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Is exercise-based cardiac rehabilitation effective: re-examination of the evidence

Systematic review and meta-analysis

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Abstract

Objectives

To determine the contemporary effectiveness of exercise-based CR.

Data sources

Studies included in, or meeting the entry criteria for the 2016 Cochrane review of exercise-based CR in patients with coronary artery disease.

Study eligibility criteria

Randomised controlled trials (RCTs) of exercise-based CR vs. a no exercise control whose participants were recruited after the year 2000.

Study appraisal and synthesis methods

Two separate reviewers independently screened the characteristics of studies. One reviewer quality appraised any new studies and assessed their risk of bias using the Cochrane Collaboration's recommended risk of bias tool. Data were reported as the risk difference (95% CI).

Results

We included 22 studies with 4,834 participants (mean age 59.5 years. 78.4% male). We found no differences in outcomes at their longest follow-up period for: all-cause mortality (19 studies; n=4,194; risk difference 0.00, 95% CI -0.02 to 0.01, p=0.38), cardiovascular mortality (9 studies; n = 1,182; risk difference -0.01, 95% CI -0.02 to 0.01, p=0.25) and hospital admissions (11 studies; n= 1,768; risk difference -0.05, 95% CI -0.10 to -0.00, p=0.05).

Conclusions and implications of key findings

These data do not support the continued use of exercise-based CR for secondary prevention in people with coronary artery disease.

Systematic review registration number

Prospero: International prospective register of systematic reviews. 2017. 42017073616. Available from: https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017073616

Strengths and Limitations of this study

- To our knowledge, this is the first systematic review of exercise-based CR that has pooled data relevant to the current medical management of patients diagnosed with coronary artery disease.

- For analysis, we present the data as the risk difference (95% CI), which ensures all studies reporting data on the outcomes of interest were included.

- This systematic review pools data from studies that deliver an intervention recognised as best practice in exercise-based Cardiac Rehabilitation, where multiple approaches, including educational/psychosocial components, as well as the exercise component were used.

- We have not done a de novo quality assessment of 21/22 studies included in this review and instead rely on previous Cochrane assessment.

- We did not include health-related quality of life as an outcome measure as this unsuitable for meta-analysis.

Keywords

Coronary artery disease, exercise-based cardiac rehabilitation, all-cause mortality, cardiovascular mortality, hospital admissions.

Background

Cardiovascular disease is the world's biggest killer, accounting for 15 million deaths in 2015(1).

Secondary prevention of coronary artery disease through exercise-based CR in those who have a diagnosis of coronary artery disease has the potential to reduce mortality, reduce hospital admissions and increase quality of life. Guidelines internationally endorse the use of exercise-based CR programmes(2-5).

Typically, exercise-based CR aims to achieve 20-60 minutes of moderate intensity continuous exercise, 3-5 times a week, with muscular strength and endurance exercises prescribed in conjunction(6). Additionally, most programmes include supplementary education (coronary risk factors and cardiac misconceptions), advice on diet and access to psychological support to supplement the exercise training(2,4,7,8). Typically exercise-based CR is delivered in a supervised centre-based setting, although home-based programmes are used(9).

A 2016 Cochrane review (63 studies, n=14,486 participants) found benefits of exercise-based CR for patients with coronary artery disease. Both cardiovascular mortality (27 studies, RR 0.74, 95% CI 0.64 to 0.86) and hospital re-admissions were reduced (15 studies, RR 0.82, 95% CI 0.70 to 0.96), when compared to a no exercise control. However, in contrast to previous systematic reviews and meta-analyses, there was no reduction in risk of re-infarction (36 studies, RR 0.90, 95% CI 0.79 to 1.04) or all-cause mortality (47 studies, RR 0.96, 95% CI 0.88 to 1.04)(10).

Over recent decades, the medical management of coronary artery disease has been transformed. The introduction of primary percutaneous coronary intervention has reduced short-term major adverse cardiac events and increased long-term survival(11-14). Simultaneously, there have also been widespread

advances in secondary preventative medical therapy. This includes the introduction of aspirin and beta-blockers in the 1980s(15,16), lipid-lowering statins and angiotensin converting enzyme inhibitors in the 1990s(17,18) and more recently, the introduction of clopidogrel, a secondary anti-platelet, in 2007(19,20). Age-adjusted mortality has decreased substantially in this population(21). Systematic reviews and meta-analyses that include data from older studies may not correctly assess the potential effect of exercise-based CR. We hypothesise that previous reviews have overestimated the potential health gain from exercise-based CR.

Objectives

To determine the contemporary effectiveness of exercise-based CR on all-cause mortality, cardiovascular mortality, and hospital readmissions in patients with coronary artery disease.

Methods

Search Strategy

To identify relevant studies, we started with the latest Cochrane review of exercise-based CR in patients with coronary artery disease(10). Studies identified as 'awaiting assessment' or 'on-going' in this review were re-visited to establish whether publication had been reached. To identify any new studies published since the completion of the Cochrane review, an updated search was run on the 28/2/2017. This search used the same search strategies as the latest Cochrane review(10). We searched Cochrane Central Register of Controlled Trials (CENTRAL) *(appendix 1)*, MEDLINE (Ovid), EMBASE (Ovid) and CINAHL (EBSCO) databases. This approach allowed us to efficiently identify all relevant studies. Where appropriate, we contacted original authors for clarification of any new included studies.

Two separate reviewers (RP and GM) independently screened the characteristics of studies in the latest Cochrane review, studies identified as 'awaiting assessment' or 'on-going' and studies identified in the updated search. Full text publications were retrieved to allow for further examination and to verify study inclusion. Any discrepancies were resolved by a third reviewer (MU).

Criteria for considering studies

In 1996, The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology first recommended early (within two hours) primary percutaneous interventions in preference to thrombolytic therapy for acute myocardial infarction(22). Two years later, guidelines set by the Joint British recommendations on prevention of Coronary Heart Disease in Clinical Practice were published outlining the recommendations for best practice for secondary prevention medical therapies(23). Although there have been some changes, notably the introduction of a second anti-platelet agent in the early 2000s(19,20), the approach to secondary prevention medical therapies has not changed since then. Allowing time for implementation of these guidelines and recommendations, we

identified and included studies whose participants were recruited after the year 2000, to represent a contemporary population engaging in exercise-based CR.

Where there was no indication of recruitment period, the diagnosis and the secondary preventative medical therapy received by participants included in the trial determined the inclusion or exclusion of the study in the analysis.

Types of studies

We included randomised controlled trials of exercise-based CR compared to a no exercise control with a minimum follow-up period of six months. Data reported at the longest follow-up period were included in the analysis.

Types of participants

We used the same entry criterion as previous Cochrane reviews.

- People who have had a myocardial infarction, or who had undergone revascularisation (coronary artery bypass grafting or percutaneous coronary intervention) or who have angina pectoris or coronary artery disease defined by angiography.
- On optimal secondary preventative medical therapy.
- Recruited to hospital-based, community-based or home-based CR programmes.

Types of intervention(s)

Randomised controlled trials consisted of supervised or non-supervised exercise-based CR. The intervention was exercise alone or exercise as part of a comprehensive CR programme (consisting of educational/psychosocial components). 'No exercise control' consisted of standard medical care, including optimal secondary preventative medical therapy, education and advice about diet and exercise, psychosocial support but with no formal exercise intervention.

Types of outcome measures

We extracted data on: all-cause mortality, cardiovascular mortality and hospital re-admissions. We did not include health-related quality of life as the authors of the 2016 Cochrane review found this unsuitable for meta-analysis.

Data collection, statistical analysis and quality assessment

We pooled data using Review Manager 5.3(24). Previous Cochrane reviews have presented the data as individual and pooled risk ratio (95% CI). Using risk ratios automatically removed studies with

no events in either study arm from the analysis. Nine studies (n= 936 participants) reporting on all-cause mortality, cardiovascular mortality or hospital re-admissions, were excluded from one or more meta-analyses in the 2016 Cochrane review for this reason. We therefore present the data as the risk difference (95% CI), which ensures all studies reporting data on the outcomes of interest were included.

We applied a random-effects model to all analyses given the clinical heterogeneity of individual studies. Heterogeneity of included studies were tested statistically using the χ^2 test of heterogeneity and I^2 statistic(25).

We did not repeat quality assurance checks already completed by the authors of the Cochrane review. For separate study risk of bias breakdown for these studies, we refer the reader to the existing *characteristics of studies*(10). For studies identified as 'awaiting assessment' or 'on-going' in the latest Cochrane review, or in the updated search, we quality appraised these studies and assessed their risk of bias using the Cochrane Collaboration's recommended risk of bias tool(26).

Assessment of risk of bias in additional included study

One reviewer (RP) assessed the risk of bias in any additional included studies *(table 1)*. Assessment of three further quality domains as outlined in the latest Cochrane review was also conducted (Groups balanced at baseline, Intention-to-treat analysis, Groups received comparable treatment (except exercise)). A breakdown of the criteria used for assessing these three domains can be found in the latest Cochrane review. Risk of bias assessments were checked by a second reviewer (GM) and any discrepancies were resolved by a third reviewer (MU).

Patient Involvement

No patients were involved in setting the objectives or outcome measures of this review, nor were they involved in the design or implementation. No patients were involved in the analysis or interpretation of the results, nor the writing of any drafts. There are no plans to disseminate the results of the review to participants included in the studies of the review or any relevant patient networks.

Results

Studies retrieved

Of the sixty-three studies included in the Cochrane review, twenty-one studies met our entry criteria. We identified two additional relevant papers not included in the 2016 Cochrane review(27,28). One was excluded because data for our specific research question were not available in a useable format(27). In total, twenty-two studies (n=4,834 participants) contributed to the analysis. For the study identified from the updated search(28), there was a low risk of bias in all eight domains, apart from the intention-to-treat analysis, where there was no evidence of this analysis being conducted (*table 1)*.

Three studies (3/22; 14%) reported on all three outcomes of interest, eleven studies (11/22; 50%) reported on two outcomes of interest and eight studies (8/22; 36%) reported on one outcome of interest.

Two studies for all-cause mortality(29,30) and one study for cardiovascular mortality(29) reported data at varying follow-up periods (6 to 12 months; >12 to 36 months; >3 years). Data from these studies were taken at their longest follow-up period.

Flow diagram

(figure 1).

Sample size, gender, age and study origin

Of our twenty-two studies, ten studies were in Europe(28-37) and twelve from outside of Europe(38-49). We included a total of 4,834 participants (3,788 (78.4%) males). Four studies included males only(29,33,44,46) and one study included women only(50). Participants mean age was 59.5 years. The mean age for individual studies ranged from 47.5 to 76.9 years (*table 2).*

Incomplete outcome data

The majority of trials (18/22; 82%) reported complete follow-up data, regardless of participants who were lost to follow-up or who dropped out. In four studies, outcome data were incomplete for 75 (75/4,834; 1.6%) participants with no description of withdrawal or drop-out(40,46,47,49).

Participant diagnosis of coronary artery disease and treatment received

The diagnosis of participants recruited to the studies was described in the majority of studies (21/22; 95%). Thirteen studies enrolled participants with mixed diagnoses, including angina pectoralis or coronary artery disease defined by angiography, myocardial infarction, percutaneous coronary interventions or coronary artery bypass grafts(31,35-41,43,45-47,49). Six studies enrolled participants following acute myocardial infarction only(28,30,32,33,42,48) and two studies enrolled participants diagnosed with angina pectoralis (unstable and stable angina) only(29,34). It was unclear from one study whether participants following myocardial infarction were included and instead, the population was defined as 'patients after coronary artery bypass graft surgery'(44) (*table 2).*

Six studies only recruited participants following percutaneous coronary intervention only(29,31, 32,34,40,45) and one study recruited participants following coronary artery bypass grafting only(44). Twelve studies included participants who had received thrombolysis, percutaneous coronary intervention, coronary artery bypass grafting and/or no revascularization procedure(30,35-39,41-43,46,47,49). Three studies did not provide any breakdown of coronary intervention or surgical procedure received by participants prior to enrollment(28,33,48) (*table 2).*

Medication

A full description and breakdown of the medication received by the participants, comparable to optimal secondary prevention medical therapy defined by the Joint British recommendations on prevention of Coronary Heart Disease in Clinical Practice set in 1998(23), was provided by 13/22 studies (59%)(29-32,34-39,42,48,49). References to co-existing medical therapies were made in 7/22 (32%), but no breakdowns were provided(28,33,40,41,44-46). One study referred to the prescription of anti-hypertensive and hypolipidemic medications without reference to other recommended medications(47). One study failed to provide any description or breakdown of co-existing medical therapies(43) (*table 2)*.

Clearly defined recruitment period

Seven studies (7/22; 32%) were explicit that they recruited participants after the year 2000(35,37,41,43-45,48). In three studies, participants were recruited either just before or during the year 2000(29,30,40). Due to participant diagnosis, treatment received and co-existing medical therapies, it was agreed by all reviewers to include these studies.

The remaining twelve studies failed to provide a recruitment period. Following further examination of the full papers, due to adequate description of patient diagnosis, treatment received and co-existing medical therapies, it was agreed by all reviewers to include these studies *(table 2)*.

Content of the interventions

The content of the interventions tested were heterogeneous in nature with multiple approaches being adopted. Sixteen studies (16/22; 73%) compared exercise in combination with other therapies (education, psychosocial management), whilst six studies compared exercise as a stand-alone intervention, against a no exercise control. The exercise component alone varied considerably with respect to setting, training modality, duration, session length, frequency and intensity (*table* 3).

Overall effects of interventions

All-cause mortality

Nineteen studies (n=4,194 participants) reported all-cause mortality (*figure 2*.). There was no difference between groups at their longest follow-up (risk difference = 0.00, 95% CI -0.02 to 0.01, p=0.38).

Cardiovascular mortality

Nine studies (n = 1,182 participants) reported cardiovascular mortality (*figure 3*.). There was no difference between groups at their longest follow-up (risk difference = -0.01, 95% CI -0.02 to 0.01, p=0.25).

Hospital admissions

Eleven studies (n= 1,768 participants) reported on proportion with one or more hospital admissions (*figure 4.*). There was a reduction of borderline statistical significance (risk difference = -0.05, 95% CI -0.10 to -0.00, p=0.05).

Discussion

The majority of interventions tested in the twenty-two trials (*table 3*) have delivered an intervention recognised as best practice in exercise-based CR, where multiple approaches, including educational/psychosocial components, as well as the exercise component were used(2,3,8).

Nevertheless, for all-cause mortality, the risk difference is 0.00 (95% CI -0.02 to 0.01). The largest trial included in our analysis, the UK-based Rehabilitation after myocardial infarction trial (RAMIT) trial, sought to show a 20% reduction in relative risk based on an 11% mortality; i.e. a 2.2% risk difference(30). The limits of the 95% confidence interval for the effect do not include the RAMIT trial's pre-specified clinically important difference. We therefore conclude that it is extremely unlikely that there is a worthwhile benefit from exercise-based CR on all-cause mortality. Furthermore, it is unlikely that any further trials of similar interventions, on similar populations, will change this conclusion.

Whilst no effect was seen on cardiovascular mortality, the limits of the 95% confidence intervals do not exclude a potential benefit. Any reduction in cardiovascular mortality is of very limited clinical relevance in the context of the overwhelming evidence of no effect on all-cause mortality.

These analyses however do not quite exclude a worthwhile effect on hospital admissions. Whilst the risk difference of -0.05 (95% CI -0.10 to -0.00) is of borderline statistical significance it is probably clinically unimportant in the context of no change on overall mortality.

We do not know, however, if there is a worthwhile benefit on quality of life. The authors of the 2016 Cochrane review reported some evidence for an improvement in quality of life in at least half of the sub-scales in four of the twenty-two studies we included that reported on differences in quality of life(31,44,45,48). Nevertheless, the largest included study (n=1813) found no differences at one year in any of the eight domains of the SF-36 or the three domains of the psychological general well-being score(30). This suggests that a worthwhile benefit on health-related quality of life, measured in this way, is very unlikely.

Five of the included papers in this review included a within trial health economic evaluation(29,39,42,43,49). Of these five papers, three studies showed no difference in healthcare costs between groups(39,42,49), one found healthcare costs to be lower for exercise-based CR(29), and one failed to report a p-value for cost difference(43). Based on these data, we are unable to comment on whether exercise-based CR might be cost-effective.

Based on health outcomes of all-cause mortality, cardiovascular mortality and rate of hospital admissions, the evidence in our review is insufficient to justify the use of exercise-based CR. It is for stakeholders to acknowledge these findings and decide whether outcomes of cardiorespiratory fitness, self-confidence, return to work and/or psychosocial outcomes should instead be the focus(3,7,51,52). Whether these 'softer' outcomes are enough to convince commissioners of health care services to continue to invest in CR interventions remains unknown.

Strengths and Limitations

To our knowledge, this is the first systematic review of exercise-based CR that has pooled data relevant to the current medical management of patients diagnosed with coronary artery disease. Although we have not done a de novo quality assessment of 21/22 studies included in this review and instead relying on previous Cochrane assessment, it is unlikely we would have drawn different conclusions from such an assessment(10).

Whilst there was no evidence of statistical heterogeneity across trials for all outcome measures (P value < 0.01, I^2 >30%), there was substantial context and interventional heterogeneity. The studies came from a wide range of clinical environments and countries, and the interventions delivered ranged greatly in quality. When compared with both the BACPR 'minimum standards and core components'(8) and ACPICR guidelines(6) for the UK, there was considerable variation in the exercise component of the interventions delivered (*table 3*). Critics have questioned the exercise component delivered and reported in the RAMIT trial(30). They argued that under-dosage of exercise regarding the modality, intensity and duration of training sessions led to its inconclusive result(53). Several other studies included in this review fail to report on the intensity, modality and/or duration of the exercise component of the interventions. Any benefits of exercise in patients with coronary artery disease are likely to be 'dose-dependent'(54). If patients engaging in exercise-based CR do not reach the correct dose of exercise, it is unlikely that the physiological benefits will be achieved. It is a legitimate concern that participants in many included trials are not receiving an adequate dose of exercise. Nevertheless, if in our data there were sub-groups of participants who have received the correct dose and gained a worthwhile reduction in mortality, there must be an equal number of participants in other sub-groups who had died because of the intervention. This must be the case if the overall effect on mortality is zero.

Conclusion

Based on the outcomes of all-cause mortality, cardiovascular mortality and hospital admissions, our analysis indicates conclusively that the current approach to exercise-based CR has no effect when compared to a no exercise control.

If the provision of exercise-based CR is to continue in the UK, we recommend further research to assess its impact on other outcomes and to assess cost-effectiveness. Alternatively, we recommend different approaches to exercise which may include 'high intensity interval training'(55). This may help patients to achieve an adequate exercise 'dose' and ensure gains in cardiorespiratory fitness. We suggest these interventions and outcomes should only be delivered and measured in the context of randomised controlled trials.

Contributors

RP and MU were principally responsible for the study concept and design. RP and GM were responsible for study selection, data extraction and risk of bias assessment. RP updated and ran the searches. RP, MU and PK were responsible for statistical analysis and interpretation of data. GM and SE provided clinical advice. RP and MU wrote the first draft of the review and all co-authors contributed to review and editing of drafts of the report. All authors approved the final manuscript. RP is the study

guarantor and had full access to all trial level data in the review, takes responsibility for the integrity of the data, and accuracy of the data analysis, and had final responsibility to submit for publication.

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Competing interests

All authors have completed the *Unified Competing Interest form* (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Ethical Approval

Ethical approval not required.

Data sharing

No additional data available.

The lead author (RP) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

Tables

Table 1. Risk of bias assessment for additional study

Santaularia *et al.* 2017

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomisation list in blocks of ten was created by a computer random number generator. The randomisation list and the allocation of patients to each group were independently controlled by the Clinical Trials Unit.'
Allocation concealment (selection bias)	Low risk	A randomisation list in blocks of ten was created by a computer random number generator. The randomisation list and the allocation of patients to each group were independently controlled by the Clinical Trials Unit.'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	An independent committee that was blind to the patients' treatment group assessed the main outcomes. This committee comprised a cardiologist, a rehabilitation cardiologist and a health information manager, all from different centres.'
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no loss to follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results. Results regarding quality of life are presented in supplementary data but were not required for the current review.
Groups balanced at baseline	Low risk	No statistically significant differences in any baseline characteristics were observed between patients who agreed to participate and those who did not, except for age, which was higher in non-participants (65 vs. 60 years; $p = 0.006$)
Intention-to-treat analysis conducted	High risk	No
Groups received same treatment (apart from the intervention)	Low risk	Patients assigned to the control group received standard care given at the hospital'. In addition to standard care, patients randomised to the intervention group....'.

Table 2. Overview of participants, recruitment period, patient diagnosis and medical therapy

References, country	*N*	Mean age (years)	Male participants (%)	Recruitment period (years)	Patient diagnosis	Medication
Aronov *et al.* (2010), Russia	392	61.4	73.5	None specified	AMI, stable angina, unstable angina or myocardial revascularisation.	Standard medical therapy- β-blocker, acetylsalicyclic acid or other antithrombotic drug, nitrate, ACE inhibitor. Some patients on lipid-lowering drugs.
Belardinelli *et al.* (2001), Italy	118	61	100	None specified	CAD including AMI. Successful PCI in 1 or 2 native epicardial coronary arteries only.	According to international accepted protocols- aspirin, ticlopidine, calcium antagonists, nitrates.
Briffa *et al.*	113	47.5	89.5	None	Uncomplicated AMI or	Aspirin, antiarrhytmic agent, β-

(2005), Australia				specified.	recovery from unstable angina. PCI, CABG, thrombolytic therapy.	blocker, ACE inhibitor, calcium antagonist, long acting nitrate, diuretic.
Giallauria *et al.* (2008), Italy	61	58.5	78.5	None specified.	AMI and undergone primary or rescue PCI only.	Aspirin, β-blocker, ACE inhibitor, ARB, statin.
Hambrecht *et al.* (2004), Germany	101	56	87.3	1997-2001	Stable CAD defined by angina pectoralis and amenable to PCI. AMI patients excluded.	β-receptor antagonists, β-HMG-CoA reductase inhibitors, ACE inhibitor, acetylsalicyclic acid.
Higgins *et al.* (2001), Australia	105	60.8	81.3	1995-1997	Post-PCI patients only. No AMI 1 month pre-procedure.	Reference to medical therapy, only breakdown for lipid lowering medication.
Houle *et al.* (2012), Canada	65	51.5	100	2007-2008	Patients hospitalised for an ACS (unstable angina, non-ST-elevation or ST elevation MI). PCI, CABG or no revascularisation procedure.	Reference to medication in usual care group, but no breakdown.
Kovoor *et al.* (2006), Australia	142	51.5	100	None specified.	AMI only. Thrombolytic therapy, one patient in the exercise treatment group had primary angioplasty.	Aspirin, β-blocker, ACE inhibitor, calcium channel blockers, nitrates, cholesterol-lowering agents,
Maddison *et al.* (2014), New Zealand	171	59	20	2010-2012	Diagnosis of IHD (angina, MI, revascularisation, including angioplasty, stent, or CABG).	No description.
Maroto *et al.* (2005), Spain	180	76.9	57.5	(None specified) 2 year enrollment period.	AMI only.	Medication regimens employed in secondary prevention at discharge were clearly insufficient by standard criteria but currently meet Spanish and European guidelines'.
Munk *et al.* (2009), Norway	40	56.4	84.8	None specified.	Stable angina and unstable angina, post PCI only. AMI patients excluded.	Aspirin, β-blocker, ACE inhibitor, ARB, statin, acetylsalicyclic acid.
Mutwalli *et al.* (2012), Saudi Arabia	49	69.7	100	2008-2010	Undergone CABG surgery. Unknown whether AMI patients included.	Participants received advice that focused on medications', no breakdown.
Oerkild *et al.* (2012), Denmark	40	63.5	0	2007-2008	Recent coronary event defined as AMI, PCI, CABG or without invasive procedure.	β-blocker, antithombotics, calcium antagonists, lipid-lowering agents, diuretics.
Reid *et al.* (2012), Canada	223	54.5	87.3	2004-2007	ACS including AMI, underwent successful PCI only.	Reference to a 'descriptive summary in supplemental table', no access.
Santaularia *et al.* (2017), Spain	85	59.6	84.7	None specified.	AMI only, no evidence of revascularisation procedure.	Reference to cardiac medication, but no breakdown
Seki *et al.* (2008), Japan	39	57.8	83.8	None specified.	AMI, PCI or CABG.	Reference to 'lipid-lowering drugs and other medications', no breakdown.

Toobert *et al.* (2000), USA	25	64.5	0	None specified.	CAD defined as atherosclerosis, AMI, PCI or CABG.	Anti-hypertensive and hypolipidemic medications.
VHSG *et al.* (2003), Norway	197	64	75.8	None specified.	AMI, unstable angina pectoris or after PCI or CABG.	Aspirin, β-blocker, statin, ACE inhibitor, calcium antagonist, warfarin.
Wang *et al.* (2012), China	160	67	63.5	2005-2007	AMI only.	Anti-platelet, Nitrate, β-blocker, ACE inhibitor, calcium antagonist, statin.
West *et al.* (2012), UK	1813	51.9	93.9	1997-2000	AMI only.	Aspirin, β-blocker, ACE inhibitor, diuretic, long acting nitrate/ calcium channel blocker, statin, GTN.
Yu *et al.* (2004), China	269	56	83.9	None specified.	Recent AMI, after elective PCI or thrombolytic therapy.	Anti-platelet, β-blocker, calcium channel blocker, nitrate, statin, ACE inhibitor, diuretic.
Zwisler *et al.* (2008), Denmark	446	55.5	72.1	2000-2003	AMI, angina pectoris or after PCI or CABG.	Antithrombotics, lipid-lowering drugs, β-blocker, calcium antagonists, ACE inhibitor, diuretic, long-acting nitrates.

AMI- Acute Myocardial Infarction, CAD- Coronary Artery Disease, PCI- Percutaneous Coronary Intervention, IHD- Ischaemic Heart Disease, CABG- Coronary Artery Bypass Graft, CHD- Coronary Heart Disease, ACS- Acute Coronary Syndrome, ACE- Angiotensin-Converting-Enzyme, ARB- Angiotensin Receptor Blockers, GTN- Glyceryl Trinitrate.

Table 3. Overview of exercise interventions

References, country	**Exercise Intervention**				
	Exercise	***Modality***	***Study Duration***	***Session Duration/Frequency/Intensity***	***Additional***
Aronov *et al.* (2010), Russia	Moderate intensity physical training (unknown setting).	Cycle ergometer.	12 months	45 minutes- 60 minutes/ 3 sessions per week/ 50-60% of the performed capacity by bicycle ergometry.	None specified.
Belardinelli *et al.* (2001), Italy	Moderate intensity exercise (supervised in hospital gym).	Cycle ergometer.	6 months	53 minutes/ 3 sessions per week/ 60% of peak oxygen uptake (VO_2 Peak).	None specified.
Briffa *et al.* (2005), Australia	Aerobic circuit training (supervised in hospital).	Aerobic circuit training.	6 weeks	60-90 minutes/ 3 sessions per week/ not specified.	Education and psychosocial counselling.
Giallauria *et al.* (2008), Italy	Moderate intensity exercise (supervised in centre).	Cycle ergometer.	6 months	40 minutes/ 3 sessions per week/ 60%-70% of peak oxygen uptake (VO_2 Peak).	None specified.
Hambrecht *et al.* (2004), Germany	Moderate intensity exercise (supervised in hospital & unsupervised at home).	Cycle ergometer.	12 months	10 minutes- 42 sessions per week (hospital), 20 minutes- 7 sessions per week (home) plus 60 minutes' group training- 1 session per week/ 70% of symptom-limited max HR.	None specified.
Higgins *et al.* (2001), Australia	Moderate intensity walking programme (unsupervised at home).	Walking.	Not specified.	Not specified/ not specified/ not specified.	Psychological plus education.

Houle *et al.* (2012), Canada	Pedometer-based walking programme (unsupervised at home).	Walking.	12 months	Not specified/ not specified/ not specified.	Education plus socio-cognitive.
Kovoor *et al.* (2006), Australia	Standard Cardiac Rehabilitation programme (unknown setting).	Not specified.	5 weeks	Not specified/ 2-4 sessions per week/ not specified.	Education and counselling
Maddison *et al.* (2014), New Zealand	Automated package of text messages to increase exercise behaviour (unsupervised at home).	Moderate to vigourous aerobic exercise e.g. walking and household chores.	24 weeks	Minimum of 30 minutes/ at least 5 sessions per week/ not specified.	Optional access to other cardiac rehabilitation service or support.
Maroto *et al.* (2005), Spain	Individualised physical training (supervised in hospital gym).	Physiotherapy and aerobic training on mats or a cycle ergometer.	3 months	60 minutes/ 3 sessions per week/ 75-85% max HR.	Psychological, education plus return to work councelling.
Munk *et al.* (2009), Norway	Moderate/high intensity interval training (supervised in centre).	Cycle ergometer or running.	6 months	60 minutes/ 3 sessions per week/ 60-70% & 80-90% max HR.	Spine & abdominal resistance training.
Mutwalli *et al.* (2012), Saudi Arabia	Moderate intensity walking programme (unsupervised at home).	Walking.	6 months	30 minutes/ 7 sessions per week/ not specified.	Education.
Oerkild *et al.* (2012), Denmark	Moderate intensity exercise (unsupervised at home).	Individualised	12 months	30 minutes/ 6 sessions per week/ 11-13 on the Borg Scale.	Risk factor management.
Reid *et al.* (2012), Canada	Internet based physical activity plan and motivational tool to increase physical activity (unsupervised at home).	Not specified.	20 weeks	Not specified/ not specified/ not specified.	None specified.
Santaularia *et al.* (2017), Spain	Outpatient exercise training programme (supervised in hospital).	Cycle ergometer	10 weeks	60 minutes/ 3 sessions per week/ 75-90% max HR (RPE 11-15 on Borg Scale)	Resistance training, education and risk factor management.
Seki *et al.* (2008), Japan	Moderate intensity aerobic exercise (supervised in centre & unsupervised at home).	Walking, cycle ergometer, jogging.	6 months	50-110 minutes- 1 session per week (centre), ≥ 30 minutes- 2 sessions per week (home)/ 12-13 on the standard Borg scale.	Education.
Toobert *et al.* (2000), USA	Walking or aerobics (supervised in centre & unsupervised at home).	Walking or aerobics.	24 months	60 minutes- 7 sessions per week (centre), 60 minutes- 3 sessions per week (home)/ Individually prescribed.	Education and psychological support.
VHSG *et al.* (2003), Norway	Dynamic endurance physical activity (supervised, group sessions in centre).	Dynamic endurance training.	15 weeks	55 minutes/ 2 sessions per week/ RPE 11-13 on the Borg Scale, increased to 13-15 after 6 weeks.	Education and psychological support.
Wang *et al.* (2012), China	Not specified.	Not specified.	Not specified.	Not specified/ not specified/ not specified.	Education.

West *et al.* (2012), UK	Not specified, multi-centre (supervised in centre).	Varied by centre (exercise equipment in physiotherapy gyms).	6-8 weeks	Averaged 20 hours over 6-8 weeks/ 1-2 sessions per week/ not specified.	Education plus psychological support.
Yu *et al.* (2004), China	Ambulatory and aerobic cardiovascular training (supervised in hospital and centre, unsupervised at home).	Walking, treadmill, cycle ergometry, rowing, stepper, arm ergometry, dumbbell.	8 1/2 months	2 hours/ 2 sessions per week (centre), not specified (home)/ 65-85% of maximal aerobic capacity (VO2 Peak).	Resistance training and education.
Zwisler *et al.* (2008), Denmark	Intensive CR programme (supervised in centre).	Not specified.	6 weeks	Not specified/ 2 sessions per week/ not specified.	Education and psychosocial support.

HR- Heart Rate, VO_2 Peak- Peak Oxygen Uptake

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Legends

Figure 1. Summary of study selection process

Figure 2. All-cause mortality for studies at their longest follow-up period. Filled squares represent the risk difference for individual studies at the longest reported follow-up. The boxes are proportional to the weight of each study and the lines represent their 95% confidence interval (CI). The filled diamond represents the pooled risk difference. Weights are from random effects analysis. CR-Cardiac Rehabilitation.

Figure 3. Cardiovascular mortality for studies at their longest follow-up period. Filled squares represent the risk difference for individual studies at the longest reported follow-up. The boxes are proportional to the weight of each study and the lines represent their 95% confidence interval (CI). The filled diamond represents the pooled risk difference. Weights are from random effects analysis. CR- Cardiac Rehabilitation.

Figure 4. Hospital admissions for studies at their longest follow-up period. Filled squares represent the risk difference for individual studies at the longest reported follow-up. The boxes are proportional to the weight of each study and the lines represent their 95% confidence interval (CI). The filled diamond represents the pooled risk difference. Weights are from random effects analysis. CR- Cardiac Rehabilitation.

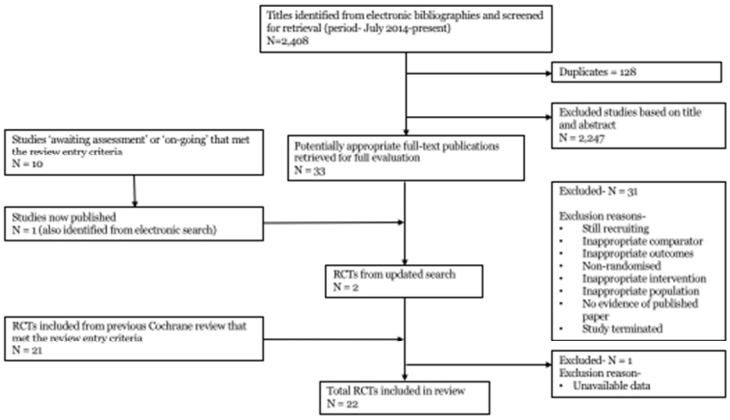

Figure 1. Summary of study selection process

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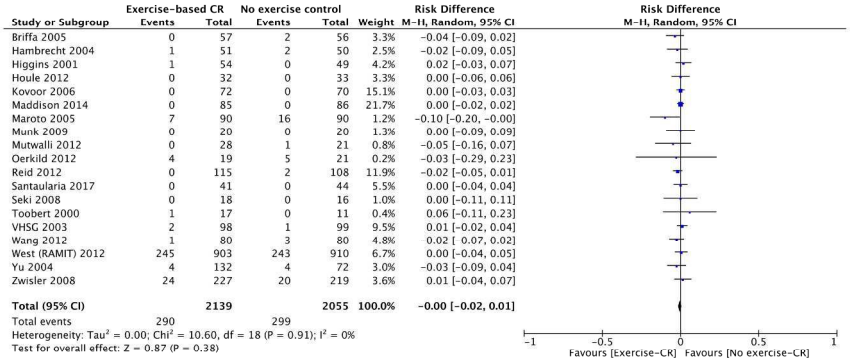

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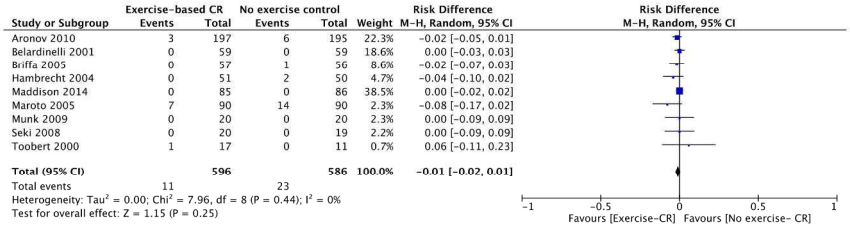

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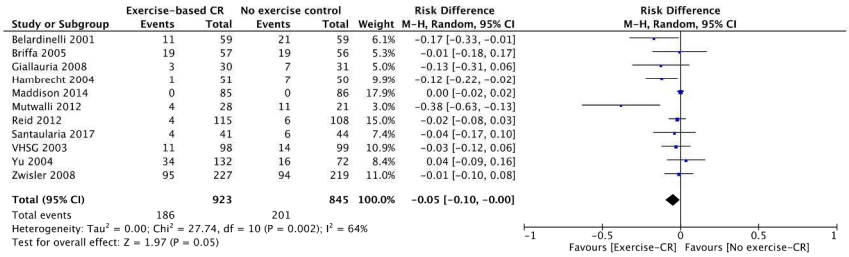

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4,5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4/appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4,5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4,5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4,5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5,6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12-15
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5, 11,12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8/figures 2,3,4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11,12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8,9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9,10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

BMJ Open

Is exercise-based cardiac rehabilitation effective: a systematic review and meta-analysis

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Secondary Subject Heading:	Cardiovascular medicine, Evidence based practice
Keywords:	Coronary heart disease < CARDIOLOGY, Ischaemic heart disease < CARDIOLOGY, Myocardial infarction < CARDIOLOGY, REHABILITATION MEDICINE

Is exercise-based cardiac rehabilitation effective: a systematic review and meta-analysis

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Word count

3716 words

Abstract

Objectives

To determine the contemporary effectiveness of exercise-based Cardiac Rehabilitation (CR).

Data sources

Studies included in, or meeting the entry criteria for the 2016 Cochrane review of exercise-based CR in patients with coronary artery disease.

Study eligibility criteria

Randomised controlled trials (RCTs) of exercise-based CR vs. a no exercise control whose participants were recruited after the year 2000.

Study appraisal and synthesis methods

Two separate reviewers independently screened the characteristics of studies. One reviewer quality appraised any new studies and assessed their risk of bias using the Cochrane Collaboration's recommended risk of bias tool. Data were reported as the risk difference (95% CI).

Results

We included 22 studies with 4,834 participants (mean age 59.5 years. 78.4% male). We found no differences in outcomes between exercise-based CR and a no exercise control at their longest follow-up period for: all-cause mortality (19 studies; n=4,194; risk difference 0.00, 95% CI -0.02 to 0.01, p=0.38) or cardiovascular mortality (9 studies; n = 1,182; risk difference -0.01, 95% CI -0.02 to 0.01, p=0.25). We found a small reduction in hospital admissions of borderline statistical significance (11 studies; n= 1,768; risk difference -0.05, 95% CI -0.10 to -0.00, p=0.05).

Conclusions and implications of key findings

Our analysis indicates conclusively that the current approach to exercise-based CR has no effect on all-cause mortality or cardiovascular mortality, when compared to a no exercise control. There may be a small reduction in hospital admissions following exercise-based CR that is unlikely to be clinically important.

Systematic review registration number

Prospero: International prospective register of systematic reviews. 2017. 42017073616. Available from: https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017073616

Strengths and Limitations of this study

- To our knowledge, this is the first systematic review of exercise-based CR that has pooled data relevant to the current medical management of patients diagnosed with coronary artery disease.

- For analysis, we present the data as the risk difference (95% CI), which ensures all studies reporting data on the outcomes of interest were included.

- This systematic review pools data from studies that deliver an intervention recognised as best practice in exercise-based CR, where multiple approaches, including educational/psychosocial components, as well as the exercise component were used.

- We have not done a de novo quality assessment of 21/22 studies included in this review and instead rely on a previous Cochrane assessment.

- We did not include health-related quality of life as an outcome measure as this is unsuitable for meta-analysis.

Keywords

Coronary artery disease, exercise-based cardiac rehabilitation, all-cause mortality, cardiovascular mortality, hospital admissions.

Background

Cardiovascular disease is the world's biggest killer, accounting for 15 million deaths in 2015(1).

Secondary prevention of coronary artery disease through exercise-based CR in those who have a diagnosis of coronary artery disease, has the potential to reduce mortality, reduce hospital admissions and increase quality of life. Guidelines internationally endorse the use of exercise-based CR programmes(2-5).

Typically, exercise-based CR aims to achieve 20-60 minutes of moderate intensity continuous exercise, 3-5 times a week, with muscular strength and endurance exercises prescribed in conjunction(6). Additionally, most programmes include supplementary education (coronary risk factors and cardiac misconceptions), advice on diet and access to psychological support(2, 4, 7, 8). Typically exercise-based CR is delivered in a supervised centre-based setting, although home-based programmes are used(9).

A 2016 Cochrane review (63 studies, n=14,486 participants) found benefits of exercise-based CR for patients with coronary artery disease. Both cardiovascular mortality (27 studies, RR 0.74, 95% CI 0.64 to 0.86) and hospital re-admissions were reduced (15 studies, RR 0.82, 95% CI 0.70 to 0.96), when compared to a no exercise control. However, in contrast to previous systematic reviews and meta-

analyses, there was no significant reduction in risk of re-infarction (36 studies, RR 0.90, 95% CI 0.79 to 1.04) or all-cause mortality (47 studies, RR 0.96, 95% CI 0.88 to 1.04)(10).

Over recent decades, the medical management of coronary artery disease has been transformed. The introduction of primary percutaneous coronary intervention has reduced short-term major adverse cardiac events and increased long-term survival(11-14). Simultaneously, there have also been widespread advances in secondary preventative medical therapy. This includes the introduction of aspirin and beta-blockers in the 1980s(15, 16), lipid-lowering statins and angiotensin converting enzyme inhibitors in the 1990s(17, 18) and more recently, the introduction of clopidogrel, a secondary anti-platelet, in 2007(19, 20). Age-adjusted mortality has decreased substantially in this population(21). Systematic reviews and meta-analyses that include data from older studies may not correctly assess the potential effect of exercise-based CR. We hypothesise that previous reviews have overestimated the benefit of exercise-based CR.

Objectives

To determine the contemporary effectiveness of exercise-based CR on all-cause mortality, cardiovascular mortality, and hospital readmissions in patients with coronary artery disease.

Methods

We conducted and reported this meta-analysis in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)(22).

Search Strategy

To identify relevant studies, we started with the latest Cochrane review of exercise-based CR in patients with coronary artery disease(10). Studies identified as 'awaiting assessment' or 'on-going' in this review were re-visited to establish whether publication had been reached. To identify any new studies published since the completion of the Cochrane review, an updated search was run on the 28/2/2017. This search used the same search strategies as the latest Cochrane review(10). We searched Cochrane Central Register of Controlled Trials (CENTRAL) *(appendix 1)*, MEDLINE (Ovid), EMBASE (Ovid) and CINAHL (EBSCO) databases. This approach allowed us to efficiently identify all relevant studies. Where appropriate, we contacted original authors for clarification of any new included studies.

Two separate reviewers (RP and GM) independently screened the characteristics of studies in the latest Cochrane review, studies identified as 'awaiting assessment' or 'on-going' and studies identified in the updated search. Full text publications were retrieved to allow for further examination and to verify study inclusion. Any discrepancies were resolved by a third reviewer (MU).

Criteria for considering studies

In 1996, The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology first recommended early (within two hours) primary percutaneous interventions in preference to thrombolytic therapy for acute myocardial infarction(23). Two years later, guidelines set by the Joint British recommendations on prevention of Coronary Heart Disease in Clinical Practice were published outlining the recommendations for best practice for secondary prevention medical therapies(24). Although there have been some changes, notably the introduction of a second anti-platelet agent in the early 2000s(19, 20), the approach to secondary prevention medical therapies has not changed since then. Allowing time for implementation of these guidelines and recommendations, we identified and included studies whose participants were recruited after the year 2000, to represent a contemporary population engaging in exercise-based CR.

Where there was no indication of recruitment period, the diagnosis and the secondary preventative medical therapy received by participants included in the trial determined the inclusion or exclusion of the study in the analysis.

Types of studies

We included randomised controlled trials of exercise-based CR compared to a no exercise control with a minimum follow-up period of six months. Data reported at the longest follow-up period were included in the analysis.

Types of participants

We used the same entry criterion as previous Cochrane reviews.

- People who have had a myocardial infarction, or who had undergone revascularisation (coronary artery bypass grafting or percutaneous coronary intervention) or who have angina pectoris or coronary artery disease defined by angiography.

- On optimal secondary preventative medical therapy defined by the Joint British recommendations on prevention of Coronary Heart Disease in Clinical Practice(24).

- Recruited to hospital-based, community-based or home-based CR programmes.

Types of intervention(s)

Randomised controlled trials consisted of supervised or non-supervised exercise-based CR. The intervention was exercise alone or exercise as part of a comprehensive CR programme (consisting of educational/psychosocial components). 'No exercise control' consisted of standard medical care, including optimal secondary preventative medical therapy, education and advice about diet and exercise, psychosocial support but with no formal exercise intervention.

Types of outcome measures

We extracted data on: all-cause mortality, cardiovascular mortality and hospital re-admissions. We did not include health-related quality of life as the authors of the 2016 Cochrane review found this unsuitable for meta-analysis.

Data collection, statistical analysis and quality assessment

We pooled data using Review Manager 5.3(25). Previous Cochrane reviews have presented the data as individual and pooled risk ratio (95% CI). Using risk ratios automatically removed studies with no events in either study arm from the analysis. Nine studies (n= 936 participants) reporting on all-cause mortality, cardiovascular mortality or hospital re-admissions, were excluded from one or more meta-analyses in the 2016 Cochrane review for this reason. We therefore present the data as the risk difference (95% CI), which ensures all studies reporting data on the outcomes of interest were included.

We applied a random-effects model to all analyses given the clinical heterogeneity of individual studies. Heterogeneity of included studies were tested statistically using the χ^2 test of heterogeneity and I^2 statistic(26).

We did not repeat quality assurance checks already completed by the authors of the Cochrane review. For separate study risk of bias breakdown for these studies, we refer the reader to the existing *characteristics of studies*(10). For studies identified as 'awaiting assessment' or 'on-going' in the latest Cochrane review, or in the updated search, we quality appraised these studies and assessed their risk of bias using the Cochrane Collaboration's recommended risk of bias tool(27).

Assessment of risk of bias in additional included study

One reviewer (RP) assessed the risk of bias in any additional included studies *(table 1)*. Assessment of three further quality domains as outlined in the latest Cochrane review was also conducted (Groups balanced at baseline, Intention-to-treat analysis, Groups received comparable treatment (except exercise)). A breakdown of the criteria used for assessing these three domains can be found in the latest Cochrane review. Risk of bias assessments were checked by a second reviewer (GM) and any discrepancies were resolved by a third reviewer (MU).

Patient Involvement

No patients were involved in setting the objectives or outcome measures of this review, nor were they involved in the design or implementation. No patients were involved in the analysis or interpretation of the results, nor the writing of any drafts. There are no plans to disseminate the results of the review to participants included in the studies of the review or any relevant patient networks.

Results

Studies retrieved

Of the sixty-three studies included in the Cochrane review, twenty-one studies met our entry criteria. We identified two additional relevant papers not included in the 2016 Cochrane review(28, 29). One was excluded because data for our specific research question were not available in a useable format(28). In total, twenty-two studies (n=4,834 participants) contributed to the analysis *(figure 1)*. For the study identified from the updated search(29), there was a low risk of bias in all eight domains, apart from the intention-to-treat analysis, where there was no evidence of this analysis being conducted (*table 1)*.

Three studies (3/22; 14%) reported on all three outcomes of interest, eleven studies (11/22; 50%) reported on two outcomes of interest and eight studies (8/22; 36%) reported on one outcome of interest.

Two studies for all-cause mortality(30, 31) and one study for cardiovascular mortality(30) reported data at varying follow-up periods (6 to 12 months; >12 to 36 months; >3 years). Data from these studies were taken at their longest follow-up period. Mean maximum follow-up period was 24.7 months. Maximum follow-up period ranged from 24 weeks to 10 years *(table 2)*.

Flow diagram

(figure 1).

Sample size, gender, age and study origin

Of our twenty-two studies, ten studies were in Europe(29-38) and twelve from outside of Europe(39-50). We included a total of 4,834 participants (3,788 (78.4%) males). Four studies included males only(30, 34, 45, 47) and one study included women only(51). Participants mean age was 59.5 years. The mean age for individual studies ranged from 47.5 to 76.9 years (*table 2)*.

Incomplete outcome data

The majority of trials (18/22; 82%) reported complete follow-up data, regardless of participants who were lost to follow-up or who dropped out. In four studies, outcome data were incomplete for 75 (75/4,834; 1.6%) participants with no description of withdrawal or drop-out(41, 47, 48, 50).

Participant diagnosis of coronary artery disease and treatment received

The diagnosis of participants recruited to the studies was described in the majority of studies (21/22; 95%). Thirteen studies enrolled participants with mixed diagnoses, including angina pectoralis or coronary artery disease defined by angiography, myocardial infarction, percutaneous coronary interventions or coronary artery bypass grafts(32, 36-42, 44, 46-48, 50). Six studies enrolled participants following acute myocardial infarction only(29, 31, 33, 34, 43, 49) and two studies enrolled

participants diagnosed with angina pectoralis (unstable and stable angina) only(30, 35). It was unclear from one study whether participants following myocardial infarction were included and instead, the population was defined as 'patients after coronary artery bypass graft surgery'(45) (*table 2)*.

Six studies recruited participants following percutaneous coronary intervention only(30, 32, 33, 35, 41, 46) and one study recruited participants following coronary artery bypass grafting only(45). Twelve studies included participants who had received thrombolysis, percutaneous coronary intervention, coronary artery bypass grafting and/or no revascularization procedure(31, 36-40, 42-44, 47, 48, 50). Three studies did not provide any breakdown of coronary intervention or surgical procedure received by participants prior to enrollment(29, 34, 49) (*table 2)*.

Medication

A full description and breakdown of the medication received by the participants, comparable to optimal secondary prevention medical therapy defined by the Joint British recommendations on prevention of Coronary Heart Disease in Clinical Practice set in 1998(24), was provided by 13/22 studies (59%)(30-33, 35-40, 43, 49, 50). References to co-existing medical therapies were made in 7/22 (32%), but no breakdowns were provided(29, 34, 41, 42, 45-47). One study referred to the prescription of anti-hypertensive and hypolipidemic medications without reference to other recommended medications(48). One study failed to provide any description or breakdown of co-existing medical therapies(44) (*table 2)*.

Clearly defined recruitment period

Seven studies (7/22; 32%) were explicit that they recruited participants after the year 2000(36, 38, 42, 44-46, 49). In three studies, participants were recruited either just before or during the year 2000(30, 31, 41). Due to participant diagnosis, treatment received and co-existing medical therapies, it was agreed by all reviewers to include these studies.

The remaining twelve studies failed to provide a recruitment period. Following further examination of the full papers, due to adequate description of patient diagnosis, treatment received and co-existing medical therapies, it was agreed by all reviewers to include these studies *(table 2)*.

Content of the interventions

The content of the interventions tested was heterogeneous with multiple approaches being adopted. Sixteen studies (16/22; 73%) compared exercise in combination with other therapies (education, psychosocial management), whilst six studies compared exercise as a stand-alone intervention, against a no exercise control. The exercise component alone varied considerably with respect to setting, training modality, duration, session length, frequency and intensity (*table* 3).

Overall effects of interventions

All-cause mortality

Nineteen studies (n=4,194 participants) reported all-cause mortality (*figure 2*.). There was no difference between groups at their longest follow-up (risk difference = 0.00, 95% CI -0.02 to 0.01, p=0.38). There was no evidence of statistical heterogeneity across trials (P value=0.91, I^2=0%).

(figure 2).

Cardiovascular mortality

Nine studies (n = 1,182 participants) reported cardiovascular mortality (*figure 3*.). There was no difference between groups at their longest follow-up (risk difference = -0.01, 95% CI -0.02 to 0.01, p=0.25). There was no evidence of statistical heterogeneity across trials (P value=0.44, I^2=0%).

(figure 3).

Hospital admissions

Eleven studies (n= 1,768 participants) reported on proportion with one or more hospital admissions (*figure 4*.). There was a reduction of borderline statistical significance (risk difference = -0.05, 95% CI -0.10 to -0.00, p=0.05). There was evidence of statistical heterogeneity across trials (P value=0.002, I^2=64%).

(figure 4).

Discussion

The effectiveness of exercise-based CR in patients with coronary artery disease has been determined by Cochrane systematic reviews and meta-analyses, providing clinicians and academics with the highest level of evidence over the last 17 years(10, 52, 53). The latest Cochrane review, conducted in 2016, found benefits of exercise-based CR in terms of reduced cardiovascular mortality and hospital admissions, but unlike previous Cochrane reviews, found no effect on all-cause mortality(10). We identified that data from studies included in this review dated back as far as 1975(54). By including such historical data, this Cochrane review may not be correctly assessing the potential effect of contemporary exercise-based CR.

The current review aimed to assess the effect of exercise-based CR in the era of improved reperfusion strategies and simultaneous advances in pharmacological management, by only including studies whose participants were recruited after the year 2000. The majority of interventions tested in the twenty-two included trials (*table 3*) delivered an intervention recognised as best practice in exercise-based CR, where multiple approaches, including educational/psychosocial components, as well as the exercise component were used(2, 3, 8).

The current analyses demonstrated no improvement in all-cause mortality from participation in exercise-based CR: the risk difference was 0.00 (95% CI -0.02 to 0.01). The largest trial included in our analysis, the UK-based Rehabilitation after myocardial infarction trial (RAMIT) trial, sought to show a

20% reduction in relative risk based on an 11% mortality; i.e. a 2.2% risk difference(24). The limits of the 95% confidence interval for the effect size in our analysis do not include the RAMIT trial's pre-specified clinically important difference. We therefore conclude that it is extremely unlikely that there is a worthwhile benefit from exercise-based CR on all-cause mortality. Furthermore, it is unlikely that future trials of similar interventions and populations, will change this conclusion. This is supported by a recent meta-analysis which included participants with other forms of atherosclerotic cardiovascular disease i.e. peripheral artery disease, ischaemic cerebrovascular accidents, diabetes and hypertension. They too found a zero effect on all-cause mortality (relative risk 1.00, 95% CI 0.88 to 1.14)(55). With the mean follow-up period for all studies included in our review being 24.7 months, it may be that any benefits on mortality will accrue over a longer follow-up. However, the absence of any kind of signal in this review means a substantial longer-term benefit is unlikely.

The current analyses do not quite exclude a worthwhile benefit of exercise-based CR on hospital admissions. Whilst a risk difference of -0.05 (95% CI -0.10 to -0.00) is of borderline statistical significance, it is probably clinically unimportant in the context of no change in all-cause mortality.

From the studies included in this review, we do not know if there is a worthwhile benefit on quality of life, as a meta-analysis was not conducted. However, the authors of the 2016 Cochrane review reported that in four of the twenty-two studies included in this review, there was a significantly higher quality of life in at least half or more of the sub-scales(32, 45, 46, 49).

Based on the present data, we are also unable to comment on whether exercise-based CR might be cost-effective. Five of the studies in this review included a within trial health economic evaluation(30, 40, 43, 44, 50). Of these five papers, three studies showed no difference in healthcare costs between groups(40, 43, 50), one found healthcare costs to be lower for exercise-based CR(30), and one failed to report a p-value for cost difference(44). Whilst a decrease, of borderline statistical significance, in hospital admissions may improve quality of life for patients, it is unclear if this confers any economic benefit, in the absence of robust cost-effectiveness analyses.

It may be that exercise-based CR has an effect on other outcomes, not specifically addressed in this review, such as cardiorespiratory fitness, lifestyle risk factor management, adherence to medication, diet, smoking cessation, psychosocial health and return to work(7, 8, 56, 57). If the focus of future research is on measuring and improving these outcomes, attention will be needed to develop the best multi-component intervention.

Strengths and Limitations

To our knowledge, this is the first systematic review of exercise-based CR that has pooled data relevant to contemporary medical management of patients diagnosed with coronary artery disease. Although we have not done a de novo quality assessment of 21/22 studies included in this review and instead are relying on a previous Cochrane assessment, it is unlikely that we would have drawn different conclusions from such an assessment(10).

The current review does not provide information on participant baseline characteristics. In the majority of studies (20/22; 91%), however, baseline characteristics were comparable between the intervention and control groups(10, 29).

Whilst there was no evidence of statistical heterogeneity across trials for all outcome measures (P value<0.01, I^2>30%), except for hospital admissions, there was substantial context and interventional heterogeneity. The studies came from a wide range of clinical environments and countries, and the interventions delivered ranged greatly in quality. When compared with both the BACPR 'minimum standards and core components'(8) and ACPICR guidelines(6), there was considerable variation in the exercise interventions delivered (*table 3*). Critics have questioned the exercise component reported in the largest included study, the RAMIT trial (n=1813)(31). They argued that under-dosage of exercise intensity and duration may have led to the inconclusive result(58). Several other studies included in this review also fail to report on the intensity, modality and/or duration of the exercise intervention. Exercise and physical activity has a 'dose-response' relationship with cardiovascular disease risk(59). Moreover, a higher exercise capacity (VO_2 peak) is associated with an improvement in mortality risk(60, 61). If patients engaging in exercise-based CR do not achieve the correct dose of exercise, a physiological benefit is unlikely. It is a legitimate concern that participants in many included trials may not have received an adequate dose of exercise. In the era of contemporary medical management, higher intensity exercise protocols might be appropriate and effective(62).

One major concern is the reporting of adherence to, and fidelity of, exercise interventions(10). Whilst the majority of studies included in this review report the intended prescription exercise dose (*table 3*), it is not possible to determine adherence and fidelity. Without basic reporting of these parameters, the actual exercise dose received cannot be quantified. This may have a significant bearing on intervention efficacy and the results of this meta-analysis.

Conclusion

Based on the outcomes of all-cause mortality and cardiovascular mortality, our analysis indicates conclusively that the current approach to exercise-based CR has no effect when compared to a no exercise control. There may be a small reduction in hospital admissions following exercise-based CR that is unlikely to be clinically important.

The continued delivery of exercise-based CR needs to be supported by new research to show its impact on health-related quality of life and whether it is a cost-effective intervention.

Contributors

RP and MU were principally responsible for the study concept and design. RP and GM were responsible for study selection, data extraction and risk of bias assessment. RP updated and ran the searches. RP, MU and PK were responsible for statistical analysis and interpretation of data. GM and SE provided clinical advice. RP and MU wrote the first draft of the review and all co-authors contributed to review and editing of drafts of the report. All authors approved the final manuscript. RP is the study guarantor and had full access to all trial level data in the review, takes responsibility for the integrity of the data, and accuracy of the data analysis, and had final responsibility to submit for publication.

Copyright

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Competing interests

All authors have completed the *Unified Competing Interest form* (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Ethical Approval

Ethical approval not required.

Data sharing

No additional data available.

The lead author (RP) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

Tables

Table 1. Risk of bias assessment for additional study

Santaularia *et al.* 2017		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence	Low risk	A randomisation list in blocks of ten was created by a computer random number generator. The randomisation list and the allocation

generation (selection bias)		of patients to each group were independently controlled by the Clinical Trials Unit.'
Allocation concealment (selection bias)	Low risk	A randomisation list in blocks of ten was created by a computer random number generator. The randomisation list and the allocation of patients to each group were independently controlled by the Clinical Trials Unit.'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	An independent committee that was blind to the patients' treatment group assessed the main outcomes. This committee comprised a cardiologist, a rehabilitation cardiologist and a health information manager, all from different centres.'
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no loss to follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results. Results regarding quality of life are presented in supplementary data but were not required for the current review.
Groups balanced at baseline	Low risk	No significant differences between groups were observed, with the exception of gender: 23% of the control group were women compared with 7% in the intervention group (p=0.049).
Intention-to-treat analysis conducted	High risk	No analysis was conducted.
Groups received same treatment (apart from the intervention)	Low risk	Patients assigned to the control group received standard care given at the hospital'. In addition to standard care, patients randomised to the intervention group....'.

Table 2. Overview of participants, recruitment period, patient diagnosis and medical therapy

References, country	*N*	Mean age (years)	Male participants (%)	Recruitment period (years)	Maximum follow-up period	Patient diagnosis	Medication
Aronov *et al.* (2010), Russia	392	61.4	73.5	None specified	1 year	AMI, stable angina, unstable angina or myocardial revascularisation.	Standard medical therapy-β-blocker, acetylsalicyclic acid or other antithrombotic drug, nitrate, ACE inhibitor. Some patients on lipid-lowering drugs.
Belardinelli *et al.* (2001), Italy	118	61	100	None specified	33 months	CAD including AMI. Successful PCI in 1 or 2 native epicardial coronary arteries only.	According to international accepted protocols-aspirin, ticlopidine, calcium antagonists, nitrates.
Briffa *et al.* (2005), Australia	113	47.5	89.5	None specified.	1 year	Uncomplicated AMI or recovery from unstable angina. PCI, CABG, thrombolytic therapy.	Aspirin, antiarrhytmic agent, β-blocker, ACE inhibitor, calcium antagonist, long acting nitrate, diuretic.

Giallauria *et al.* (2008), Italy	61	58.5	78.5	None specified.	6 months	AMI and undergone primary or rescue PCI only.	Aspirin, β-blocker, ACE inhibitor, ARB, statin.
Hambrecht *et al.* (2004), Germany	101	56	87.3	1997-2001	1 year	Stable CAD defined by angina pectoralis and amenable to PCI. AMI patients excluded.	β-receptor antagonists, β-HMG-CoA reductase inhibitors, ACE inhibitor, acetylsalicyclic acid.
Higgins *et al.* (2001), Australia	105	60.8	81.3	1995-1997	51 weeks	Post-PCI patients only. No AMI 1 month pre-procedure.	Reference to medical therapy, only breakdown for lipid lowering medication.
Houle *et al.* (2012), Canada	65	51.5	100	2007-2008	12 months	Patients hospitalised for an ACS (unstable angina, non-ST-elevation or ST elevation MI). PCI, CABG or no revascularisation procedure.	Reference to medication in usual care group, but no breakdown.
Kovoor *et al.* (2006), Australia	142	51.5	100	None specified.	6 months	AMI only. Thrombolytic therapy, one patient in the exercise treatment group had primary angioplasty.	Aspirin, β-blocker, ACE inhibitor, calcium channel blockers, nitrates, cholesterol-lowering agents,
Maddison *et al.* (2014), New Zealand	171	59	20	2010-2012	24 weeks	Diagnosis of IHD (angina, MI, revascularisation, including angioplasty, stent, or CABG).	No description.
Maroto *et al.* (2005), Spain	180	76.9	57.5	(None specified) 2 year enrollment period.	10 years AMI only.		Medication regimens employed in secondary prevention at discharge were clearly insufficient by standard criteria but currently meet Spanish and European guidelines'.
Munk *et al.* (2009), Norway	40	56.4	84.8	None specified.	6 months	Stable angina and unstable angina, post PCI only. AMI patients excluded.	Aspirin, β-blocker, ACE inhibitor, ARB, statin, acetylsalicyclic acid.
Mutwalli *et al.* (2012), Saudi Arabia	49	69.7	100	2008-2010	6 months	Undergone CABG surgery. Unknown whether AMI patients included.	Participants received advice that focused on medications', no breakdown.
Oerkild *et al.* (2012), Denmark	40	63.5	0	2007-2008	12 months (mortality data after 5.5 years)	Recent coronary event defined as AMI, PCI, CABG or without invasive procedure.	β-blocker, antithombotics, calcium antagonists, lipid-lowering agents, diuretics.
Reid *et al.* (2012), Canada	223	54.5	87.3	2004-2007	12 months	ACS including AMI, underwent successful PCI only.	Reference to a 'descriptive summary in supplemental table', no access.
Santaularia *et al.* (2017),	85	59.6	84.7	None specified.	12 months	AMI only, no evidence of revascularisation	Reference to cardiac medication, but no breakdown

Spain						procedure.	
Seki *et al.* (2008), Japan	39	57.8	83.8	None specified.	NR	AMI, PCI or CABG.	Reference to 'lipid-lowering drugs and other medications', no breakdown.
Toobert *et al.* (2000), USA	25	64.5	0	None specified.	24 months	CAD defined as atherosclerosis, AMI, PCI or CABG.	Anti-hypertensive and hypolipidemic medications.
VHSG *et al.* (2003), Norway	197	64	75.8	None specified.	2 years	AMI, unstable angina pectoris or after PCI or CABG.	Aspirin, β-blocker, statin, ACE inhibitor, calcium antagonist, warfarin.
Wang *et al.* (2012), China	160	67	63.5	2005-2007	6 months	AMI only.	Anti-platelet, Nitrate, β-blocker, ACE inhibitor, calcium antagonist, statin.
West *et al.* (2012), UK	1813	51.9	93.9	1997-2000	7 to 9 years	AMI only.	Aspirin, β-blocker, ACE inhibitor, diuretic, long acting nitrate/ calcium channel blocker, statin, GTN.
Yu *et al.* (2004), China	269	56	83.9	None specified.	2 years	Recent AMI, after elective PCI or thrombolytic therapy.	Anti-platelet, β-blocker, calcium channel blocker, nitrate, statin, ACE inhibitor, diuretic.
Zwisler *et al.* (2008), Denmark	446	55.5	72.1	2000-2003	1 year	AMI, angina pectoris or after PCI or CABG.	Antithrombotics, lipid-lowering drugs, β-blocker, calcium antagonists, ACE inhibitor, diuretic, long-acting nitrates.

AMI- Acute Myocardial Infarction, CAD- Coronary Artery Disease, PCI- Percutaneous Coronary Intervention, IHD- Ischaemic Heart Disease, CABG- Coronary Artery Bypass Graft, CHD- Coronary Heart Disease, ACS- Acute Coronary Syndrome, ACE- Angiotensin-Converting-Enzyme, ARB- Angiotensin Receptor Blockers, GTN- Glyceryl Trinitrate.

Table 3. Overview of exercise interventions

References, country	**Exercise Intervention**				
	Exercise	***Modality***	***Study Duration***	***Session Duration/Frequency/Intensity***	***Additional***
Aronov *et al.* (2010), Russia	Moderate intensity physical training (unknown setting).	Cycle ergometer.	12 months	45 minutes- 60 minutes/ 3 sessions per week/ 50-60% of the performed capacity by bicycle ergometry.	None specified.
Belardinelli *et al.* (2001), Italy	Moderate intensity exercise (supervised in hospital gym).	Cycle ergometer.	6 months	53 minutes/ 3 sessions per week/ 60% of peak oxygen uptake (VO_2 Peak).	None specified.
Briffa *et al.* (2005), Australia	Aerobic circuit training (supervised in hospital).	Aerobic circuit training.	6 weeks	60-90 minutes/ 3 sessions per week/ not specified.	Education and psychosocial counselling.
Giallauria *et al.* (2008), Italy	Moderate intensity exercise (supervised in centre).	Cycle ergometer.	6 months	40 minutes/ 3 sessions per week/ 60%-70% of peak oxygen uptake (VO_2 Peak).	None specified.
Hambrecht *et al.*	Moderate intensity exercise (supervised in	Cycle ergometer.	12 months	10 minutes- 42 sessions per week (hospital), 20 minutes- 7 sessions per	None specified.

(2004), Germany	hospital & unsupervised at home).			week (home) plus 60 minutes' group training- 1 session per week/ 70% of symptom-limited max HR.	
Higgins *et al.* (2001), Australia	Moderate intensity walking programme (unsupervised at home).	Walking.	Not specified.	Not specified/ not specified/ not specified.	Psychological plus education.
Houle *et al.* (2012), Canada	Pedometer-based walking programme (unsupervised at home).	Walking.	12 months	Not specified/ not specified/ not specified.	Education plus socio-cognitive.
Kovoor *et al.* (2006), Australia	Standard Cardiac Rehabilitation programme (unknown setting).	Not specified.	5 weeks	Not specified/ 2-4 sessions per week/ not specified.	Education and counselling
Maddison *et al.* (2014), New Zealand	Automated package of text messages to increase exercise behaviour (unsupervised at home).	Moderate to vigourous aerobic exercise e.g. walking and household chores.	24 weeks	Minimum of 30 minutes/ at least 5 sessions per week/ not specified.	Optional access to other cardiac rehabilitation service or support.
Maroto *et al.* (2005), Spain	Individualised physical training (supervised in hospital gym).	Physiotherapy and aerobic training on mats or a cycle ergometer.	3 months	60 minutes/ 3 sessions per week/ 75-85% max HR.	Psychological, education plus return to work councelling.
Munk *et al.* (2009), Norway	Moderate/high intensity interval training (supervised in centre).	Cycle ergometer or running.	6 months	60 minutes/ 3 sessions per week/ 60-70% & 80-90% max HR.	Spine & abdominal resistance training.
Mutwalli *et al.* (2012), Saudi Arabia	Moderate intensity walking programme (unsupervised at home).	Walking.	6 months	30 minutes/ 7 sessions per week/ not specified.	Education.
Oerkild *et al.* (2012), Denmark	Moderate intensity exercise (unsupervised at home).	Individualised	12 months	30 minutes/ 6 sessions per week/ 11-13 on the Borg Scale.	Risk factor management.
Reid *et al.* (2012), Canada	Internet based physical activity plan and motivational tool to increase physical activity (unsupervised at home).	Not specified.	20 weeks	Not specified/ not specified/ not specified.	None specified.
Santaularia *et al.* (2017), Spain	Outpatient exercise training programme (supervised in hospital).	Cycle ergometer	10 weeks	60 minutes/ 3 sessions per week/ 75-90% max HR (RPE 11-15 on Borg Scale)	Resistance training, education and risk factor management.
Seki *et al.* (2008), Japan	Moderate intensity aerobic exercise (supervised in centre & unsupervised at home).	Walking, cycle ergometer, jogging.	6 months	50-110 minutes- 1 session per week (centre), ≥ 30 minutes- 2 sessions per week (home)/ 12-13 on the standard Borg scale.	Education.
Toobert *et al.* (2000), USA	Walking or aerobics (supervised in centre & unsupervised at home).	Walking or aerobics.	24 months	60 minutes- 7 sessions per week (centre), 60 minutes- 3 sessions per week (home)/ Individually prescribed.	Education and psychological support.

VHSG *et al.* (2003), Norway	Dynamic endurance physical activity (supervised, group sessions in centre).	Dynamic endurance training.	15 weeks	55 minutes/ 2 sessions per week/ RPE 11-13 on the Borg Scale, increased to 13-15 after 6 weeks.	Education and psychological support.
Wang *et al.* (2012), China	Not specified.	Not specified.	Not specified.	Not specified/ not specified/ not specified.	Education.
West *et al.* (2012), UK	Not specified, multi-centre (supervised in centre).	Varied by centre (exercise equipment in physiotherapy gyms).	6-8 weeks	Averaged 20 hours over 6-8 weeks/ 1-2 sessions per week/ not specified.	Education plus psychological support.
Yu *et al.* (2004), China	Ambulatory and aerobic cardiovascular training (supervised in hospital and centre, unsupervised at home).	Walking, treadmill, cycle ergometry, rowing, stepper, arm ergometry, dumbbell.	8 1/2 months	2 hours/ 2 sessions per week (centre), not specified (home)/ 65-85% of maximal aerobic capacity (VO2 Peak).	Resistance training and education.
Zwisler *et al.* (2008), Denmark	Intensive CR programme (supervised in centre).	Not specified.	6 weeks	Not specified/ 2 sessions per week/ not specified.	Education and psychosocial support.

HR- Heart Rate, VO_2 Peak- Peak Oxygen Uptake

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Legends

Figure 1. Summary of study selection process

Figure 2. All-cause mortality for studies at their longest follow-up period. Filled squares represent the risk difference for individual studies at the longest reported follow-up. The boxes are proportional to the weight of each study and the lines represent their 95% confidence interval (CI). The filled diamond represents the pooled risk difference. Weights are from random effects analysis. CR- Cardiac Rehabilitation.

Figure 3. Cardiovascular mortality for studies at their longest follow-up period. Filled squares represent the risk difference for individual studies at the longest reported follow-up. The boxes are proportional to the weight of each study and the lines represent their 95% confidence interval (CI). The filled diamond represents the pooled risk difference. Weights are from random effects analysis. CR- Cardiac Rehabilitation.

Figure 4. Hospital admissions for studies at their longest follow-up period. Filled squares represent the risk difference for individual studies at the longest reported follow-up. The boxes are proportional to the weight of each study and the lines represent their 95% confidence interval (CI). The filled diamond represents the pooled risk difference. Weights are from random effects analysis. CR- Cardiac Rehabilitation.

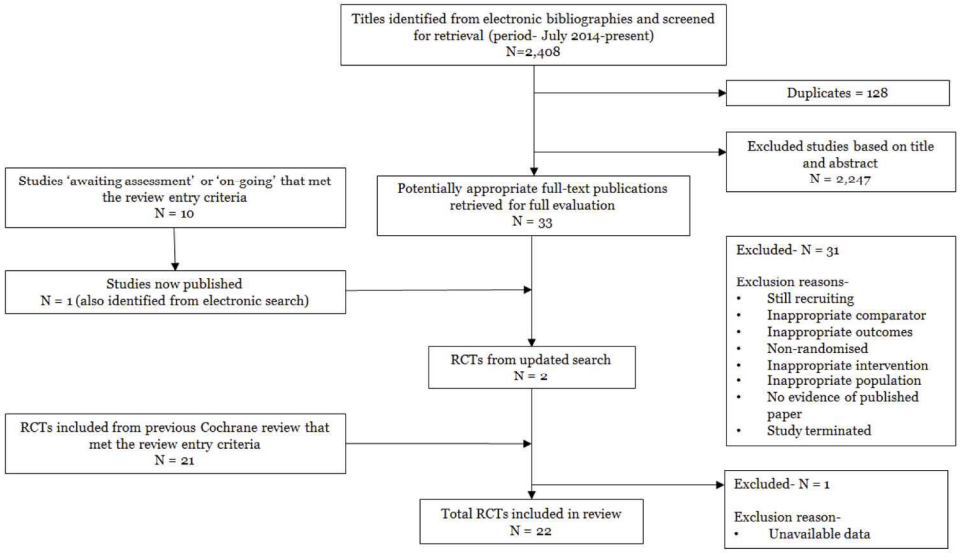

Figure 1. Summary of study selection process

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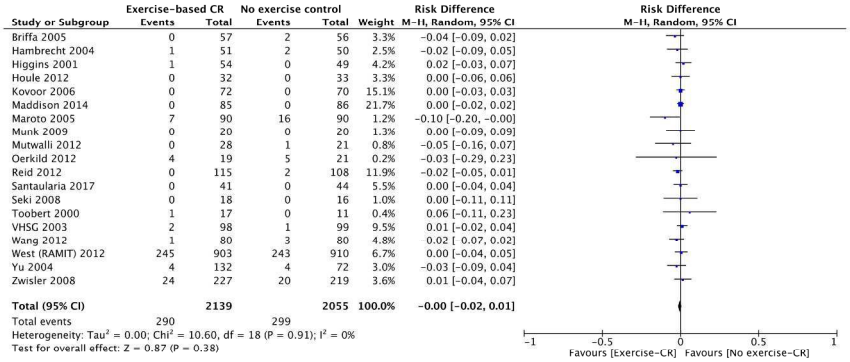

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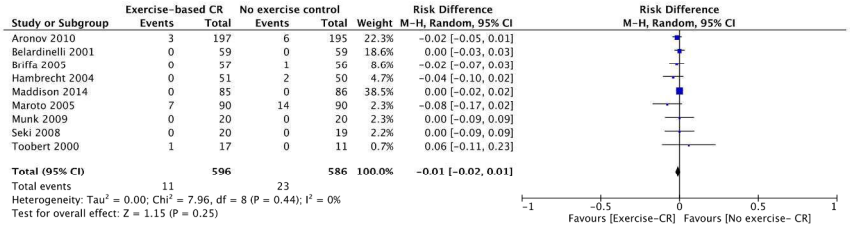

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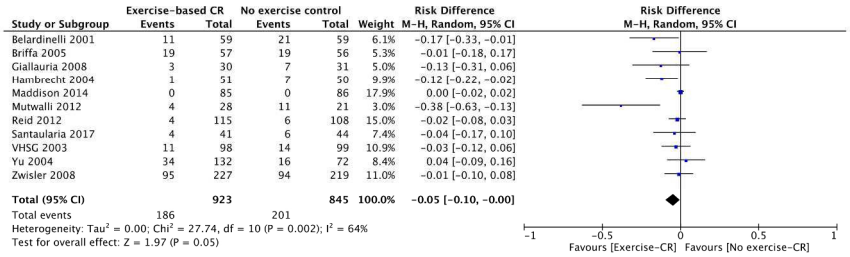

Figure 4. Hospital admissions for studies at their longest follow-up period. Filled squares represent the risk difference for individual studies at the longest reported follow-up. The boxes are proportional to the weight of each study and the lines represent their 95% confidence interval (CI). The filled diamond represents the pooled risk difference. Weights are from random effects analysis. CR- Cardiac Rehabilitation.

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Appendix 1

Search Name: CENTRAL repeat search- limited 2014-2017
Last Saved: 28/02/2017 14:50:03.214
Description: 28/02/17
ID Search

#1 MeSH descriptor: [Myocardial Ischemia] explode all trees
#2 (myocard* near isch*mi*):ti,ab,kw
#3 isch*mi* near heart:ti,ab,kw
#4 MeSH descriptor: [Coronary Artery Bypass] explode all trees
#5 myocard* near infarct*:ti,ab,kw
#6 heart near infarct*:ti,ab,kw
#7 angina:ti,ab,kw
#8 coronary near (disease* or bypass or thrombo* or angioplast*):ti,ab,kw
#9 MeSH descriptor: [Percutaneous Coronary Intervention] explode all trees
#10 (percutaneous next coronary near/2 (interven* or revascular*))
#11 MeSH descriptor: [Angioplasty] explode all trees
#12 angioplast*
#13 ((coronary or arterial) near/4 dilat*)
#14 endoluminal next repair*

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4,5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4/appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4,5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4,5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5,6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12-17
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6, 12,13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8,9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8,9/figures 2,3,4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8,9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9,10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10,11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Is exercise-based cardiac rehabilitation effective: a systematic review and meta-analysis to re-examine the evidence.

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Secondary Subject Heading:	Cardiovascular medicine, Evidence based practice
Keywords:	Coronary heart disease < CARDIOLOGY, Ischaemic heart disease < CARDIOLOGY, Myocardial infarction < CARDIOLOGY, REHABILITATION MEDICINE

Is exercise-based cardiac rehabilitation effective: a systematic review and meta-analysis to re-examine the evidence.

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Abstract

Objectives

To determine the contemporary effectiveness of exercise-based Cardiac Rehabilitation (CR) in terms of all-cause mortality, cardiovascular mortality and hospital admissions.

Data sources

Studies included in, or meeting the entry criteria for the 2016 Cochrane review of exercise-based CR in patients with coronary artery disease.

Study eligibility criteria

Randomised controlled trials (RCTs) of exercise-based CR vs. a no exercise control whose participants were recruited after the year 2000.

Study appraisal and synthesis methods

Two separate reviewers independently screened the characteristics of studies. One reviewer quality appraised any new studies and assessed their risk of bias using the Cochrane Collaboration's recommended risk of bias tool. Data were reported as the risk difference (95% CI).

Results

We included 22 studies with 4,834 participants (mean age 59.5 years. 78.4% male). We found no differences in outcomes between exercise-based CR and a no exercise control at their longest follow-up period for: all-cause mortality (19 studies; n=4,194; risk difference 0.00, 95% CI -0.02 to 0.01, p=0.38) or cardiovascular mortality (9 studies; n = 1,182; risk difference -0.01, 95% CI -0.02 to 0.01, p=0.25). We found a small reduction in hospital admissions of borderline statistical significance (11 studies; n= 1,768; risk difference -0.05, 95% CI -0.10 to -0.00, p=0.05).

Conclusions and implications of key findings

Our analysis indicates conclusively that the current approach to exercise-based CR has no effect on all-cause mortality or cardiovascular mortality, when compared to a no exercise control. There may be a small reduction in hospital admissions following exercise-based CR that is unlikely to be clinically important.

Systematic review registration number

Prospero: International prospective register of systematic reviews. 2017. 42017073616. Available from: https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017073616

Strengths and Limitations of this study

- To our knowledge, this is the first systematic review of exercise-based CR that has pooled data relevant to the current medical management of patients diagnosed with coronary artery disease.
- For analysis, we present the data as the risk difference (95% CI), which ensures all studies reporting data on the outcomes of interest were included.
- This systematic review pools data from studies that deliver an intervention recognised as best practice in exercise-based CR, where multiple approaches, including educational/psychosocial components, as well as the exercise component were used.
- We have not done a de novo quality assessment of 21/22 studies included in this review and instead rely on a previous Cochrane assessment.
- We did not include health-related quality of life as an outcome measure as this is unsuitable for meta-analysis.

Keywords

Coronary artery disease, exercise-based cardiac rehabilitation, all-cause mortality, cardiovascular mortality, hospital admissions.

Background

Cardiovascular disease is the world's biggest killer, accounting for 15 million deaths in 2015(1).

Secondary prevention of coronary artery disease through exercise-based CR in those who have a diagnosis of coronary artery disease, has the potential to reduce mortality, reduce hospital admissions and increase quality of life. Guidelines internationally endorse the use of exercise-based CR programmes(2-5).

Typically, exercise-based CR aims to achieve 20-60 minutes of moderate intensity continuous exercise, 3-5 times a week, with muscular strength and endurance exercises prescribed in conjunction(6). Additionally, most programmes include supplementary education (coronary risk factors and cardiac misconceptions), advice on diet and access to psychological support(2, 4, 7, 8). Typically exercise-based CR is delivered in a supervised centre-based setting, although home-based programmes are used(9).

A 2016 Cochrane review (63 studies, n=14,486 participants) found benefits of exercise-based CR for patients with coronary artery disease. Both cardiovascular mortality (27 studies, RR 0.74, 95% CI

0.64 to 0.86) and hospital re-admissions were reduced (15 studies, RR 0.82, 95% CI 0.70 to 0.96), when compared to a no exercise control. However, in contrast to previous systematic reviews and meta-analyses, there was no significant reduction in risk of re-infarction (36 studies, RR 0.90, 95% CI 0.79 to 1.04) or all-cause mortality (47 studies, RR 0.96, 95% CI 0.88 to 1.04)(10).

Over recent decades, the medical management of coronary artery disease has been transformed. The introduction of primary percutaneous coronary intervention has reduced short-term major adverse cardiac events and increased long-term survival(11-14). Simultaneously, there have also been widespread advances in secondary preventative medical therapy. This includes the introduction of aspirin and beta-blockers in the 1980s(15, 16), lipid-lowering statins and angiotensin converting enzyme inhibitors in the 1990s(17, 18) and more recently, the introduction of clopidogrel, a secondary anti-platelet, in 2007(19, 20). Age-adjusted mortality has decreased substantially in this population(21). Systematic reviews and meta-analyses that include data from older studies may not correctly assess the potential effect of exercise-based CR. We hypothesise that previous reviews have overestimated the benefit of exercise-based CR.

Objectives

To determine the contemporary effectiveness of exercise-based CR on all-cause mortality, cardiovascular mortality, and hospital readmissions in patients with coronary artery disease.

Methods

We conducted and reported this meta-analysis in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)(22).

Search Strategy

To identify relevant studies, we started with the latest Cochrane review of exercise-based CR in patients with coronary artery disease(10). Studies identified as 'awaiting assessment' or 'on-going' in this review were re-visited to establish whether publication had been reached. To identify any new studies published since the completion of the Cochrane review, an updated search was run on the 28/2/2017. This search used the same search strategies as the latest Cochrane review(10). We searched Cochrane Central Register of Controlled Trials (CENTRAL) *(appendix 1)*, MEDLINE (Ovid), EMBASE (Ovid) and CINAHL (EBSCO) databases. This approach allowed us to efficiently identify all relevant studies. Where appropriate, we contacted original authors for clarification of any new included studies.

Two separate reviewers (RP and GM) independently screened the characteristics of studies in the latest Cochrane review, studies identified as 'awaiting assessment' or 'on-going' and studies identified in the updated search. Full text publications were retrieved to allow for further examination and to verify study inclusion. Any discrepancies were resolved by a third reviewer (MU).

Criteria for considering studies

In 1996, The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology first recommended early (within two hours) primary percutaneous interventions in preference to thrombolytic therapy for acute myocardial infarction(23). Two years later, guidelines set by the Joint British recommendations on prevention of Coronary Heart Disease in Clinical Practice were published outlining the recommendations for best practice for secondary prevention medical therapies(24). Although there have been some changes, notably the introduction of a second anti-platelet agent in the early 2000s(19, 20), the approach to secondary prevention medical therapies has not changed since then. Allowing time for implementation of these guidelines and recommendations, we identified and included studies whose participants were recruited after the year 2000, to represent a contemporary population engaging in exercise-based CR.

Where there was no indication of recruitment period, the diagnosis and the secondary preventative medical therapy received by participants included in the trial determined the inclusion or exclusion of the study in the analysis.

Types of studies

We included randomised controlled trials of exercise-based CR compared to a no exercise control with a minimum follow-up period of six months. Data reported at the longest follow-up period were included in the analysis.

Types of participants

We used the same entry criterion as previous Cochrane reviews.

- People who have had a myocardial infarction, or who had undergone revascularisation (coronary artery bypass grafting or percutaneous coronary intervention) or who have angina pectoris or coronary artery disease defined by angiography.

- On optimal secondary preventative medical therapy defined by the Joint British recommendations on prevention of Coronary Heart Disease in Clinical Practice(24).

- Recruited to hospital-based, community-based or home-based CR programmes.

Types of intervention(s)

Randomised controlled trials consisted of supervised or non-supervised exercise-based CR. The intervention was exercise alone or exercise as part of a comprehensive CR programme (consisting of educational/psychosocial components). 'No exercise control' consisted of standard medical care,

including optimal secondary preventative medical therapy, education and advice about diet and exercise, psychosocial support but with no formal exercise intervention.

Types of outcome measures

We extracted data on: all-cause mortality, cardiovascular mortality and hospital re-admissions. We did not include health-related quality of life as the authors of the 2016 Cochrane review found this unsuitable for meta-analysis.

Data collection, statistical analysis and quality assessment

We pooled data using Review Manager 5.3(25). Previous Cochrane reviews have presented the data as individual and pooled risk ratio (95% CI). Using risk ratios automatically removed studies with no events in either study arm from the analysis. Nine studies (n= 936 participants) reporting on all-cause mortality, cardiovascular mortality or hospital re-admissions, were excluded from one or more meta-analyses in the 2016 Cochrane review for this reason. We therefore present the data as the risk difference (95% CI), which ensures all studies reporting data on the outcomes of interest were included.

We applied a random-effects model to all analyses given the clinical heterogeneity of individual studies. Heterogeneity of included studies were tested statistically using the χ^2 test of heterogeneity and I^2 statistic(26).

We did not repeat quality assurance checks already completed by the authors of the Cochrane review. For separate study risk of bias breakdown for these studies, we refer the reader to the existing *characteristics of studies*(10). For studies identified as 'awaiting assessment' or 'on-going' in the latest Cochrane review, or in the updated search, we quality appraised these studies and assessed their risk of bias using the Cochrane Collaboration's recommended risk of bias tool(27).

Assessment of risk of bias in additional included study

One reviewer (RP) assessed the risk of bias in any additional included studies *(table 1)*. Assessment of three further quality domains as outlined in the latest Cochrane review was also conducted (Groups balanced at baseline, Intention-to-treat analysis, Groups received comparable treatment (except exercise)). A breakdown of the criteria used for assessing these three domains can be found in the latest Cochrane review. Risk of bias assessments were checked by a second reviewer (GM) and any discrepancies were resolved by a third reviewer (MU).

Patient Involvement

No patients were involved in setting the objectives or outcome measures of this review, nor were they involved in the design or implementation. No patients were involved in the analysis or interpretation of the results, nor the writing of any drafts. There are no plans to disseminate the results of the review to participants included in the studies of the review or any relevant patient networks.

Results

Studies retrieved

Of the sixty-three studies included in the Cochrane review, twenty-one studies met our entry criteria. We identified two additional relevant papers not included in the 2016 Cochrane review(28, 29). One was excluded because data for our specific research question were not available in a useable format(28). In total, twenty-two studies (n=4,834 participants) contributed to the analysis *(figure 1)*. For the study identified from the updated search(29), there was a low risk of bias in all eight domains, apart from the intention-to-treat analysis, where there was no evidence of this analysis being conducted (*table 1)*.

Three studies (3/22; 14%) reported on all three outcomes of interest, eleven studies (11/22; 50%) reported on two outcomes of interest and eight studies (8/22; 36%) reported on one outcome of interest.

Two studies for all-cause mortality(30, 31) and one study for cardiovascular mortality(30) reported data at varying follow-up periods (6 to 12 months; >12 to 36 months; >3 years). Data from these studies were taken at their longest follow-up period. Mean maximum follow-up period was 24.7 months. Maximum follow-up period ranged from 24 weeks to 10 years *(table 2)*.

Flow diagram

(figure 1).

Sample size, gender, age and study origin

Of our twenty-two studies, ten studies were in Europe(29-38) and twelve from outside of Europe(39-50). We included a total of 4,834 participants (3,788 (78.4%) males). Four studies included males only(30, 34, 45, 47) and one study included women only(51). Participants mean age was 59.5 years. The mean age for individual studies ranged from 47.5 to 76.9 years (*table 2)*.

Incomplete outcome data

The majority of trials (18/22; 82%) reported complete follow-up data, regardless of participants who were lost to follow-up or who dropped out. In four studies, outcome data were incomplete for 75 (75/4,834; 1.6%) participants with no description of withdrawal or drop-out(41, 47, 48, 50).

Participant diagnosis of coronary artery disease and treatment received

The diagnosis of participants recruited to the studies was described in the majority of studies (21/22; 95%). Thirteen studies enrolled participants with mixed diagnoses, including angina pectoralis

or coronary artery disease defined by angiography, myocardial infarction, percutaneous coronary interventions or coronary artery bypass grafts(32, 36-42, 44, 46-48, 50). Six studies enrolled participants following acute myocardial infarction only(29, 31, 33, 34, 43, 49) and two studies enrolled participants diagnosed with angina pectoralis (unstable and stable angina) only(30, 35). It was unclear from one study whether participants following myocardial infarction were included and instead, the population was defined as 'patients after coronary artery bypass graft surgery'(45) (*table 2)*.

Six studies recruited participants following percutaneous coronary intervention only(30, 32, 33, 35, 41, 46) and one study recruited participants following coronary artery bypass grafting only(45). Twelve studies included participants who had received thrombolysis, percutaneous coronary intervention, coronary artery bypass grafting and/or no revascularization procedure(31, 36-40, 42-44, 47, 48, 50). Three studies did not provide any breakdown of coronary intervention or surgical procedure received by participants prior to enrollment(29, 34, 49) (*table 2)*.

Medication

A full description and breakdown of the medication received by the participants, comparable to optimal secondary prevention medical therapy defined by the Joint British recommendations on prevention of Coronary Heart Disease in Clinical Practice set in 1998(24), was provided by 13/22 studies (59%)(30-33, 35-40, 43, 49, 50). References to co-existing medical therapies were made in 7/22 (32%), but no breakdowns were provided(29, 34, 41, 42, 45-47). One study referred to the prescription of anti-hypertensive and hypolipidemic medications without reference to other recommended medications(48). One study failed to provide any description or breakdown of co-existing medical therapies(44) (*table 2)*.

Clearly defined recruitment period

Seven studies (7/22; 32%) were explicit that they recruited participants after the year 2000(36, 38, 42, 44-46, 49). In three studies, participants were recruited either just before or during the year 2000(30, 31, 41). Due to participant diagnosis, treatment received and co-existing medical therapies, it was agreed by all reviewers to include these studies.

The remaining twelve studies failed to provide a recruitment period. Following further examination of the full papers, due to adequate description of patient diagnosis, treatment received and co-existing medical therapies, it was agreed by all reviewers to include these studies *(table 2)*.

Content of the interventions

The content of the interventions tested was heterogeneous with multiple approaches being adopted. Sixteen studies (16/22; 73%) compared exercise in combination with other therapies (education, psychosocial management), whilst six studies compared exercise as a stand-alone intervention, against a no exercise control. The exercise component alone varied considerably with respect to setting, training modality, duration, session length, frequency and intensity (*table* 3).

Overall effects of interventions

All-cause mortality

Nineteen studies (n=4,194 participants) reported all-cause mortality (*figure 2*.). There was no difference between groups at their longest follow-up (risk difference = 0.00, 95% CI -0.02 to 0.01, p=0.38). There was no evidence of statistical heterogeneity across trials (P value=0.91, I^2=0%).

(figure 2).

Cardiovascular mortality

Nine studies (n = 1,182 participants) reported cardiovascular mortality (*figure 3*.). There was no difference between groups at their longest follow-up (risk difference = -0.01, 95% CI -0.02 to 0.01, p=0.25). There was no evidence of statistical heterogeneity across trials (P value=0.44, I^2=0%).

(figure 3).

Hospital admissions

Eleven studies (n= 1,768 participants) reported on proportion with one or more hospital admissions (*figure 4*.). There was a reduction of borderline statistical significance (risk difference = -0.05, 95% CI -0.10 to -0.00, p=0.05). There was evidence of statistical heterogeneity across trials (P value=0.002, I^2=64%).

(figure 4).

Discussion

The effectiveness of exercise-based CR in patients with coronary artery disease has been determined by Cochrane systematic reviews and meta-analyses, providing clinicians and academics with the highest level of evidence over the last 17 years(10, 52, 53). The latest Cochrane review, conducted in 2016, found benefits of exercise-based CR in terms of reduced cardiovascular mortality and hospital admissions, but unlike previous Cochrane reviews, found no effect on all-cause mortality(10). We identified that data from studies included in this review dated back as far as 1975(54). By including such historical data, this Cochrane review may not be correctly assessing the potential effect of contemporary exercise-based CR.

The current review aimed to assess the effect of exercise-based CR in the era of improved reperfusion strategies and simultaneous advances in pharmacological management, by only including studies whose participants were recruited after the year 2000. The majority of interventions tested in the twenty-two included trials (*table 3*) delivered an intervention recognised as best practice in exercise-based CR, where multiple approaches, including educational/psychosocial components, as well as the

exercise component were used(2, 3, 8). The interventions were tested against a no exercise control consisting of educational and psychosocial components alone (*table 3*).

The current analyses demonstrated no improvement in all-cause mortality from participation in exercise-based CR: the risk difference was 0.00 (95% CI -0.02 to 0.01). The largest trial included in our analysis, the UK-based Rehabilitation after myocardial infarction trial (RAMIT) trial, sought to show a 20% reduction in relative risk based on an 11% mortality; i.e. a 2.2% risk difference(24). The limits of the 95% confidence interval for the effect size in our analysis do not include the RAMIT trial's pre-specified clinically important difference. We therefore conclude that it is extremely unlikely that there is a worthwhile benefit from exercise-based CR on all-cause mortality. Furthermore, it is unlikely that future trials of similar interventions and populations, will change this conclusion. This is supported by a recent meta-analysis which included participants with other forms of atherosclerotic cardiovascular disease i.e. peripheral artery disease, ischaemic cerebrovascular accidents, diabetes and hypertension. They too found a zero effect on all-cause mortality (relative risk 1.00, 95% CI 0.88 to 1.14)(55). With the mean follow-up period for all studies included in our review being 24.7 months, it may be that any benefits on mortality will accrue over a longer follow-up. However, the absence of any kind of signal in this review means a substantial longer-term benefit is unlikely.

The current analyses do not quite exclude a worthwhile benefit of exercise-based CR on hospital admissions. Whilst a risk difference of -0.05 (95% CI -0.10 to -0.00) is of borderline statistical significance, it is probably clinically unimportant in the context of no change in all-cause mortality.

From the studies included in this review, we do not know if there is a worthwhile benefit on quality of life, as a meta-analysis was not conducted. However, the authors of the 2016 Cochrane review reported that in four of the twenty-two studies included in this review, there was a significantly higher quality of life in at least half or more of the sub-scales(32, 45, 46, 49).

Based on the present data, we are also unable to comment on whether exercise-based CR might be cost-effective. Five of the studies in this review included a within trial health economic evaluation(30, 40, 43, 44, 50). Of these five papers, three studies showed no difference in healthcare costs between groups(40, 43, 50), one found healthcare costs to be lower for exercise-based CR(30), and one failed to report a p-value for cost difference(44). Whilst a decrease, of borderline statistical significance, in hospital admissions may improve quality of life for patients, it is unclear if this confers any economic benefit, in the absence of robust cost-effectiveness analyses.

It may be that exercise-based CR has an effect on other outcomes, not specifically addressed in this review, such as cardiorespiratory fitness, lifestyle risk factor management, adherence to medication, diet, smoking cessation, psychosocial health and return to work(7, 8, 56, 57). If the focus of future research is on measuring and improving these outcomes, attention will be needed to develop the best multi-component intervention.

Strengths and Limitations

To our knowledge, this is the first systematic review of exercise-based CR that has pooled data relevant to contemporary medical management of patients diagnosed with coronary artery disease. Although we have not done a de novo quality assessment of 21/22 studies included in this review and

instead are relying on a previous Cochrane assessment, it is unlikely that we would have drawn different conclusions from such an assessment(10).

The current review does not provide information on participant baseline characteristics. In the majority of studies (20/22; 91%), however, baseline characteristics were comparable between the intervention and control groups(10, 29).

Whilst there was no evidence of statistical heterogeneity across trials for all outcome measures (P value<0.01, I^2>30%), except for hospital admissions, there was substantial context and interventional heterogeneity. The studies came from a wide range of clinical environments and countries, and the interventions delivered ranged greatly in quality. When compared with both the BACPR 'minimum standards and core components'(8) and ACPICR guidelines(6), there was considerable variation in the exercise interventions delivered (*table 3*). Critics have questioned the exercise component reported in the largest included study, the RAMIT trial (n=1813)(31). They argued that under-dosage of exercise intensity and duration may have led to the inconclusive result(58). Several other studies included in this review also fail to report on the intensity, modality and/or duration of the exercise intervention. Exercise and physical activity has a 'dose-response' relationship with cardiovascular disease risk(59). Moreover, a higher exercise capacity (VO_2 peak) is associated with an improvement in mortality risk(60, 61). If patients engaging in exercise-based CR do not achieve the correct dose of exercise, a physiological benefit is unlikely. It is a legitimate concern that participants in many included trials may not have received an adequate dose of exercise. In the era of contemporary medical management, higher intensity exercise protocols might be appropriate and effective(62).

One major concern is the reporting of adherence to, and fidelity of, exercise interventions(10). Whilst the majority of studies included in this review report the intended prescription exercise dose(29, 30, 32-37, 39, 40, 47, 50) (*table 3*), it is not possible to determine adherence and fidelity. Without basic reporting of these parameters, the actual exercise dose received cannot be quantified. This may have a significant bearing on intervention efficacy and the results of this meta-analysis. Moving forward, the introduction of checklists and reporting standards of interventional studies should improve reporting quality and trial interpretation(63).

Conclusion

Based on the outcomes of all-cause mortality and cardiovascular mortality, our analysis indicates conclusively that the current approach to exercise-based CR has no effect when compared to a no exercise control. There may be a small reduction in hospital admissions following exercise-based CR that is unlikely to be clinically important.

The continued delivery of exercise-based CR needs to be supported by new research to show its impact on health-related quality of life and whether it is a cost-effective intervention.

Contributors

RP and MU were principally responsible for the study concept and design. RP and GM were responsible for study selection, data extraction and risk of bias assessment. With the assistance of University Hospital Coventry & Warwickshire library services, RP updated and ran the searches. RP, MU

and PK were responsible for statistical analysis and interpretation of data. GM and SE provided clinical advice. RP and MU wrote the first draft of the review and all co-authors contributed to review and editing of drafts of the report. All authors approved the final manuscript. RP is the study guarantor and had full access to all trial level data in the review, takes responsibility for the integrity of the data, and accuracy of the data analysis, and had final responsibility to submit for publication.

Copyright

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Competing interests

All authors have completed the *Unified Competing Interest form* (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Ethical Approval

Ethical approval not required.

Data sharing

No additional data available.

The lead author (RP) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

Tables

Table 1. Risk of bias assessment for additional study

Santaularia *et al.* 2017

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomisation list in blocks of ten was created by a computer random number generator. The randomisation list and the allocation of patients to each group were independently controlled by the Clinical Trials Unit.'
Allocation concealment (selection bias)	Low risk	A randomisation list in blocks of ten was created by a computer random number generator. The randomisation list and the allocation of patients to each group were independently controlled by the Clinical Trials Unit.'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	An independent committee that was blind to the patients' treatment group assessed the main outcomes. This committee comprised a cardiologist, a rehabilitation cardiologist and a health information manager, all from different centres.'
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no loss to follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results. Results regarding quality of life are presented in supplementary data but were not required for the current review.
Groups balanced at baseline	Low risk	No significant differences between groups were observed, with the exception of gender: 23% of the control group were women compared with 7% in the intervention group (p=0.049).
Intention-to-treat analysis conducted	High risk	No analysis was conducted.
Groups received same treatment (apart from the intervention)	Low risk	Patients assigned to the control group received standard care given at the hospital'. In addition to standard care, patients randomised to the intervention group....'.

Table 2. Overview of participants, recruitment period, patient diagnosis and medical therapy

References, country	*N*	Mean age (years)	Male participants (%)	Recruitment period (years)	Maximum follow-up period	Patient diagnosis	Medication
Aronov *et al.* (2010), Russia	392	61.4	73.5	None specified	1 year	AMI, stable angina, unstable angina or myocardial revascularisation.	Standard medical therapy-β-blocker, acetylsalicyclic acid or other antithrombotic drug, nitrate, ACE inhibitor. Some patients on lipid-lowering drugs.

Belardinelli *et al.* (2001), Italy	118	61	100	None specified	33 months	CAD including AMI. Successful PCI in 1 or 2 native epicardial coronary arteries only.	According to international accepted protocols- aspirin, ticlopidine, calcium antagonists, nitrates.
Briffa *et al.* (2005), Australia	113	47.5	89.5	None specified.	1 year	Uncomplicated AMI or recovery from unstable angina. PCI, CABG, thrombolytic therapy.	Aspirin, antiarrhytmic agent, β-blocker, ACE inhibitor, calcium antagonist, long acting nitrate, diuretic.
Giallauria *et al.* (2008), Italy	61	58.5	78.5	None specified.	6 months	AMI and undergone primary or rescue PCI only.	Aspirin, β-blocker, ACE inhibitor, ARB, statin.
Hambrecht *et al.* (2004), Germany	101	56	87.3	1997-2001	1 year	Stable CAD defined by angina pectoralis and amenable to PCI. AMI patients excluded.	β-receptor antagonists, β-HMG-CoA reductase inhibitors, ACE inhibitor, acetylsalicyclic acid.
Higgins *et al.* (2001), Australia	105	60.8	81.3	1995-1997	51 weeks	Post-PCI patients only. No AMI 1 month pre-procedure.	Reference to medical therapy, only breakdown for lipid lowering medication.
Houle *et al.* (2012), Canada	65	51.5	100	2007-2008	12 months	Patients hospitalised for an ACS (unstable angina, non-ST-elevation or ST elevation MI). PCI, CABG or no revascularisation procedure.	Reference to medication in usual care group, but no breakdown.
Kovoor *et al.* (2006), Australia	142	51.5	100	None specified.	6 months	AMI only. Thrombolytic therapy, one patient in the exercise treatment group had primary angioplasty.	Aspirin, β-blocker, ACE inhibitor, calcium channel blockers, nitrates, cholesterol-lowering agents,
Maddison *et al.* (2014), New Zealand	171	59	20	2010-2012	24 weeks	Diagnosis of IHD (angina, MI, revascularisation, including angioplasty, stent, or CABG).	No description.
Maroto *et al.* (2005), Spain	180	76.9	57.5	(None specified) 2 year enrollment period.	10 years	AMI only.	Medication regimens employed in secondary prevention at discharge were clearly insufficient by standard criteria but currently meet Spanish and European guidelines'.
Munk *et al.* (2009), Norway	40	56.4	84.8	None specified.	6 months	Stable angina and unstable angina, post PCI only. AMI patients excluded.	Aspirin, β-blocker, ACE inhibitor, ARB, statin, acetylsalicyclic acid.
Mutwalli *et al.* (2012), Saudi Arabia	49	69.7	100	2008-2010	6 months	Undergone CABG surgery. Unknown whether AMI patients included.	Participants received advice that focused on medications', no breakdown.

Oerkild *et al.* (2012), Denmark	40	63.5	0	2007-2008	12 months (mortality data after 5.5 years)	Recent coronary event defined as AMI, PCI, CABG or without invasive procedure.	β-blocker, antithombotics, calcium antagonists, lipid-lowering agents, diuretics.
Reid *et al.* (2012), Canada	223	54.5	87.3	2004-2007	12 months	ACS including AMI, underwent successful PCI only.	Reference to a 'descriptive summary in supplemental table', no access.
Santaularia *et al.* (2017), Spain	85	59.6	84.7	None specified.	12 months	AMI only, no evidence of revascularisation procedure.	Reference to cardiac medication, but no breakdown
Seki *et al.* (2008), Japan	39	57.8	83.8	None specified.	NR	AMI, PCI or CABG.	Reference to 'lipid-lowering drugs and other medications', no breakdown.
Toobert *et al.* (2000), USA	25	64.5	0	None specified.	24 months	CAD defined as atherosclerosis, AMI, PCI or CABG.	Anti-hypertensive and hypolipidemic medications.
VHSG *et al.* (2003), Norway	197	64	75.8	None specified.	2 years	AMI, unstable angina pectoris or after PCI or CABG.	Aspirin, β-blocker, statin, ACE inhibitor, calcium antagonist, warfarin.
Wang *et al.* (2012), China	160	67	63.5	2005-2007	6 months	AMI only.	Anti-platelet, Nitrate, β-blocker, ACE inhibitor, calcium antagonist, statin.
West *et al.* (2012), UK	1813	51.9	93.9	1997-2000	7 to 9 years	AMI only.	Aspirin, β-blocker, ACE inhibitor, diuretic, long acting nitrate/ calcium channel blocker, statin, GTN.
Yu *et al.* (2004), China	269	56	83.9	None specified.	2 years	Recent AMI, after elective PCI or thrombolytic therapy.	Anti-platelet, β-blocker, calcium channel blocker, nitrate, statin, ACE inhibitor, diuretic.
Zwisler *et al.* (2008), Denmark	446	55.5	72.1	2000-2003	1 year	AMI, angina pectoris or after PCI or CABG.	Antithrombotics, lipid-lowering drugs, β-blocker, calcium antagonists, ACE inhibitor, diuretic, long-acting nitrates.

AMI- Acute Myocardial Infarction, CAD- Coronary Artery Disease, PCI- Percutaneous Coronary Intervention, IHD- Ischaemic Heart Disease, CABG- Coronary Artery Bypass Graft, CHD- Coronary Heart Disease, ACS- Acute Coronary Syndrome, ACE-Angiotensin-Converting-Enzyme, ARB- Angiotensin Receptor Blockers, GTN- Glyceryl Trinitrate.

Table 3. Overview of exercise interventions

References, country	**Exercise Intervention**					
	Exercise	***Modality***	***Study Duration***	***Session Duration/Frequency/Intensity***	***Additional***	***Control (comparator)***
Aronov *et al.* (2010), Russia	Moderate intensity physical training (unknown setting).	Cycle ergometer.	12 months	45 minutes- 60 minutes/ 3 sessions per week/ 50-60% of the performed capacity by bicycle ergometry.	None specified.	Standard medical therapy.

Belardinelli *et al.* (2001), Italy	Moderate intensity exercise (supervised in hospital gym).	Cycle ergometer.	6 months	53 minutes/ 3 sessions per week/ 60% of peak oxygen uptake (VO_2 Peak).	None specified.	Recommended to perform basic daily mild physical activities but to avoid any physical training.
Briffa *et al.* (2005), Australia	Aerobic circuit training (supervised in hospital).	Aerobic circuit training.	6 weeks	60-90 minutes/ 3 sessions per week/ not specified.	Education and psychosocial counselling.	Education, pharmacotherapy and lifestyle counselling.
Giallauria *et al.* (2008), Italy	Moderate intensity exercise (supervised in centre).	Cycle ergometer.	6 months	40 minutes/ 3 sessions per week/ 60%-70% of peak oxygen uptake (VO_2 Peak).	None specified.	Generic instructions on maintaining physical activity and a correct lifestyle.
Hambrecht *et al.* (2004), Germany	Moderate intensity exercise (supervised in hospital & unsupervised at home).	Cycle ergometer.	12 months	10 minutes- 42 sessions per week (hospital), 20 minutes- 7 sessions per week (home) plus 60 minutes' group training- 1 session per week/ 70% of symptom-limited max HR.	None specified.	Standard medical therapy.
Higgins *et al.* (2001), Australia	Moderate intensity walking programme (unsupervised at home).	Walking.	Not specified.	Not specified/ not specified/ not specified.	Psychological plus education.	Psychological support, education, counselling and guidance.
Houle *et al.* (2012), Canada	Pedometer-based walking programme (unsupervised at home).	Walking.	12 months	Not specified/ not specified/ not specified.	Education plus socio-cognitive.	Socio-cognitive support and advice regarding physical activity, diet and medication.
Kovoor *et al.* (2006), Australia	Standard Cardiac Rehabilitation programme (unknown setting).	Not specified.	5 weeks	Not specified/ 2-4 sessions per week/ not specified.	Education and counselling	Encouraged to exercise at home and return to normal activities.
Maddison *et al.* (2014), New Zealand	Automated package of text messages to increase exercise behaviour (unsupervised at home).	Moderate to vigourous aerobic exercise e.g. walking and household chores.	24 weeks	Minimum of 30 minutes/ at least 5 sessions per week/ not specified.	Optional access to other cardiac rehabilitation service or support.	Behaviour change therapy, encouragement to be physically active and advice to attend a cardiac club.
Maroto *et al.* (2005), Spain	Individualised physical training (supervised in hospital gym).	Physiotherapy and aerobic training on mats or a cycle ergometer.	3 months	60 minutes/ 3 sessions per week/ 75-85% max HR.	Psychological support, education plus return to work counselling	Psychological support, education plus return to work counselling.

Munk *et al.* (2009), Norway	Moderate/high intensity interval training (supervised in centre).	Cycle ergometer or running.	6 months	60 minutes/ 3 sessions per week/ 60-70% & 80-90% max HR.	Spine & abdominal resistance training.	Usual care, including drug therapy.
Mutwalli *et al.* (2012), Saudi Arabia	Moderate intensity walking programme (unsupervised at home).	Walking.	6 months	30 minutes/ 7 sessions per week/ not specified.	Education.	Education, standard hospital care.
Oerkild *et al.* (2012), Denmark	Moderate intensity exercise (unsupervised at home).	Individualised	12 months	30 minutes/ 6 sessions per week/ 11-13 on the Borg Scale.	Risk factor management.	Usual care, no exercise education or dietary counselling.
Reid *et al.* (2012), Canada	Internet based physical activity plan and motivational tool to increase physical activity (unsupervised at home).	Not specified.	20 weeks	Not specified/ not specified/ not specified.	None specified.	Online education, physical activity guidance and an education booklet.
Santaularia *et al.* (2017), Spain	Outpatient exercise training programme (supervised in hospital).	Cycle ergometer	10 weeks	60 minutes/ 3 sessions per week/ 75-90% max HR (RPE 11-15 on Borg Scale)	Resistance training, education and risk factor management.	Standard care, risk factor management, guidance on physical activity and adherence to medication.
Seki *et al.* (2008), Japan	Moderate intensity aerobic exercise (supervised in centre & unsupervised at home).	Walking, cycle ergometer, jogging.	6 months	50-110 minutes- 1 session per week (centre), ≥ 30 minutes- 2 sessions per week (home)/ 12-13 on the standard Borg scale.	Education.	Education and outpatient follow-up with physician.
Toobert *et al.* (2000), USA	Walking or aerobics (supervised in centre & unsupervised at home).	Walking or aerobics.	24 months	60 minutes- 7 sessions per week (centre), 60 minutes- 3 sessions per week (home)/ Individually prescribed.	Education and psychological support.	Cooking classes, stress management and education.
VHSG *et al.* (2003), Norway	Dynamic endurance physical activity (supervised, group sessions in centre).	Dynamic endurance training.	15 weeks	55 minutes/ 2 sessions per week/ RPE 11-13 on the Borg Scale, increased to 13-15 after 6 weeks.	Education and psychological support.	Education and psychological support.
Wang *et al.* (2012), China	Not specified.	Not specified.	Not specified.	Not specified/ not specified/ not specified.	Education.	Education.
West *et al.* (2012), UK	Not specified, multi-centre (supervised in centre).	Varied by centre (exercise equipment in physiotherapy gyms).	6-8 weeks	Averaged 20 hours over 6-8 weeks/ 1-2 sessions per week/ not specified.	Education plus psychological support.	Education plus psychological support.

	Ambulatory and aerobic cardiovascular training (supervised in hospital and centre, unsupervised at home).	Walking, treadmill, cycle ergometry, rowing, stepper, arm ergometry, dumbbell.	8 1/2 months	2 hours/ 2 sessions per week (centre), not specified (home)/ 65-85% of maximal aerobic capacity (VO2 Peak).	Resistance training and education.	Conventional medical therapy and education.
Yu *et al.* (2004), China						
Zwisler *et al.* (2008), Denmark	Intensive CR programme (supervised in centre).	Not specified.	6 weeks	Not specified/ 2 sessions per week/ not specified.	Education and psychosocial support.	Education and psychosocial support.

HR- Heart Rate, VO_2 Peak- Peak Oxygen Uptake

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Legends

Figure 1. Summary of study selection process

Figure 2. All-cause mortality for studies at their longest follow-up period. Filled squares represent the risk difference for individual studies at the longest reported follow-up. The boxes are proportional to the weight of each study and the lines represent their 95% confidence interval (CI). The filled diamond represents the pooled risk difference. Weights are from random effects analysis. CR- Cardiac Rehabilitation.

Figure 3. Cardiovascular mortality for studies at their longest follow-up period. Filled squares represent the risk difference for individual studies at the longest reported follow-up. The boxes are proportional to the weight of each study and the lines represent their 95% confidence interval (CI). The filled diamond represents the pooled risk difference. Weights are from random effects analysis. CR- Cardiac Rehabilitation.

Figure 4. Hospital admissions for studies at their longest follow-up period. Filled squares represent the risk difference for individual studies at the longest reported follow-up. The boxes are proportional to the weight of each study and the lines represent their 95% confidence interval (CI). The filled diamond represents the pooled risk difference. Weights are from random effects analysis. CR- Cardiac Rehabilitation.

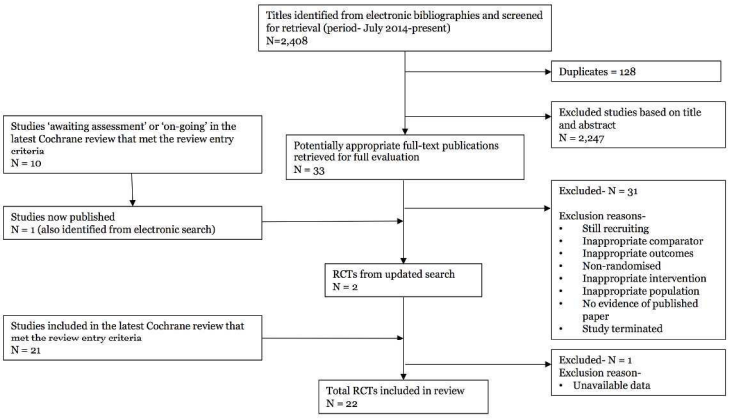

Figure 1. Summary of study selection process.

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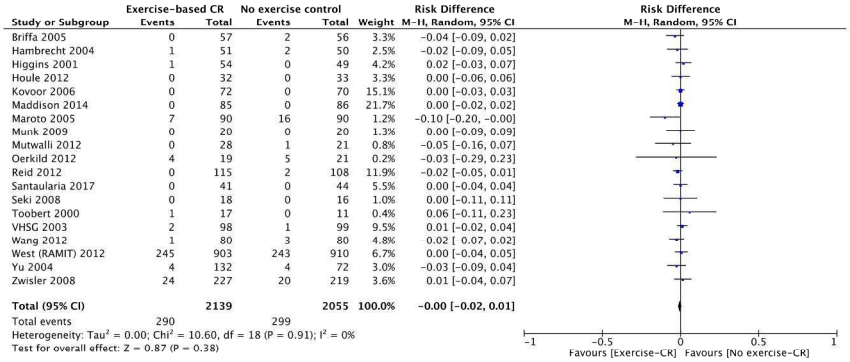

Figure 2. All-cause mortality for studies at their longest follow-up period. Filled squares represent the risk difference for individual studies at the longest reported follow-up. The boxes are proportional to the weight of each study and the lines represent their 95% confidence interval (CI). The filled diamond represents the pooled risk difference. Weights are from random effects analysis. CR- Cardiac Rehabilitation.

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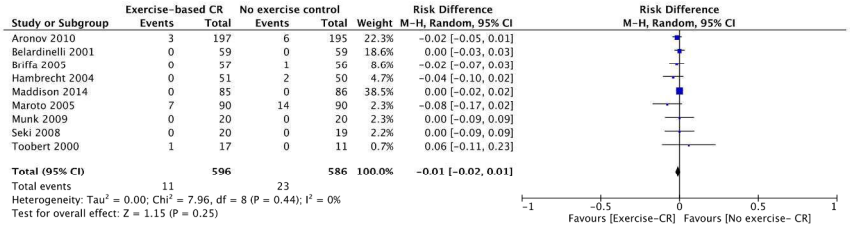

Figure 3. Cardiovascular mortality for studies at their longest follow-up period. Filled squares represent the risk difference for individual studies at the longest reported follow-up. The boxes are proportional to the weight of each study and the lines represent their 95% confidence interval (CI). The filled diamond represents the pooled risk difference. Weights are from random effects analysis. CR- Cardiac Rehabilitation.

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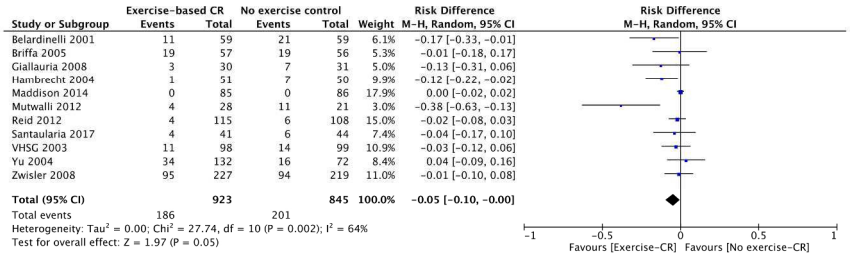

Figure 4. Hospital admissions for studies at their longest follow-up period. Filled squares represent the risk difference for individual studies at the longest reported follow-up. The boxes are proportional to the weight of each study and the lines represent their 95% confidence interval (CI). The filled diamond represents the pooled risk difference. Weights are from random effects analysis. CR- Cardiac Rehabilitation.

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Appendix 1

Search Name: CENTRAL repeat search- limited 2014-2017
Last Saved: 28/02/2017 14:50:03.214
Description: 28/02/17
ID Search

#1 MeSH descriptor: [Myocardial Ischemia] explode all trees
#2 (myocard* near isch*mi*):ti,ab,kw
#3 isch*mi* near heart:ti,ab,kw
#4 MeSH descriptor: [Coronary Artery Bypass] explode all trees
#5 myocard* near infarct*:ti,ab,kw
#6 heart near infarct*:ti,ab,kw
#7 angina:ti,ab,kw
#8 coronary near (disease* or bypass or thrombo* or angioplast*):ti,ab,kw
#9 MeSH descriptor: [Percutaneous Coronary Intervention] explode all trees
#10 (percutaneous next coronary near/2 (interven* or revascular*))
#11 MeSH descriptor: [Angioplasty] explode all trees
#12 angioplast*
#13 ((coronary or arterial) near/4 dilat*)
#14 endoluminal next repair*

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4,5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4/appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4,5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4,5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5,6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12-17
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6, 12,13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8,9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8,9/figures 2,3,4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8,9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9,10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10,11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

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