias was high in 10 of the 16 studies.

The results of this systematic review and meta-analysis showed that exercise-based CR improved cardiorespiratory fitness (CRF) in patients with implantable cardiac devices. Extensive evidence from the last three decades has demonstrated that CRF is a strong and independent predictor of all-cause [33,34] and cardiovascular mortality [35], with unfit individuals having up to three times the risk of cardiovascular mortality compared to fit individuals [36]. The evidence is strong that the American Heart Association has advised that CRF is considered a clinical vital sign [37]. Data from retrospective [38] and observational [39] studies shows that exercise-based CR is associated with reduced mortality in patients with implantable cardiac devices. This association may be mediated by the improvement in CRF. There is, however, a lack of randomized controlled trials in this area [40]; therefore, more research is required to assess the causal relationship between exercise and mortality in this population.

In general, findings from published observational studies are in line with the results of the present review. The retrospective study by Buckley et al. on 12,016 patients with any cardiac implantable electronic device showed that an exercise-based CR programme was associated with a decrease in the risk of all-cause mortality and re-hospitalization, but with a higher rate of hospitalization for arrhythmias in the CR group [39]. Lau and colleagues evaluated, in a pre- and post-intervention study design, the efficacy and safety of an early home-based walking programme in participants with their first-time ICD

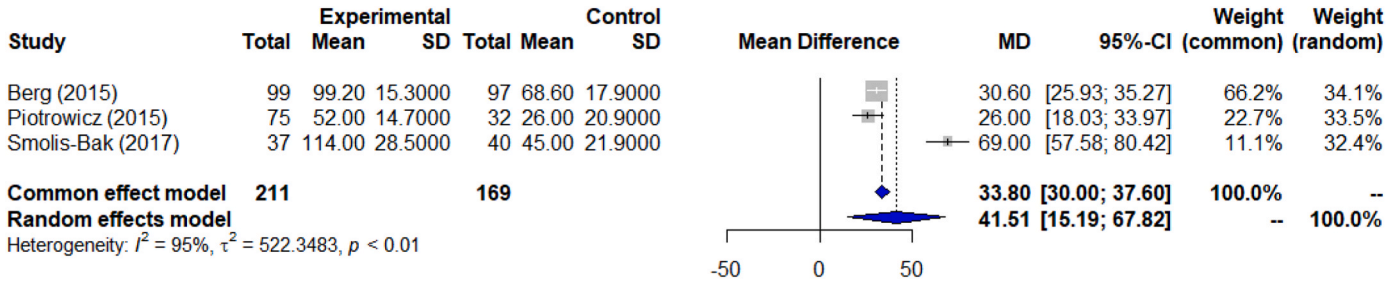

Fig. 3. Change in 6-min walk test distance.

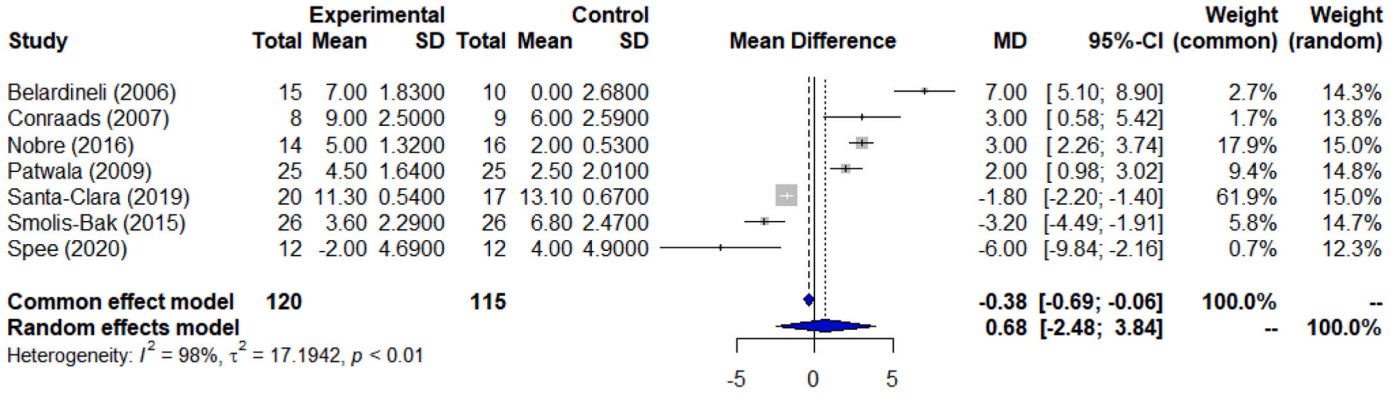

Fig. 4. Change in left ventricular ejection fraction – CRT group.

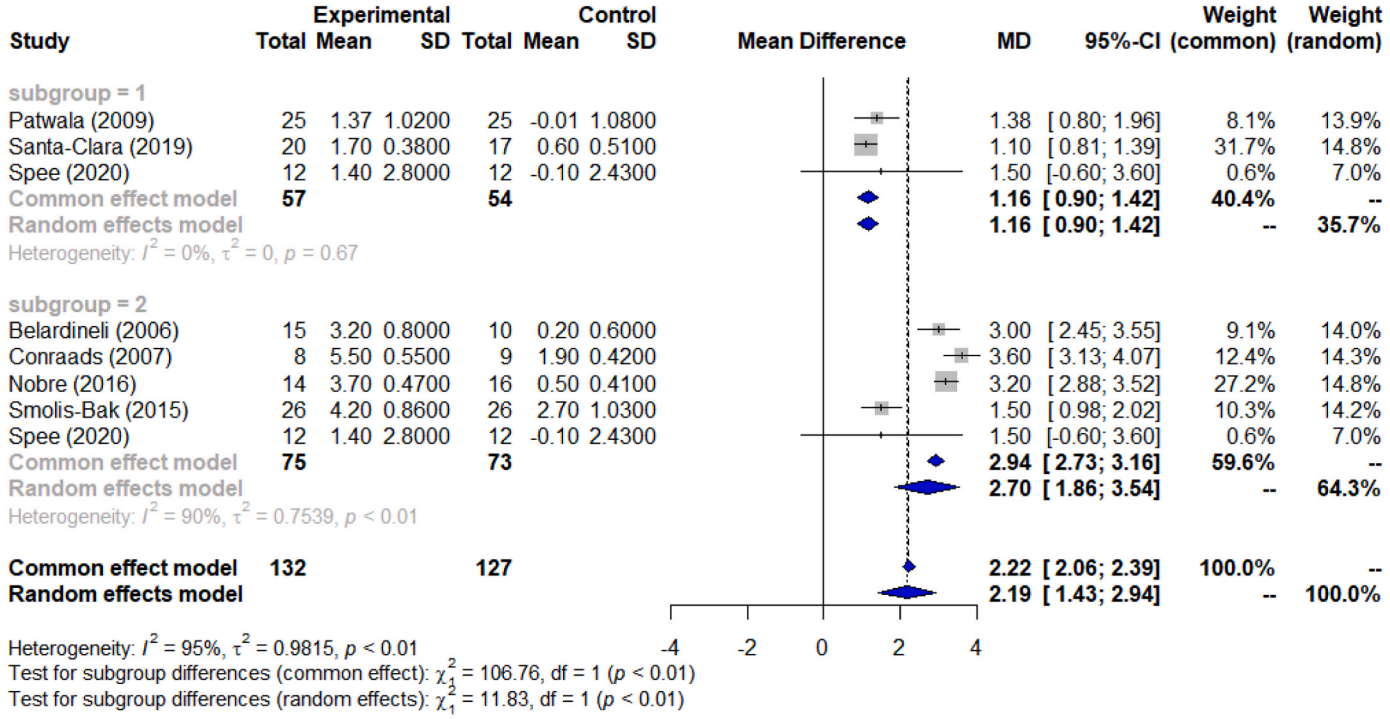

Fig. 5. Change in peak oxygen uptake according to exercise intensity Subgroup 1 represents High intensity and Subgroup2 represents non-high intensity training.

(N = 301). The authors concluded that an early walking programme after an ICD implantation was safe, effective, and resulted in few ICD shocks [2]. In a prospective, non-randomized controlled study, Isaksen et al. assessed short- and long-term impact of 12-week aerobic interval training programme in ischemic heart failure patients with ICD. The authors concluded that the programme led to significant improvement QoL measures [41]. In patients with CRT, Martens et al. showed that a structured multidisciplinary CR programme was safe and resulted in improvement of both functional (NYHA class, reverse remodeling) and clinical outcomes (mortality and hospitalization for heart failure) [38].

In a systematic review without a meta-analysis published by Alswyan et al. the authors identified studies on exercise interventions in patients with cardiac implantable electronic devices, including ICDs, CRT devices, and ventricular assist devices. They concluded that exercise interventions at moderate to high intensity with or without psychoeducational components were safe and improved cardiopulmonary outcomes [42]. A Cochrane review of eight randomized trials by Nielsen et al. [4], enrolled ICD patients with or without CRT, all of which are included in our systematic review [18,20,21,23–26,31]. The authors concluded that exercise-based CR improved exercise capacity based on very low-quality studies (pooled peak VO_2 MD: 0.91 ml/kg/min; 95% CI: 0.60–1.21; I^2 = 78%). In addition, they were unable to confirm the benefit with regards to mortality, health-related QoL, and serious adverse events [4]. Unlike the Cochrane review, we opted to classify the device groups as ICD and CRT with or without ICD group given the fact that a CRT, not an ICD, device can lead to improvement in cardiac function, namely LVEF [43].

Guo et al. tested the effect of exercise training in chronic heart failure patients with CRT by performing a systematic review and meta-analysis of seven randomized trials, all of which were also included in the present paper [18,27–32]. The authors stratified their analyses based on high [29,30,32] or non-high [18,27,28,31] intensity training. According to their analysis, they found that only non-high intensity training improved exercise capacity (change in peak VO_2: MD 3.05 ml/kg/min; 95% CI: 2.53–3.56 ml/kg/min, P < 0.00001; I^2 = 0%), cardiac function (change in LVEF: MD 4.97%; 95% CI: 1.44–8.49%, P = 0.006; I^2 = 59%), and health-related QoL (change in Minnesota living with heart failure questionnaire: MD -19.96; 95% CI: −21.57 to −18.34, P < 0.00001; I^2 = 0%) [11]. Our subgroups analysis showed the improvement in peak VO_2 regardless of exercise intensity. This is mainly since Santa-Clara et al.

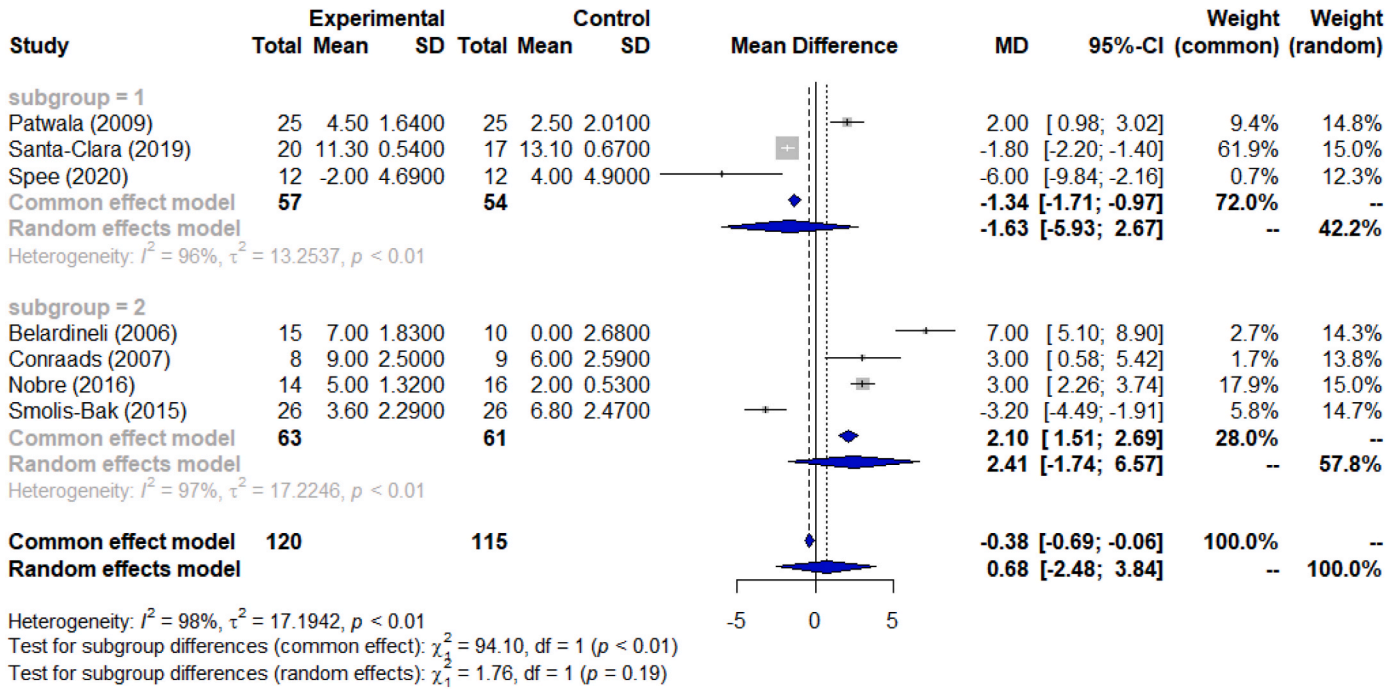

Fig. 6. Change in left ventricular ejection fraction according to exercise intensity Subgroup 1 represents High intensity and Subgroup 2 represents non-high intensity training.

study [30] was more conservative and used data based on intention to treat analysis, while in our study we used data based on per protocol analysis. Guo and colleagues justified the absence of benefit with high intensity training by the high rate of loss to follow up in one study [30], unbalanced baseline characteristics in another study [32], and by the fact that chronic heart failure patients may be unable to carry out extensive exercise levels [11]. Our pooled analysis to the QoL using SF-36 physical reported by two studies was not possible.

This comprehensive systematic review presented updated evidence on the effect of exercise training on the outcomes of patients with implanted ICD or CRT, with meta-analysis of pooled outcomes of interest in this setting. A comprehensive systematic literature search was conducted using broad terms to identify all possible RCTs. However, there are limitations that should be acknowledged. The open-label design of the studies, which can be justified given the nature of the intervention. Only one study stated to have blinded the assessors who performed data collection and management [20]. Furthermore, outcomes were blindly analysed. Most of the included trials were of low quality (i.e., high risk of bias) and small size, and reported few clinical and safety outcomes. There was clear heterogeneity in the aspects and components of the CR programmes and settings. It is not clear whether the results can be generalised to females or certain ethnicity or be considered cost-effective. This systematic review highlights the inconsistency in the scales used to evaluate QoL and psychological components of the programmes, as well as the inconsistencies in reporting participant outcomes. As a result, the authors suggest that well-designed, sufficiently powered RCTs are needed to robustly assess the effect of exercise-based CR in patients with implanted cardiac devices. The authors note that three additional clinical trials are awaited and referenced in Table S4.

5. Conclusion

Exercise-based CR programmes appear to be safe when enrolling participants with implantable cardiac devices, and lead to favourable functional outcomes.

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CRediT authorship contribution statement

Rasha Kaddoura: Conceptualization, Formal analysis, Methodology, Writing – original draft. **Hassan Al-Tamimi:** Conceptualization, Methodology, Writing – review & editing. **Dina Abushanab:** Methodology, Writing – review & editing. **Sajad Hayat:** Methodology, Writing – review & editing. **Theodoros Papasavvas:** Formal analysis, Methodology, Writing – review & editing.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2024.200255.

References

[1] G.M. Calvagna, G. Torrisi, C. Giuffrida, S. Patanè, Pacemaker, implantable cardioverter defibrillator, CRT, CRT-D, psychological difficulties and quality of life, Int. J. Cardiol. 174 (2) (2014) 378–380.
[2] E.T. Lau, E.A. Thompson, R.L. Burr, C.M. Dougherty, Safety and efficacy of an early home-based walking program after receipt of an initial implantable cardioverter-defibrillator, Arch. Phys. Med. Rehabil. 97 (8) (2016) 1228–1236.

[3] R. Tung, P. Zimetbaum, M.E. Josephson, A critical appraisal of implantable cardioverter-defibrillator therapy for the prevention of sudden cardiac death, J. Am. Coll. Cardiol. 52 (14) (2008) 1111–1121.
[4] K.M. Nielsen, A.D. Zwisler, R.S. Taylor, et al., Exercise-based cardiac rehabilitation for adult patients with an implantable cardioverter defibrillator, Cochrane Database Syst. Rev. 2 (2) (2019) CD011828.
[5] L. Sagnak, H. Ersoy, N. Karakoyunlu, et al., Evaluation of erectile dysfunction in permanent pacemaker implanted patients with cardiac rhythm disorder prediagnosis, Scot. Med. J. 58 (1) (2013) 7–11.
[6] J.R. Wilson, J. Groves, G. Rayos, Circulatory status and response to cardiac rehabilitation in patients with heart failure, Circulation 94 (7) (1996) 1567–1572.
[7] L. Anderson, D.R. Thompson, N. Oldridge, et al., Exercise-based cardiac rehabilitation for coronary heart disease, Cochrane Database Syst. Rev. 2016 (1) (2016) CD001800.
[8] J.P.T. Higgins, J. Thomas, J. Chandler, M. Cumpston, T. Li, M.J. Page, V.A. Welch, et al., Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (Updated February 2021), Cochrane, 2021. Available from: Cochrane Handbook for Systematic Reviews of Interventions | Cochrane Training. (Accessed 1 March 2022).
[9] D. Moher, A. Liberati, J. Tetzlaff, et al., PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, BMJ 339 (2009) b2535.
[10] M.J. Page, J.E. McKenzie, P.M. Bossuyt, et al., The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, BMJ 372 (2021) n71.
[11] R. Guo, Y. Wen, Y. Xu, et al., The impact of exercise training for chronic heart failure patients with cardiac resynchronization therapy: a systematic review and meta-analysis, Medicine (Baltim.) 100 (13) (2021) e25128.
[12] J.A.C. Sterne, J. Savović, M.J. Page, et al., RoB 2: a revised tool for assessing risk of bias in randomised trials, BMJ 366 (2019) l4898.
[13] M.L. McHugh, Interrater reliability: the kappa statistic, Biochem. Med. 22 (3) (2012) 276–282.
[14] J.P.T. Higgins, S. Green, Cochrane Handbook for Systematic Reviews of Interventions, The Cochrane Collaboration, 2011 [updated March, Version 5.1.0. www.handbook.cochrane.org. (Accessed 20 June 2022). Chapter: 9.5.2 Identifying and measuring heterogeneity (cochrane.org).
[15] D. Jackson, R. Turner, Power analysis for random-effects meta-analysis, Res. Synth. Methods 8 (3) (2017) 290–302.
[16] R.M. Turner, S.M. Bird, J.P. Higgins, The impact of study size on meta-analyses: examination of underpowered studies in Cochrane reviews, PLoS One 8 (3) (2013) e59202.
[17] J. Ahn, B.J. Lee, S.Y. Roh, et al., Role of early short-term cardiac rehabilitation in patients undergoing pacemaker implantation, Rev. Cardiovasc. Med. 22 (4) (2021) 1603–1610.
[18] R. Belardinelli, F. Capestro, A. Misiani, P. Scipione, D. Georgiou, Moderate exercise training improves functional capacity, quality of life, and endothelium-dependent vasodilation in chronic heart failure patients with implantable cardioverter defibrillators and cardiac resynchronization therapy, Eur. J. Cardiovasc. Prev. Rehabil. 13 (5) (2006) 818–825.
[19] M. Rakhshan, L. Ansari, Z. Molazem, N. Zare, Complications of heart rhythm management devices after cardiac rehabilitation program, Clin. Nurse Spec. 31 (3) (2017) E1–E6.
[20] S.K. Berg, P.U. Pedersen, A.D. Zwisler, et al., Comprehensive cardiac rehabilitation improves outcome for patients with implantable cardioverter defibrillator. Findings from the COPE-ICD randomised clinical trial, Eur. J. Cardiovasc. Nurs. 14 (1) (2015) 34–44.
[21] C.M. Dougherty, R.W. Glenny, R.L. Burr, G.L. Flo, P.J. Kudenchuk, Prospective randomized trial of moderately strenuous aerobic exercise after an implantable cardioverter defibrillator, Circulation 131 (21) (2015) 1835–1842.
[22] A. Fitchet, P.J. Doherty, C. Bundy, W. Bell, A.P. Fitzpatrick, C.J. Garratt, Comprehensive cardiac rehabilitation programme for implantable cardioverter-defibrillator patients: a randomised controlled trial, Heart 89 (2) (2003) 155–160.
[23] D.J. Frizelle, R.J. Lewin, G. Kaye, et al., Cognitive-behavioural rehabilitation programme for patients with an implanted cardioverter defibrillator: a pilot study, Br. J. Health Psychol. 9 (Pt 3) (2004) 381–392.
[24] J.P. Piccini, A.S. Hellkamp, D.J. Whellan, et al., Exercise training and implantable cardioverter-defibrillator shocks in patients with heart failure: results from HF-ACTION (heart failure and A controlled trial investigating outcomes of exercise TraiNing), JACC Heart Fail 1 (2) (2013) 142–148.
[25] E. Piotrowicz, T. Zieliński, R. Bodalski, et al., Home-based telemonitored Nordic walking training is well accepted, safe, effective and has high adherence among heart failure patients, including those with cardiovascular implantable electronic devices: a randomised controlled study, Eur J Prev Cardiol 22 (11) (2015) 1368–1377.
[26] E. Smolis-Bąk, H. Rymuza, B. Kazimierska, et al., Improvement of exercise tolerance in cardiopulmonary testing with sustained safety after regular training in outpatients with systolic heart failure (NYHA III) and an implantable cardioverter-defibrillator. Prospective 18-month randomized study, Arch. Med. Sci. 13 (5) (2017) 1094–1101.
[27] V.M. Conraads, M. Vanderheyden, B. Paelinck, et al., The effect of endurance training on exercise capacity following cardiac resynchronization therapy in chronic heart failure patients: a pilot trial, Eur. J. Cardiovasc. Prev. Rehabil. 14 (1) (2007) 99–106.
[28] T.S. Nobre, L.M. Antunes-Correa, R.V. Groehs, et al., Exercise training improves neurovascular control and calcium cycling gene expression in patients with heart failure with cardiac resynchronization therapy, Am. J. Physiol. Heart Circ. Physiol. 311 (5) (2016) H1180–H1188.
[29] A.Y. Patwala, P.R. Woods, L. Sharp, D.F. Goldspink, L.B. Tan, D.J. Wright, Maximizing patient benefit from cardiac resynchronization therapy with the addition of structured exercise training: a randomized controlled study, J. Am. Coll. Cardiol. 53 (25) (2009) 2332–2339.
[30] H. Santa-Clara, A. Abreu, X. Melo, et al., High-intensity interval training in cardiac resynchronization therapy: a randomized control trial, Eur. J. Appl. Physiol. 119 (8) (2019) 1757–1767.
[31] E. Smolis-Bąk, R. Dąbrowski, E. Piotrowicz, et al., Hospital-based and telemonitoring guided home-based training programs: effects on exercise tolerance and quality of life in patients with heart failure (NYHA class III) and cardiac resynchronization therapy. A randomized, prospective observation, Int. J. Cardiol. 199 (2015) 442–447.
[32] R.F. Spee, V.M. Niemeijer, T. Schoots, et al., High intensity interval training after cardiac resynchronization therapy: an explorative randomized controlled trial, Int. J. Cardiol. 299 (2020) 169–174.
[33] M.P. Harber, L.A. Kaminsky, R. Arena, et al., Impact of cardiorespiratory fitness on all-cause and disease-specific mortality: advances since 2009, Prog. Cardiovasc. Dis. 60 (1) (2017) 11–20.
[34] Y. Ezzatvar, M. Izquierdo, J. Núñez, J. Calatayud, R. Ramírez-Vélez, A. García-Hermoso, Cardiorespiratory fitness measured with cardiopulmonary exercise testing and mortality in patients with cardiovascular disease: a systematic review and meta-analysis, J Sport Health Sci 10 (6) (2021) 609–619.
[35] M.H. Al-Mallah, S. Sakr, A. Al-Qunaibet, Cardiorespiratory fitness and cardiovascular disease prevention: an update, Curr. Atherosclerosis Rep. 20 (1) (2018) 1.
[36] V.W. Barry, J.L. Caputo, M. Kang, The joint association of fitness and fatness on cardiovascular disease mortality: a meta-analysis, Prog. Cardiovasc. Dis. 61 (2) (2018) 136–141.
[37] R. Ross, S.N. Blair, R. Arena, et al., Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American heart association, Circulation 134 (24) (2016) e653–e699.
[38] P. Martens, G. Jacobs, M. Dupont, W. Mullens, Effect of multidisciplinary cardiac rehabilitation on the response to cardiac resynchronization therapy, Cardiovasc Ther 36 (6) (2018) e12467.
[39] B.J.R. Buckley, S.L. Harrison, P. Underhill, D.J. Wright, D.H.J. Thijssen, G.Y.H. Lip, Exercise-based cardiac rehabilitation for cardiac implantable electronic device recipients, Eur J Prev Cardiol 29 (4) (2022) e153–e155.
[40] S. Yamamoto, K. Hotta, E. Ota, A. Matsunaga, R. Mori, Exercise-based cardiac rehabilitation for people with implantable ventricular assist devices, Cochrane Database Syst. Rev. 9 (9) (2018) CD012222.
[41] K. Isaksen, P.S. Munk, R. Giske, A.I. Larsen, Effects of aerobic interval training on measures of anxiety, depression and quality of life in patients with ischaemic heart failure and an implantable cardioverter defibrillator: a prospective non-randomized trial, J. Rehabil. Med. 48 (3) (2016) 300–306.
[42] A.H. Alswyan, A.C.S. Liberato, C.M. Dougherty, A systematic review of exercise training in patients with cardiac implantable devices, J Cardiopulm Rehabil Prev 38 (2) (2018) 70–84.
[43] V. Kutyifa, K. Vermilye, S.D. Solomon, S. McNitt, A.J. Moss, U.A. Daimee, Long-term outcomes of cardiac resynchronization therapy by left ventricular ejection fraction, Eur. J. Heart Fail. 21 (3) (2019) 360–369.