Exercise-based cardiac rehabilitation for coronary heart disease – an updated Cochrane systematic review and meta-analysis

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Text abstract

Background: Coronary heart disease (CHD) is the most common reason for referral to exercise-based cardiac rehabilitation (CR) globally. However, the generalisability of previous meta-analyses of randomised controlled trials (RCTs) is questioned. Therefore, a contemporary updated meta-analysis was undertaken.

Methods: Database and trial registry searches were conducted to September 2020, seeking RCTs of exercise-based interventions with ≥6 months' follow-up, compared with no exercise control for adults with myocardial infarction (MI), angina pectoris, or following coronary artery bypass graft (CABG), or percutaneous coronary intervention (PCI). The outcomes of (mortality, recurrent clinical events, health-related quality of life (HRQoL)) were pooled using random-effects meta-analysis and cost-effectiveness data were narratively synthesised. Meta-regression was used to examine effect modification. Study quality was assessed using the Cochrane risk of bias (ROB) tool.

Results: A total of 85 RCTs in 23,430 participants with median 12 months follow-up were included. Overall, exercise-based CR was associated with significant risk reductions in cardiovascular mortality (RR: 0.74, 95%CI: 0.64 to 0.86, number needed to treat [NNT]: 37), hospitalisations (RR: 0.77, 95%CI: 0.67 to 0.89, NNT: 37), and MI (RR: 0.82, 95%CI: 0.70 to 0.96, NNT: 100). There was some evidence of significantly improved HRQoL with CR participation, and that CR is cost-effective. There was no significant impact on overall mortality (RR: 0.96, 95%CI: 0.89 to 1.04), CABG (RR: 0.96, 95%CI: 0.80 to 1.15), or PCI (RR: 0.84, 95%CI: 0.69 to 1.02). No significant difference in effects were found across different patient groups, CR delivery models, dose, follow-up, or ROB.

Conclusions: This review confirms participation in exercise-based CR by patients with CHD receiving contemporary medical management reduces cardiovascular mortality, recurrent cardiac events, and hospitalisations and provides additional evidence supporting the improvement in HRQoL and the cost-effectiveness of CR.

Key words: coronary heart disease; cardiac rehabilitation; exercise training; physical activity; secondary prevention

Structured graphical abstract

Key question

Compared to no exercise control, what are the clinical benefits of exercise-based cardiac rehabilitation (CR) for patients with coronary heart disease (CHD)?

Key finding

In this meta-analysis of 85 randomised controlled trials of 23,430 CHD patients, exercise-based CR reduced the risk of cardiovascular mortality, recurrent cardiac events, and hospitalisation, and improved health-related quality of life and was cost-effective.

Take-home message

Exercise-based CR provides important benefits to CHD patients including improved quality of life, and recent trials that include more representative populations and a wider range of delivery settings, increases the potential generalisability of these findings to clinical practice and policy.

Introduction

Coronary heart disease (CHD) is the most common cause of death globally.[1-2] With increasing numbers of people living longer with CHD, accessible and effective health services for the management of CHD are crucial. Exercise-based cardiac rehabilitation (CR) is recognised as a key component of comprehensive CHD management and is Class I Grade A recommendation in international guidelines.[3-4]

Although meta-analyses of randomised controlled trials (RCTs) have shown the beneficial effect of CR in patients with CHD,[5-7] this evidence base has been questioned on the grounds of: (1) uncertainty in the impact on mortality; (2) lack of data on health-related quality of life (HRQoL); (3) inclusion of RCTs limited to low-risk patients and conducted in high income country settings, and (4) lack of trials conducted during the era of modern CHD therapy.[7-9]

To address these uncertainties, we undertook a contemporary update of the Cochrane systematic review and meta-analyses of RCTs to assess the effects of exercise-based CR in patients with CHD on mortality, clinical events, HRQoL, and cost-effectiveness. We also sought to explore whether intervention effects varied with patient case mix, and study and intervention characteristics, and CR delivery settings.

Methods

We conducted and report this meta-analysis in accordance with the Cochrane Handbook for Interventional Reviews and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and Synthesis without meta-analysis (SWiM) statements respectively.[10-12]

Search Strategy and Study Selection

We undertook update literature searches of Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, CINAHL and Science Citation Index Expanded from June 2014 (the search end date of the Cochrane 2016 review[5]) to September 2020 (strategy provided in supplementary file 1). We also searched two clinical trials registers (World Health Organisation's International Clinical Trials Registry Platform [ICTRP] and Clinicaltrials.gov), and hand-searched reference lists of retrieved articles and recent systematic reviews. Records collected from trial registry searches were used to identify trials not picked up in database searches, as well as ongoing studies. We sought RCTs of exercise-based CR (exercise training alone or in combination with psychosocial or educational interventions) compared to no exercise or usual care control, with at least 6-months post-baseline follow-up outcome measures. All patients in both intervention and control groups were generally reported to receive (local or national) guideline recommended medical treatment.

Two reviewers (GOD, JF) independently confirmed trial eligibility. Disagreements were resolved by discussion or by a third reviewer (RST) if necessary.

Patient Population

We included adults (≥18 years), in either hospital- or community-based settings, who had a myocardial infarction (MI), who had undergone revascularisation (coronary artery bypass grafting [CABG], or percutaneous coronary intervention [PCI]), or who had angina pectoris or coronary artery disease (CAD) defined by angiography.

Data Abstraction and Quality Appraisal

Two reviewers (GOD, JF) independently completed data extraction and assessed study quality using the Cochrane Risk of Bias tool (ROB),[13] which was checked by a third reviewer (RST). Trials were assessed on random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, and selective reporting. Information regarding study methods (country, design, follow-up, setting), participant characteristics (numbers randomised, age, sex, diagnosis, and inclusion/exclusion criteria), intervention (exercise mode, duration, frequency, intensity) and control (description i.e., usual care, no exercise), outcomes, funding sources and notable author conflicts of interest were obtained.

Outcomes and Certainty of Evidence

Clinical event outcomes included overall and cardiovascular mortality, fatal and/or non-fatal MI (as reported by studies), CABG, PCI, overall hospitalisation, and cardiovascular hospitalisation. Other outcomes included HRQoL and CR costs, and cost-effectiveness per quality-adjusted life-year (QALY). One reviewer (GOD) assessed certainty of evidence using GRADE (Grading of Recommendations Assessment, Development and Evaluation)[14-15], and checked by a second reviewer (RST). GRADE assessment was applied to clinical event outcomes (overall and cardiovascular mortality, fatal and/or non-fatal MI, CABG, PCI, overall hospitalisation, and cardiovascular hospitalisation) at 6-12 months follow-up, the

most frequently reported follow-up timepoint across trials. Evidence was downgraded from high certainty by one level based on the following domains: limitations in study design or execution (risk of bias), inconsistency of results, indirectness of evidence, imprecision, and publication bias.

Statistical Analysis

Outcome data were pooled at longest reported follow-up and at three separate time periods: 'short-term' (6 to 12 months), 'medium-term' (13 to 36 months), and 'long-term' (more than 36 months) follow-up. Given the level of clinical heterogeneity (variation in CR interventions and populations) we purposively undertook random-effects meta-analyses, using the DerSimonian and Laird random-effects meta-analysis method, assuming that each study estimates a different underlying intervention effect. Dichotomous outcomes (overall and cardiovascular mortality, MI, CABG, PCI and all-cause and cardiovascular hospitalisation) are expressed as risk ratios (RR) with 95% confidence intervals (CI). For those clinical event outcomes with significant risk reductions, we calculated the number needed to treat for an additional beneficial outcome (NNT).[16] Where ≥2 trials reported the same validated HRQoL measures and domains (i.e., Short-Form-36 [SF-36], EQ-5D), continuous outcomes were pooled separately by each scale and reported as mean difference (MD) and 95% CI. Given the heterogeneity in HRQoL outcome measures and reporting, for comprehensiveness, we used a vote-counting approach to synthesis in addition to meta-analyses, where the number of positive, negative, and non-significant results were summed. Cost-effectiveness data were synthesised narratively. Statistical heterogeneity was considered substantial where I^2 statistic > 50%. For outcomes with ≥10 trials included in meta-analysis, we used funnel plot and Egger test to examine small study bias.[17] Two-sided P values <0.05 were considered statistically significant. Univariate random-effects meta-regression was used

to explore heterogeneity and examine the following pre-defined treatment effect modifiers across clinical event outcomes only: (1) case mix (% patients presenting with MI), (2) 'dose' of exercise (dose[units]=number of weeks of exercise training x average sessions per week x average duration of each session in minutes), (3) type of CR (exercise-only vs comprehensive CR), (4) length of follow-up (longest follow-up used where multiple time-points assessed), (5) publication year, (6) sample size, (7) CR setting (home or centre-based), (8) ROB (low in <3 of 5 domains), (9) study continent (Europe, North America, Australia/Asia, or Other), (10) study country status (low-middle- or high-income countries [LMIC (low-middle income country) or HIC (high income country), respectively] according to The World Bank Group[18]). Given the number of statistical comparisons performed in this review, results interpretation was primarily based on 95% Cis rather than P-values. Statistical analyses were performed in RevMan Web version 3.12.1, and STATA version 16.1.

Results

Search and Selection of Studies

The search selection process is summarised in Figure 1. Updated database and trial registry searches resulted in a total of 13,783 hits of which 11,056 unique records were identified, and 244 were selected for full-text review. The main reasons for exclusion were study design (e.g., non-RCT, <6 months follow-up), or use of exercise comparators. Twenty-two new RCTs (7,795 participants; 43 publications, references provided in supplementary file 2[24,33-41,44-48,51-54,71-74,86-87,90,109-116,120-121,138,146,149-150,160,164]) were identified in this update, providing a total evidence base of 85 RCTs (145 publications, 23,430 participants) comparing exercise-based CR to a no exercise control group in patients with CHD.[22-166] The participants of the newly included trials represent approximately one third of all participants included in this study (33%).

[Insert Figure 1 approximately here]

A summary of study, participant, intervention, and comparator characteristics of the 85 included studies is presented in Table 1. Seventy-nine (93%) of the 85 studies were two-arm parallel RCTs, with four studies comparing more than two arms, (two types of CR vs control),[34,44-48,110-111,134-137] one study using quasi randomisation methods,[149-150] and one cluster RCT.[75] Sixteen of the 22 new trials identified were undertaken in LMICs,[24,33-34,44-48,51-54,71,74,90,109-116,146,149-150,160,164] resulting in a total of 21 RCTs in LMICs. Three large multicentre trials contributed a total of 8956 participants (~40% overall).[113-116,156-157] The median age of participants across studies was 56 years, and over the last decade the % of female patients included in trials increased from 11% to 17%. The median CR intervention duration and trial follow-up were 6 and 12 months respectively. Thirty-eight of the 85 (45%)

interventions were exercise-only,[22-23,25-26,30-31,33-41,43-48,55,61,67-69,74,80,85,92,95-100,109-112,117-121,130-137,139-145,151,158-160,164] with 47 (55%) involving multiple components including education (20 trials),[42,49-54,56-60,62,70-71,75,86-88,101,113-116,122-129,146,149-150,155,161,162-163] psychosocial (7 trials),[28,63-66,91,93,103-105,138,152] or a combination of both (16 trials),[24,27,32,76,77-79,81,82-84,89-90,94,147-148,153-154,156-157,165-166] or other components (i.e., controlled diet, risk factor management, smoking cessation, relaxation; 4 trials).[29,72-73,102,106-108] Exercise was typically aerobic with inclusion of resistance training reported in 27% trials (23/85).[22,25-26,28-29,32,35-39,55,72-73,80,85,90,99-100,118,120-121,128-129,134-137,139,158-163] The dose of exercise interventions varied widely, with frequency ranging between 1-7 sessions per week, length of sessions ranging between 20-90 minutes, and intensity ranging between 50-90% of maximal or peak heart rate, 50-95% of aerobic capacity, or at a rating of perceived exertion between 11 and 16. Of the 21 home-based exercise programmes,[25-27,49-54,62,70,75-76,81,86-87,89-91,95-98,101-102,117,138,149-150,155] four were delivered electronically via mobile phones or the internet.[51-54,86-87,91,117]

[Insert Table 1 approximately here]

Risk of Bias and GRADE Assessment

The overall ROB of included trials was judged to be low or unclear (supplementary Figure 1), and the quality of reporting improved since 2010 (80% of studies had <3 low ROB domains pre-2010 versus 55% post-2010). Thirty (35%) trials reported sufficient and appropriate details of random sequence generation,[22,27,30,32,34-41,44-48,51-54,61,68-70,74,80-81,86-87,90-91,99-100,102,109-111,113-117,120-121,138,146,155,158-159,165-166] and 23 (27%) reported appropriate allocation concealment,[27,32,34-41,44-48,51-54,70,80,83-84,86-87,90-91,99-100,102,109,113-117,122-127,138,153-154,156,165-166] with 24 (28%) reporting sufficient details of outcome assessment blinding.[40-41,44-48,51-54,62,67-69,74,80,86-87,89,91,92-93,99-100,106-108,113-117,119-127,138,156,158,165-166] Thirty-eight (44%) of trials were assessed to have low risk of bias for incomplete outcome data,[23,24,27,31-32,40-41,51-55,67-

[69,71,74,82,85-88,91-92,94,99-100,102,110-116,118-121,128,138,146,152,155-156,158-159,161,164-166] and 62 (73%) had low risk of bias for selective reporting.[22--32,40-50,55-70,75-84,86-89,91,93-101,103-105,113-138,140-145,151-157,161,162-166] GRADE assessments for the clinical event outcomes at short-term follow-up ranged from low to high (Table 2), downgrading for imprecision (wide confidence intervals), evidence of publication bias, or substantial statistical heterogeneity.

Outcomes

A summary of pooled clinical events across all four follow-up timepoints (longest reported follow-up, short-term [6-12 months], medium-term [13-36 months], and long-term [>36 months]) is presented in Table 2. GRADE assessments for certainty of evidence at short-term (6-12 months) follow-up across clinical event outcomes ranged from low to high certainty. We downgraded overall mortality, cardiovascular mortality, PCI, and cardiovascular hospitalisation by one level for imprecision, due to wide confidence intervals that overlapped the boundary for no effect. We downgraded MI and all-cause hospitalisation by one level due to evidence of publication bias. We downgraded cardiovascular hospitalisation by an additional level due to evidence of substantial heterogeneity.

[Insert Table 2 approximately here]

Mortality

Sixty trials (61 comparisons) reported overall mortality, and 13 trials reported zero events in both arms. There was no difference in risk of overall mortality at short-term follow-up (6-12 months) (RR: 0.87, 95%CI: 0.73 to 1.04, I^2=0%; moderate certainty evidence) or longest follow-up (47 trials, RR: 0.96, 95%CI: 0.89 to 1.04, I^2=0%, Figure 2).

[Insert Figure 2 approximately here]

Across 33 trials (35 comparisons) reporting cardiovascular mortality, 7 trials reported zero events in both arms. A 26% reduction in risk of cardiovascular mortality was seen at longest reported follow-up (26 trials, RR: 0.74, 95%CI: 0.64 to 0.86, I^2=0%, Figure 3) with an NNT of 37. At short-term (6-12 months) follow-up there was no significant difference in cardiovascular mortality (RR: 0.88, 95%CI: 0.68 to 1.14, I^2=0%, moderate certainty).

Fatal and/or non-fatal MI

Across 42 trials (44 comparisons) reporting fatal and non-fatal MI, 3 trials reported zero events in both arms. An 18% reduction in risk was shown at longest follow-up (39 trials, RR: 0.82, 95%CI: 0.70 to 0.96, I^2=9%, Figure 4) with an NNT of 100. The overall risk was driven by significant reductions in the short-term (6-12 months; RR: 0.72, 95%CI: 0.55 to 0.93, I^2=7%, high certainty evidence) and long-term (>36 months; RR: 0.67, 95%CI: 0.50 to 0.90, I^2=0%) with no difference in the medium-term follow-up (13-36 months; RR: 1.07, 95%CI: 0.91 to 1.27, I^2=0%).

[Insert Figure 3 approximately here]

[Insert Figure 4 approximately here]

Revascularisation events

Thirty-one trials (33 comparisons) reported CABG, with 2 trials reporting zero events in both arms. There was no difference in risk of CABG at longest follow-up (29 trials, RR: 0.96, 95%CI: 0.80 to 1.15, I^2=0%, Figure 5). Twenty trials (21 comparisons) reported PCI with 3 trials reporting zero events in both arms. There was no significant difference in risk of PCI (17 trials, RR: 0.84, 95%CI: 0.69 to 1.02, I^2=0%, Figure 6).

[Insert Figure 5 approximately here]

[Insert Figure 6 approximately here]

Hospitalisation

Twenty-two trials (24 comparisons) reported overall hospitalisation with one trial reporting zero events in both arms. A 23% reduction in overall hospitalisation risk with participation in exercise-based CR was shown at longest follow-up (21 trials, RR: 0.77, 95%CI: 0.67 to 0.89, I^2=32%, Figure 7) with an NNT of 37. Nine trials reported cardiovascular hospitalisations and one trial reported zero events in both arms. There was no significant difference in cardiovascular hospitalisation at longest follow-up (8 trials, RR: 0.85, 95%CI: 0.67 to 1.08, I^2=12%, Figure 8).

[Insert Figure 7 approximately here]

[Insert Figure 8 approximately here]

Health-Related Quality of Life

Six trials reported SF-36 summary component scores with up to 12 months follow-up (Figure 9). There was evidence of increases in both mental component score (MCS) (MD: 2.14, 95%CI: 1.07 to 3.22, I^2=21%) and physical component score (PCS) (MD: 1.70, 95%CI: -0.08 to 3.47, I^2=73%) with exercise-based CR. These findings were supported by improvements in selected SF-36 individual domain scores (Figure 10) that included physical functioning, physical performance, general health, vitality, social functioning, and mental health. There was no evidence of an improvement in pooled EQ-5D visual analogue scores (VAS) (MD 0.05, 95%CI -0.01 to 0.10, I^2=69%; Figure 11).

[Insert Figure 9 approximately here]

[Insert Figure 10 approximately here]

[Insert Figure 11 approximately here]

Vote-counting across the 32 trials that assessed HRQoL using a range of validated generic or disease-specific outcome measures confirmed the benefit of CR, with 20 (63%) trials reporting higher levels of HRQoL with exercise-based CR compared to control in one or more subscales and 12 (38%) reporting higher levels of HRQoL in >50% of the subscales (supplementary table 1).

Costs and Cost-effectiveness

Only eight of the 85 studies reported data on healthcare costs of CR with 5 studies reporting overall healthcare costs in both groups (Table 3). Total healthcare costs were lower with exercise-based CR than usual care in three studies (mean US$ 2378,[67-68] €1083,[71-72] and US$ 415[161-162] less per patient), higher healthcare costs were reported for exercise-based CR than usual care in three studies (mean US$ 395,[31] and US$ 4,839,[92] and US$ 480[102-104] more per patient) and no difference was reported in one study. However, the difference was significant in only one (mean US$ 2,378/patient; P<0.001). Acceptable cost-effectiveness ratios per QALY in favour of exercise-based CR were reported in three trials (US$ 42,535,[31] and €15,247,[90] and US$ 9,200[102-103])

[Insert Table 3 approximately here]

Small study bias

Egger tests and visual inspection of funnel plots indicated there was no evidence of small study bias for overall mortality (Egger test: P=0.05; supplementary Figure 2), cardiovascular mortality (Egger test: P=0.20; supplementary Figure 3), CABG (Egger test: P=0.12; supplementary Figure 4) and PCI (Egger test: P=0.39; supplementary Figure 5). However, there was evidence of small study bias with funnel plot asymmetry and significant

Egger tests for MI (Egger test: P=0.001; supplementary Figure 6) and all-cause hospitalisation (Egger test: P<0.001; supplementary Figure 7).

Meta-regression

There was no evidence of statistically significant differences in treatment effects across patient, intervention, and study characteristics for all clinical event outcomes (supplementary Table 2).

Discussion

This updated Cochrane review and meta-analysis of RCTs incorporated data from >23,000 CHD patients and confirms the benefits of participation in exercise-based CR that include reductions in risk of cardiovascular mortality, MI, and all-cause hospitalisation at median follow-up of 12 months. No significant differences in effect were found across patient case mix, the type or setting of CR programme, the dose of exercise prescribed, study sample size, location, length of follow-up, year of publication, and ROB. Reduced hospitalisations are likely to have benefits for both health care services as well as for patients in terms of health resource usage and associated costs, and early return home to families and community support networks. Importantly, this updated review demonstrates that the benefits of CR extend across recent trials that are more representative of the modern therapeutic approach in CHD, the expanded CHD population, and low- and middle-income settings (21 trials undertaken in LMICs with 7,851 participants) where the prevalence of CHD continues to rise.[19]

Additionally, we found gains in HRQoL with increased scores across six of the eight SF-36 domains, mental component scores, EQ-5D VAS, and SWiM analysis across 32 trials reporting HRQoL data. Based on the minimally important clinical differences (MCIDs) the increases in the individual domain scores were not clinically important,[20] but increases in EQ-5D VAS scores could be clinically meaningful.[21] MCIDs for the summary component scores are yet to be published for CHD patients. Although HRQoL is important to patients and improvements have been demonstrated in generic measures, this finding might have been more convincing if a generic measure had been accompanied with the additional use of a CHD disease-specific HRQoL measure. To provide more persuasive evidence, we recommend that future trials consider routinely incorporating both types of HRQoL outcome

measures for at least 12 months to delineate which, if any, aspects of HRQoL may yield an improvement. Trial-based economic evaluations showed that CR is a cost-effective use of healthcare resources compared to usual care.

CHD is clinically changing from a life-threatening disease to a chronic disease trajectory as reflected in the terminology of current clinical guidelines on chronic coronary syndromes.[4] This crucial shift strongly calls for interventions that contribute to improvement in rehospitalisation rate and improvement of well-being and HRQoL whilst living with chronic disease. Thus, this latest Cochrane review of RCTs still reinforces the importance of exercise-based CR as part of integrated CHD care alongside modern invasive and pharmacological therapy.

Limitations

Our review has a number of potential limitations. First, although we found that the methodological quality and reporting of studies has improved over the last decade and that poor reporting did not appear to alter the review findings, several ROB assessments across trials were judged to be unclear, with many studies inadequately reporting methodologies. Second, this update sought to combine evidence across a range of CHD indications and studies that employed exercise-based CR interventions with varying dose of exercise, delivery setting, and duration of follow-up. However, we applied random-effect meta-analysis to take account of this potential clinical heterogeneity across studies. Furthermore, the GRADE assessment framework also considers heterogeneity in the evidence. For example, the outcomes all-cause mortality, cardiovascular mortality, PCI, and cardiovascular hospitalisation were downgraded in GRADE due to wide confidence intervals that crossed the boundary for no effect. Cardiovascular hospitalisation was downgraded due to evidence of statistical heterogeneity (I^2 statistic >50%). Thirdly, while studies reported a prescribed

dose of exercise, few, if any, reported the actual level of exercise undertaken by participants. So, we were not able to assess the impact of intervention adherence. Fourth, the number of trials reporting follow-up data beyond 12 months has decreased over the last decade from 48% between 2000 and 2009 to 23% between 2010 and 2020. Consequently, the number of deaths and clinical events reported in several trials were low or zero, and these data were often reported within descriptions of trial loss to follow-up rather than as primary or secondary outcomes, which also means that trials would not have been powered for these outcomes. Additionally, hazard ratios (HR) were inconsistently reported across trials, therefore no analyses using these data were possible. Finally, we also found evidence of reporting bias. For example, although 60 trials reported all-cause mortality, only 33 of these same trials reported cardiovascular mortality. Sensitivity analysis of the subgroup group of 16 trials that reported both mortality outcomes (see supplementary Figures 8 and 9) showed improvements in both pooled overall (RR 0.85, 95% CI: 0.74 to 0.96) and cardiovascular mortality (RR 0.79, 95% CI: 0.68 to 0.92). This sensitivity analysis is in contrast with our main analysis showing different effects of exercise-based CR on overall mortality and cardiovascular mortality.

Conclusions

The findings of this latest Cochrane review of 85 RCTs in 23,430 CHD patients confirms the clinical outcome benefits of reduced cardiovascular mortality, MI and hospitalisation with participation in exercise-based CR and also provides timely evidence that supports the generalisability of these benefits across patients, in the context of contemporary medical management, and across healthcare settings, including LMICs. This updated review also provides meta-analytic evidence that CR participation improves patient quality of life

based on validated HRQoL data. Our findings reinforce the need to improve access to CR for patients with CHD across the globe.

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Conflict of interest

NO declares being an author of a study that is eligible for inclusion in the work (funding source: European Society of Cardiology & European Association of Preventive Cardiology). DRT declares being an author of a study that is eligible for inclusion in the work. A-DZ declares being an author of a study that is eligible for inclusion in the work.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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Figures

Provided separately

Figure Legends

Figure 1 – PRISMA flow diagram of study selection process

Figure 2 – Forest plot: exercise-based CR vs control for overall mortality

Figure 3 – Forest plot: exercise-based CR vs control for cardiovascular mortality

Figure 4 – Forest plot: exercise-based CR vs control for MI

Figure 5 – Forest plot: exercise-based CR vs control for CABG

Figure 6 – Forest plot: exercise-based CR vs control for PCI

Figure 7 – Forest plot: exercise-based CR vs control for overall hospitalisation

Figure 8 – Forest plot: exercise-based CR vs control for cardiovascular hospitalisation

Figure 9 – Forest plot: exercise-based CR vs control for HRQoL (SF-36 summary component scores)

Figure 10 – Forest plot: exercise-based CR vs control for HRQoL (SF-36 individual domain scores)

Figure 11 – Forest plot: exercise-based CR vs control for HRQoL (EQ-5D)

Structured graphic abstract (graphic element)

CHD: coronary heart disease; RCTs: randomised controlled trials; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft

Tables

Provided separately

Table legends

Table 1: Summary of study, population, intervention and comparator characteristics.

HR, heart rate; HRR, heart rate reserve; RPE, ratings of perceived exertion; VO_2max, maximal oxygen uptake; LMIC: low-middle income country; CHD: coronary heart disease. [a]He 2020 recruited patients with MI in the absence of obstructive coronary artery disease (MINOCA). [b]Usual care plus education, guidance or advice about diet and exercise, but no formal exercise training.

Table 2: Summary of meta-analysis effects of exercise-based CR on clinical event outcomes at longest follow-up, short-term follow-up (6-12 months), medium-term follow-up (13-36 months), and long-term follow-up (>36 months).

[1] downgraded by one level due to imprecision with a wide confidence interval. [2] downgraded by one level due to evidence of publication bias. [3] downgraded by one level due to substantial heterogeneity. *p<0.05; **p<0.01; ***p<0.001. CR: cardiac rehabilitation; RR: risk ratio; CI: confidence interval; CV: cardiovascular; MI: myocardial infarction; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention

Table 3: Summary of costs of exercise-based rehabilitation and usual care.

NR: not reported; QALY: quality-adjusted life year.

Supplementary files

Provided separately