

Lessons from contemporary trials of cardiovascular prevention and rehabilitation: A systematic review and meta-analysis☆☆☆☆☆



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ARTICLE INFO

Article history:

Received 16 June 2016

Accepted 17 December 2016

Available online 23 December 2016

Keywords:

Myocardial infarction

Angina pectoris

Stroke

Peripheral arterial disease

Atherosclerotic cardiovascular diseases

Cardiac rehabilitation

Cardiovascular prevention

ABSTRACT

Background: Meta-analyses of cardiac rehabilitation trials up to 2010 showed a significant reduction in all-cause mortality but many of these trials were conducted before the modern management of acute coronary syndromes. **Methods:** We undertook a meta-analysis of contemporary randomised controlled trials published in the period 2010 to 2015, including patients with other forms of atherosclerotic cardiovascular disease, to investigate the impact of cardiovascular prevention and rehabilitation on hard outcomes including survival.

Results: 18 trials randomising 7691 patients to cardiovascular prevention and rehabilitation or usual care were selected. All-cause mortality was not reduced (RR 1.00, 95% CI 0.88 to 1.14), but cardiovascular mortality was by 58% (95% CI 0.21, 0.88). Myocardial infarction was also reduced by 30% (95% CI 0.54, 0.91) and cerebrovascular events by 60% (95% CI 0.22, 0.74). Comprehensive programmes managing six or more risk factors reduced all-cause mortality in a subgroup analysis (RR 0.63, 95% CI 0.43, 0.93) but those managing less did not. In the three programmes that prescribed and monitored cardioprotective medications for blood pressure and lipids all-cause mortality was also reduced (RR 0.35, 95% CI 0.18, 0.70).

Conclusions: Comprehensive prevention and rehabilitation programmes managing six or more risk factors, and those prescribing and monitoring medications within programmes to lower blood pressure and lipids, continue to reduce all-cause mortality. In addition, these comprehensive programmes not only reduced cardiovascular mortality and myocardial infarction but also, for the first time, cerebrovascular events, and all these outcomes across a broader spectrum of patients with atherosclerotic disease.

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1. Introduction

Coronary heart disease and cerebrovascular disease constitute the most important preventable non-communicable diseases, in which cardiac rehabilitation plays an important role [1]. It is defined by the WHO as: ‘the sum of activities required to influence favourably the underlying cause of the disease, as well as the best possible, physical, mental and social conditions, so that they (people) may, by their own efforts preserve or resume when lost, as normal a place as possible in the community. Rehabilitation cannot be regarded as an isolated form or stage of therapy but must be integrated within secondary prevention services of which it forms only one facet’ [2].

Cardiac rehabilitation programmes in the past reduced all-cause mortality. In the 2011 Cochrane review of exercise-based rehabilitation

by Heran et al. [3], total mortality was reduced by 18% during follow-up of 6 up to 12 months, and by 13% during follow-up of over one year, while cardiovascular mortality was reduced by 26%. Results of lifestyle modification programmes are similar. In 2012, Janssen et al. reported a significant reduction of a third in total mortality, while cardiac mortality was halved significantly, for lifestyle modification programmes [4]. Both Heran and Janssen included trials that contained both exercise-based rehabilitation and lifestyle modification. The effect of ‘education only programmes’ by Cochrane one year later, showed no evidence of a significant reduction in all-cause mortality (RR 0.79, 95% CI 0.55 to 1.13), or recurrent MI, revascularisation and hospitalisation [5]. This may have been due to lack of statistical power, as few studies reported on these outcomes and few events occurred. In addition, psychological interventions did not reduce total mortality or non-fatal events in another Cochrane meta-analysis [6]. Of course, such programmes may still improve psychological outcomes which are important [6].

International guidelines strongly (Class I) recommend cardiac rehabilitation for all patients following cardiac surgery or a myocardial infarction [7–11]. However, in clinical practice uptake is low at 36.5% in EUROASPIRE III across 22 countries for patients with a myocardial infarction (MI), percutaneous coronary intervention or coronary artery

* All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

☆☆ This study was supported by the Dutch Heart Foundation (NHS 2015–2).

☆☆☆ No potential conflicts exist for all authors.

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bypass graft, and with considerable heterogeneity in service provision of rehabilitation programmes between countries [12].

The acute management of cardiovascular disease, both acute coronary syndromes and stroke, has been transformed by percutaneous revascularisation, stenting, thrombolysis and cardioprotective medications reducing all-cause mortality and subsequent cardiovascular events. Against this background, we evaluated the added value of cardiovascular prevention and rehabilitation programmes published in the last five years. We broadened the scope of our analysis beyond cardiac patients by including studies of patients with other manifestations of atherosclerotic cardiovascular disease. As future cardiovascular risk is strongly related to blood pressure and lipids levels, we also assessed whether management of these risk factors within prevention and rehabilitation programmes is of value.

2. Methods

The search strategy, study selection, data extraction and analysis all took place according to a pre-defined protocol, details of which are described below. We conducted and reported this meta-analysis in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [2] and the Cochrane Handbook for Interventional Reviews [13].

2.1. Search strategy

One author (G. H.) systematically searched Medline and Embase on OvidSP. The basis of our search strategy was Heran's Cochrane analysis [3] on exercise based programmes for cardiac rehabilitation. To broaden our search to lifestyle programmes, we added Ebrahim's Cochrane [14] search strategy on health behaviour and lifestyle programmes. The main search terms were the following: "ischaemic heart diseases", "exercise based rehabilitation" and "health behaviour or lifestyle programme". The detailed search strategy is available online in Supplementary material. Reference lists of retrieved articles and systematic reviews and meta-analyses were verified to identify any studies not detected by the electronic search. The search was done on February 27, 2015, and included studies published from January 1, 2010 to February 27, 2015.

2.2. Study selection

We included randomised controlled clinical trials (RCTs) of cardiovascular prevention and rehabilitation with a follow-up period of at least six months, written in either English, Chinese, Spanish, German, French or Dutch languages.

2.2.1. Patients

We included studies of patients with myocardial infarction (MI), of patients who had undergone coronary revascularisation (coronary artery bypass grafting or percutaneous coronary intervention), or with angina pectoris or coronary artery disease established by angiography. In addition, we included trials of participants diagnosed with cardiovascular disease, e.g. peripheral arterial disease, ischaemic cerebrovascular accidents, diabetes mellitus or hypertension, if over 50% of the patients in the studies were diagnosed with coronary heart disease. Studies of participants who had undergone heart valve surgery, heart transplantation, cardiac-resynchronisation therapy or implantable defibrillator therapy or with over 50% of patients diagnosed with heart failure, were excluded.

2.2.2. Intervention

The intervention could be either an exercise or a lifestyle based programme. Criteria for exercise based programmes were derived from Heran et al. [3]. Actual physical exercise training had to be part of the rehabilitation programme. The criteria for a lifestyle modification

programme were based on Janssen et al. 2012 [4]. At least one face-to-face session between the health care provider and the patient had to take place, and the aim of the programme had to comprise improved diet and/or exercise habits. Of course, some rehabilitation programmes focussed both on exercise training and on health behaviour.

2.2.3. Comparison

The intervention had to consist of a comparison with usual care. Studies that randomised patients between standard cardiac rehabilitation and standard cardiac rehabilitation followed by extended forms of rehabilitation, were also eligible.

One investigator (G.H.) evaluated studies for possible inclusion. Non-relevant studies were excluded based on title and abstract. For potentially relevant studies, full-text was obtained and two investigators (G.H. and H.T.) independently assessed study eligibility and extracted the data on study design, patient characteristics, and outcomes. Disagreement was resolved by consensus or by discussion with a third author (K.K.).

2.2.4. Outcomes and measurements

The primary efficacy outcome of our analysis was all-cause and cardiovascular mortality. In addition, we analysed the two following – secondary – outcomes: the occurrence of MI and of cerebrovascular events (stroke and transient ischaemic attacks). All MI and cerebrovascular events were extracted, both fatal and non-fatal. Two authors (G.H. and H.T.) independently extracted the outcomes from all studies.

2.3. Study quality assessment

Quality of studies included was assessed using the Cochrane Risk of Bias tool.

2.4. Data analysis

All analyses were performed on data reported according to the intention-to-treat principle. Data from each study were pooled using the Mantel-Haenszel method. A fixed effects model was used, except in the presence of substantial ($I^2 > 50\%$) heterogeneity, in which case a random effects model was chosen. The effects of the interventions were expressed as relative risk ratio's (RR).

Potential effect modifiers were explored by pre-specified subgroup analyses focusing on the primary outcome of all-cause mortality. To this end, we considered the duration of follow-up – ≤ 12 months versus follow-up > 12 months. Furthermore, we analysed the number of risk factors managed in the programmes: < 6 versus ≥ 6 . The risk factors were based on the British Association of Cardiovascular Prevention and Rehabilitation 2012 guideline and were: smoking cessation, physical exercise training, counselling for exercise/activity, diet, blood pressure (control of values), cholesterol (control of serum values), diabetes (control of glucose values), checking medication and stress management [14]. We assessed the effect of prescription and monitoring of medication within programmes as opposed to deferring the responsibility for prescribing to others outside the programmes. We also analysed the impact of whether or not any form of standard cardiac rehabilitation was offered to the control group. We did a separate analysis for blood pressure and LDL cholesterol levels, measured as a weighted mean difference (WMD). Other subgroup analyses are included in Supplementary material online.

Publication bias was assessed by inspection of the funnel plot and Egger's test. Sensitivity analysis was conducted by removing studies one-by-one.

Review Manager 5.3 was used to analyse the data, to draw the plots and to generate the figures [15]. The meta-essentials workbook for Microsoft Excel was employed for Egger's test [16].

3. Results

3.1. Search

The search yielded 7764 titles. Seven additional studies were retrieved from meta-analyses, presentations or comments that were found within our search strategy [4,5,17–21]. After reviewing the titles and abstracts, we retrieved 71 full-text articles for possible inclusion (Fig. 1). Eighteen of these fulfilled our in- and exclusion criteria and are included in the present analyses. Details of these RCTs are given in Table 1.

3.2. Included studies

Eighteen studies were included. Trial sample sizes ranged from 34 to 1813 patients. Overall, 7691 patients were studied. The median intervention duration was 12 months and the median follow-up was 24 months.

The mean age of patients ranged from 56 to 70 years. All studies included women, ranging from 16 to 30%. One study was conducted in females only [22]. The studies by Reid et al. consisted of two separate programmes, one internet based [23], the other one by phone counselling [24] and these were named and considered accordingly. Four studies included patients with other cardiovascular diseases than coronary artery disease including peripheral vascular disease and ischaemic stroke [21,25–27]. In total, 989 patients in this meta-analysis were diagnosed with other cardiovascular diseases.

3.3. Risk of bias in included studies

Random sequence generation and allocation bias among the publications was low. Blinding of patients is not possible in rehabilitation programmes and was therefore not assessed. The blinding of the researchers that analysed the data was mostly unclear. Attrition bias – caused by incomplete outcome data – was scored as relatively high because a considerable number of trials reported >10% loss to follow-up. Furthermore, reasons for loss to follow-up and dropout were often not reported. On the other hand, the loss to follow-up was quite evenly distributed between both arms of studies. Selective outcome reporting could be a risk of bias as the smaller studies were not designed to assess treatment group differences for mortality and may not have fully reported all clinical events that occurred during the follow-up period. See Supplementary material online for an overview of risk of bias given to each study.

3.3.1. Effects of interventions

3.3.1.1. Mortality. Mortality was reported in all studies. Overall, 735 out of 7691 patients died (Fig. 2), and the median yearly mortality rate was 1.4%. Mortality was comparable among intervention and control groups (RR 1.00, 95% CI 0.88, 1.13). The effect of cardiovascular prevention and rehabilitation on mortality was not modified by the duration of the intervention programme (≤ 12 months (RR 0.99, 95% CI 0.73, 1.34) versus >12 months (RR 1.02, 95% CI 0.90, 1.17) (Supplementary material online, Fig. S1).

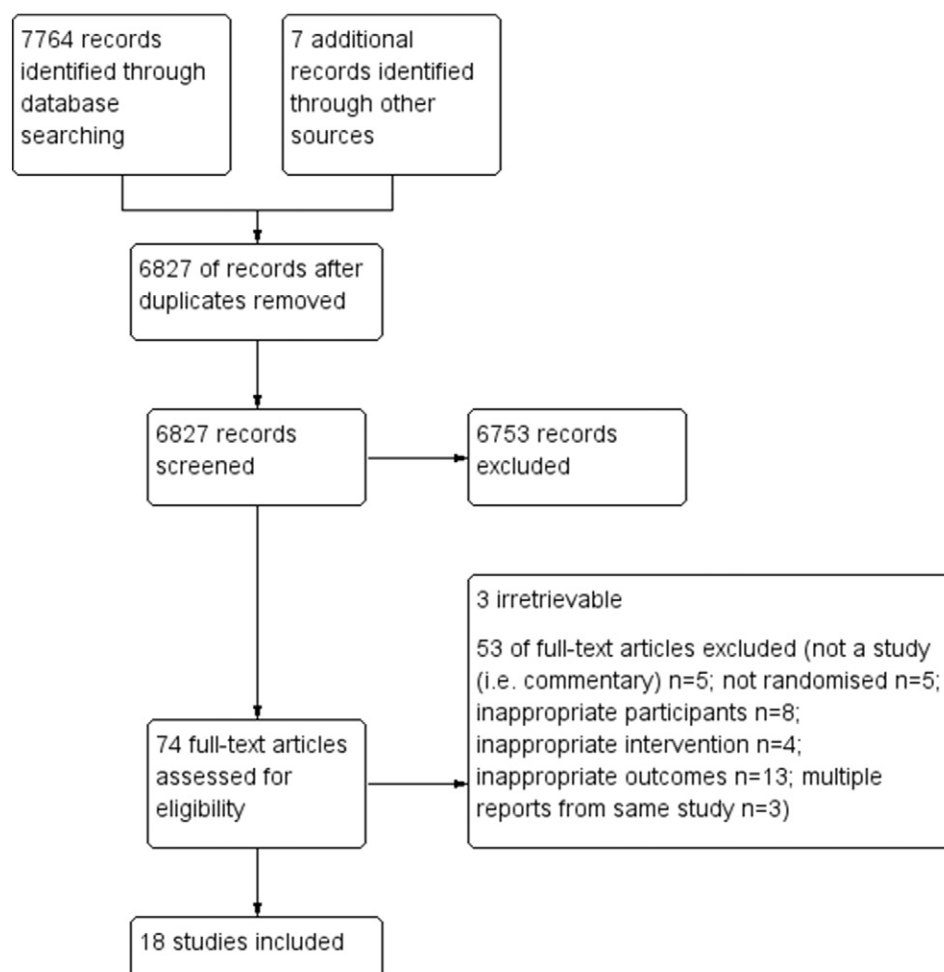


Fig. 1. Study flow diagram.

Table 1
Characteristics of studies.

Study	n	Population	Country	Men%	Mean Age	Intervention	Control	Duration of intervention	Follow-up
Astengo (2010)	62	Stable AP + planned for PCI	Sweden	77	63	Home-based training on bike ergometer, 70% of maximum capacity 5 days/week.	Two patients did a standard rehabilitation programme. Others usual care.	8mo	8mo
Brotons (2011)	1224	ACS 60%, CVA 33%, PAD 7%	Spain	70	66	Nurse-led individual sessions at Primary Health Centres for diet, exercise and smoking. Monitoring of medical treatment.	Usual care	24mo	36mo
Carrington (2013)	602	CHD 62%, Arrhythmia 20%, HF 7%, 3% valve disease.	Australia	72	70	Nurse-led home visits and phone counselling. Referring 52% to cardiac rehabilitation programme for high risk factors and monitoring medication.	Same nurse-led intake. Short cardiac rehabilitation programme.	24mo	24mo
Cohen (2014)	502	ACS	France	84	66	Nurse-led smoking consultation. Dietary and physical activity consultation.	Usual care	12mo	24mo
Haglin (2011)	48	subgroup with CHD	Sweden	73	?	Multidisciplinary programme focused on lifestyle management. In hospital programme, workshops and home programme.	Usual care	5 years	18.5 years
Hawkes (2013)	430	MI	Australia	75	61	Goal directed telephone coaching. Same cardiac rehabilitation participation as control.	Educational booklet and quarterly newsletter.	6mo	24mo
He (2012)	263	PCI	China	81	64	Behaviour change sessions on risk factors. Telephone counselling on risk factor control and medication.	Same behaviour change sessions and usual follow-up.	12mo	24mo
Janssen (2014)	210	CHD	The Netherlands	81	58	Psychologist-led programme focused on maintenance of lifestyle change. Motivational counselling intake followed by group sessions and booster sessions.	Standard comprehensive rehabilitation programme before randomisation. One psychologist's intake.	15mo	24mo
Jorstad (2013)	696	ACS	The Netherlands	80	58	Nurse-led hospital based sessions with motivational interviewing for risk factors and titration of medication. Standard cardiac rehabilitation.	Standard comprehensive cardiac rehabilitation.	12mo	24mo
Krebs (2013)	34	ACS + hyperglycaemia	New Zealand	75	63	Nurse promoted GP consultations after ACS for hyperglycaemic ACS patients to prevent diabetes mellitus type 2 and cardiac events.	Standard cardiac rehab, half of intervention and control group participated.	9mo	24mo
Moreno-Palanco (2011)	247	ACS 65%, CVA 35%	Spain	75	65	Nurse-led visits consisting of lifestyle modifications and modification of medication.	Usual care with yearly consultation.	36mo	36mo
Mosca (2010)	304	CHD	USA	0	62	Nutrition and exercise counselling. Referral to smoking cessation programme.	2 reports for the GP with unmet prevention goals according to AHA/ACC standard.	3mo	24mo
Pinto (2011)	130	MI, AP, CABG	USA	79	64	Patients were randomised after standard comprehensive cardiac rehabilitation. Case managers called to maintain exercise. Patients logged their exercise.	Standard cardiac rehabilitation.	6mo	24mo
Reid (2012) online programme	223	ACS + PCI	Canada	84	56	Online programme for patients who didn't want to participate in a cardiac rehab programme. A physiotherapist made a programme. Online activity logging, tutorials and email feedback and contact.	Activity guidance from their cardiologist.	5mo	24mo
Reid (2012) phone counselling	141	ACS + PCI	Canada	73	61	Intake followed by motivational phone counselling by a physiotherapist for physical activity in patients who didn't want to participate in cardiac rehab.	Activity guidance from their cardiologist.	12mo	24mo
Saffi (2014)	74	ACS	Brazil	74	58	Nurse-led lifestyle counselling in individual sessions and phone contact.	2 counselling sessions about medication and risk factors.	15mo	24mo
Stewart (2015)	624	CVD (CHD 70%, DM 27%, PAD 17%, CVA 13%)	Australia	71	66	Nurse-led programme. Referrals to pharmacists (9%), dietitians (13%), additional cardiac rehabilitation (30%), exercise programmes (12%) if needed. Also phone 'coaching'/home visits. If a cardiovascular rehospitalisation occurred, the health plan was revised.	Assessment with report for GP and specialists.	36mo	51mo
West (2012)	1813	MI	United Kingdom	74	65	Standard cardiac rehabilitation programmes that were already in use were the intervention. The programmes followed the British guidelines. These contained exercise training, risk factor	Patients could attend local patient support groups, but not cardiac rehabilitation.	7wks	8 years

(continued on next page)

Table 1 (continued)

Study	n	Population	Country	Men%	Mean Age	Intervention	Control	Duration of intervention	Follow-up
						and treatment education, and counselling for recovery.			
Coronary heart diseases (CHD)						Myocardial infarction			
MI						Angina pectoris			
AP									
Description of possible CHD presentation									
HF						Heart failure			
Cardiac treatment									
PCI						PTCA (Percutaneous transluminal coronary angioplasty)/PCI (percutaneous coronary intervention)/Dotter			
CABG						Coronary bypass graft			
Other cardiovascular diseases (CVD)									
CVA						Cerebrovascular Accident (ischaemic)			
PAD						Peripheral arterial disease			
DM						Diabetes mellitus			

A comma ',' denotes several patient groups that constituted the total group. For example MI, CVA would be a group of patients that had MI or CVA. Percentages are added if the authors presented the distribution of diagnoses.

'+' denotes patients that had both, for example patients with an acute coronary syndrome that underwent PCI can be written as: ACS + PCI.

Acute coronary syndrome can be used to summarise MI and UAP as a patient group: ACS = MI + UAP. CHD can be used if it exists for longer.

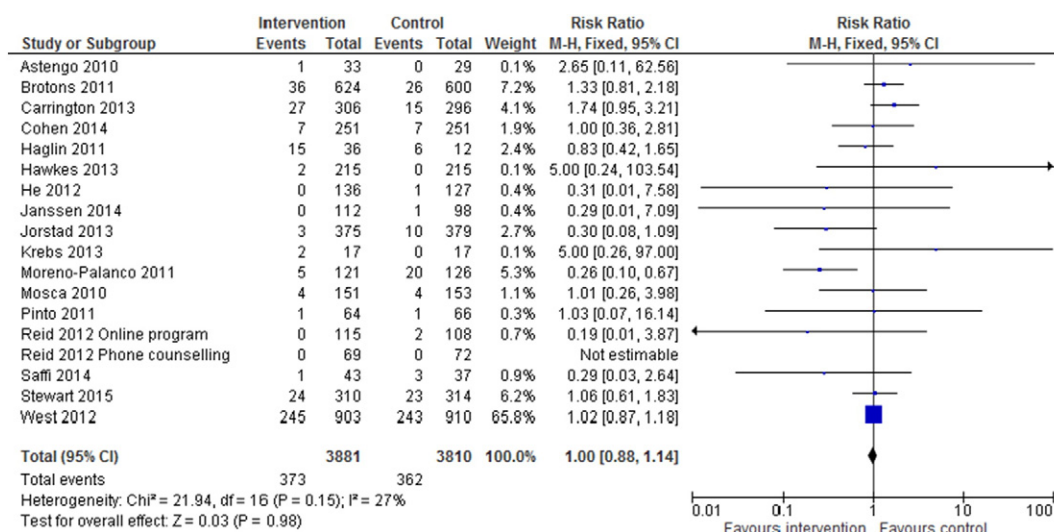
Cardiovascular mortality – with only 32 events – was reported in four RCTs ($N = 1046$) (Fig. 3). Cardiovascular mortality was reduced by cardiovascular prevention and rehabilitation (RR 0.42, 95% CI 0.21, 0.88). There was some statistical heterogeneity across trials for total and cardiovascular mortality ($I^2 = 27\%$ and $I^2 = 24\%$ respectively). In the studies that reported cardiovascular mortality, all-cause mortality was also reduced (RR 0.53, 95% CI 0.29, 0.97).

3.3.1.2. Morbidity. Four studies [20,26–28] ($N = 3416$) reported events including myocardial infarction (Fig. 4) and cerebrovascular events (Fig. 5). The total number of events amounted to 212 MI events and 49 cerebrovascular events. The occurrence of MI was reduced by cardiovascular prevention and rehabilitation (RR 0.70, 95% CI 0.54, 0.91), and cerebrovascular events were also reduced (RR 0.40, 95% CI 0.22, 0.74). In the studies that reported MI and cerebrovascular events, all-cause mortality was not reduced (RR 0.98, 95% CI 0.85, 1.13). The number needed to treat to prevent one MI was 45 and 82 for cerebrovascular events. There was no statistical heterogeneity detected across trials for any of the morbidity outcomes ($I^2 = 0\%$ for both).

3.3.2. Additional analyses

3.3.2.1. Risk factors addressed. Six studies ($N = 2470$) addressed six or more risk factors in their programme, and twelve studies ($N = 5221$) addressed less than six risk factors (Fig. 6). The subgroup that addressed six or more risk factors reduced the relative risk of all-cause mortality significantly to 0.63 (95% CI 0.43, 0.93.). This was not the case for studies that addressed less risk factors (RR 1.08 (95% CI 0.94, 1.24)). The test for subgroup differences was significant ($p = 0.01$). Heterogeneity was moderate in the six or more risk factors subgroup ($I^2 = 47\%$) and low in the less than six risk factors subgroup ($I^2 = 0\%$).

3.3.2.2. Medication prescription. Three RCTs [27–29] ($N = 1035$) incorporated prescription and monitoring of medication as part of the intervention, and 15 studies ($N = 6656$) did not prescribe medication during the intervention (Fig. 7). In the prescription of medication programmes, all-cause mortality was reduced compared to control with a relative risk of 0.35 (95% CI 0.18, 0.70). In contrast, no prescription of medication did not reduce all-cause mortality (RR 1.06 (95% CI 0.93, 1.21). The test for subgroup differences was significant ($P = 0.002$). Heterogeneity

**Fig. 2.** All-cause mortality.

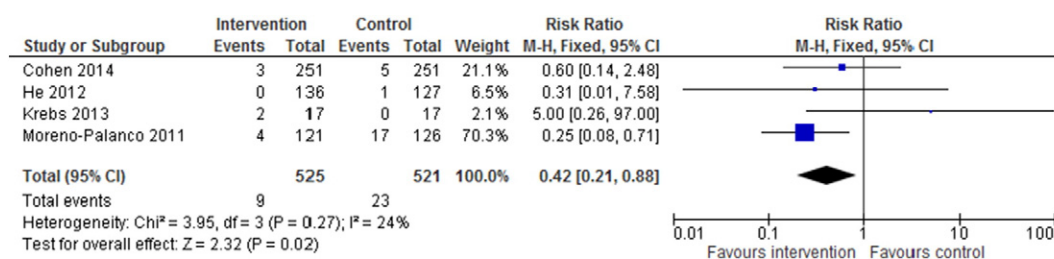


Fig. 3. Cardiovascular mortality.

was moderate in the prescription of medication subgroup ($I^2 = 43\%$) and low in the no prescription of medication subgroup ($I^2 = 0\%$).

3.3.2.3. Type of control group. Twelve studies ($N = 5108$) had usual care which did not include standard cardiac rehabilitation (Supplementary material online, Fig. S4). In six studies ($N = 2583$) usual care included standard cardiac rehabilitation. However, there was no reduction in all-cause mortality in either group (RR 0.99, 95% CI 0.86, 1.14 and 1.07, 95% CI 0.74, 1.54 respectively).

3.3.2.4. Blood pressure. Three studies [22,26,30] reported systolic and diastolic blood pressure management by the percentage of patients achieving target level. Six studies [25,27–29,31,32] ($N = 2008$) analysed both mean systolic and diastolic blood pressure. Systolic blood pressure was significantly reduced in those studies that prescribed and monitored medications within programmes (-3.16 mm Hg 95% CI $-5.55, -0.77$). The programmes that did not prescribe medications did not show a significant difference (-2.71 mm Hg 95% CI $-5.67, 0.25$) (Fig. S5). Diastolic blood pressure was not significantly decreased in the prescription of medication subgroup (-0.95 mm Hg (95% CI $-2.42, 0.52$)), nor in the subgroup of studies that did not prescribe medications (-0.30 mm Hg (95% CI $-1.86, 1.26$)) (Supplementary material online, Fig. S5). Heterogeneity was low in both analyses (both $I^2 = 0\%$).

3.3.2.5. LDL cholesterol. Five studies [27–29,31–33] ($N = 1508$) reported effects on LDL cholesterol, (Fig. S7). As heterogeneity measured by the I-square statistic was high for the LDL cholesterol analysis, a random effects model was used. LDL was significantly reduced in studies that prescribed and monitored medications within programmes (-0.31 mmol/l pooled weighted mean difference random effects model, 95% CI $-0.58, -0.04$). The programmes that did not prescribe medications did not show a significant difference (WMD -0.14 mmol/l (95% CI $-0.36, 0.07$)). The test for subgroup differences was not significant ($p = 0.35$). The I-square statistic value was high (74%) for LDL analysis.

3.3.2.6. Sensitivity analyses. Excluding studies one by one did not significantly alter the effect of prevention and rehabilitation on all-cause mortality. Even after excluding the most heavily weighted study – the study by West et al. – the effect was comparable (RR 0.97, 95% CI 0.77, 1.24). Cardiovascular mortality became insignificant after excluding Moreno-

Palanco et al. (RR 0.85, 95% CI 0.29, 2.49). The outcome of myocardial infarction also lost significance after omission of Moreno-Palanco et al. (RR 0.74, 95% CI 0.55, 1.00). The outcome of cerebrovascular events lost significance after excluding Carrington et al. (RR 0.46, 95% CI 0.21, 1.00). Thus, effect sizes changed minimally by excluding studies one by one except for the outcome of cardiovascular mortality (RR of 0.85 instead of 0.42).

3.3.2.7. Publication bias. The funnel plot for all-cause mortality did not have an uneven distribution on inspection (Fig. 8) (Egger's test $p = 0.3$). Funnel plots for cardiovascular mortality, MI and cerebrovascular events did not contain enough studies to be informative.

4. Discussion

4.1. Summary of main results

In this meta-analysis of contemporary randomised controlled trials of cardiovascular prevention and rehabilitation there was no overall impact on all-cause mortality. However, comprehensive programmes addressing six or more risk factors did reduce all-cause mortality by 37%, whereas less comprehensive programmes did not. Prescription and monitoring of medications for blood pressure and lipids within programmes was also associated with a significant reduction in all-cause mortality of 65% but those programmes not taking responsibility for medications had no impact on survival. In the four studies reporting cardiovascular mortality this was also significantly reduced by 58%, as was myocardial infarction (MI) by 30%, and for the first time cerebrovascular events by 60% in patients with coronary and other atherosclerotic disease. The number needed to treat for MI was 45 and 82 for cerebrovascular events.

4.2. Comparison with other studies

The most recent Cochrane systematic review on exercise-based cardiac rehabilitation also reports no reduction in all-cause mortality (RR 0.96, 95% CI 0.88, 1.04) based on 63 studies with 14,486 participants and a median follow-up of 12 months. Cardiovascular mortality (RR 0.74, 95% CI 0.64, 0.86) and risk of hospital admissions (RR 0.82, 95% CI 0.70, 0.96) were both significantly reduced. There was no significant effect on myocardial infarction or revascularisation [16]. This contrasts with all previous meta-analyses of cardiac rehabilitation up to 2011

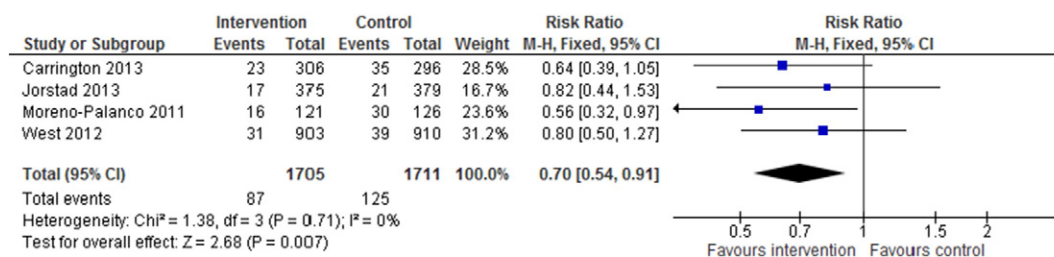


Fig. 4. Myocardial infarction.

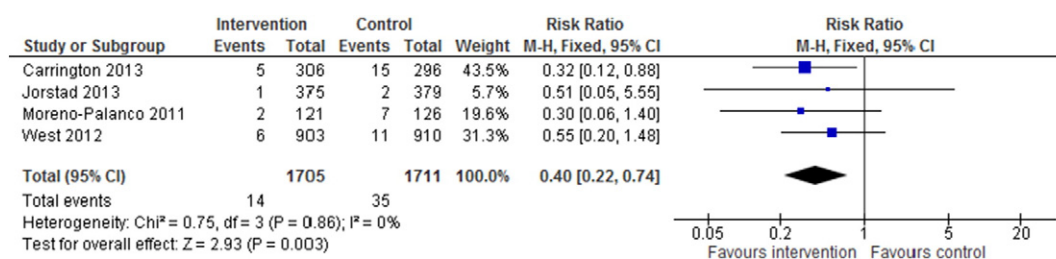


Fig. 5. Cerebrovascular events.

which consistently showed reductions in all-cause mortality and cardiovascular mortality. The previous meta-analysis by Heran et al., based on 47 studies that randomised 10,794 coronary heart disease (CHD) patients, showed that exercise-based cardiac rehabilitation was associated with a reduction in both overall (RR 0.87, 95% CI 0.75, 0.99) as well as cardiovascular mortality (RR 0.74, 95% CI 0.63, 0.87). However, the risk ratio for MI was still not significantly reduced (0.97, 95% CI 0.82, 1.15) [3].

In 2012, Janssen et al. published a meta-analysis of lifestyle programmes from 1999 to 2009 that included 23 studies which randomised 11,085 patients [4]. The control intervention could be either a standard cardiac rehabilitation programme or usual care. They found that participation in a lifestyle programme was associated with a significant reduction in total mortality of about a third, and cardiac mortality was significantly halved. However, findings from a more recent Cochrane systematic review of educational interventions for patients with CHD were somewhat different [16]. In that meta-analysis, Brown et al. included thirteen studies that randomised 68,556 men and women with CHD to educational intervention or usual care. All-cause mortality and the rate of MI were not significantly reduced by this intervention (RR 0.79, 95% CI 0.55, 1.13 and 0.63, 95% CI 0.26, 1.48 respectively). Both these meta-analyses focussed on cardiac patients while our

study investigated patients with cardiac as well as other atherosclerotic cardiovascular disease. In addition, our study was not focussed solely on exercise rehabilitation or on prevention but on all programmes aimed at reducing cardiovascular risk and increasing life expectancy.

We included only recent RCTs which may have resulted in important differences with the meta-analyses that considered studies published before 2010. For example, currently observed mortality rates following the development of coronary disease are quite low: we found that patients in our analysis had a yearly mortality rate of <2%. Of course, advances in the management of acute coronary syndromes through revascularisation and use of cardioprotective drugs are important factors [20], as these interventions have resulted in a much lower mortality rate in the whole CHD population [34]. Therefore the statistical power to show a benefit from these cardiovascular prevention and rehabilitation programmes in terms of all-cause mortality will be reduced. Our broader patient eligibility criteria including angina pectoris, stroke and peripheral arterial disease could be another explanation as the benefits of such programmes may not be the same as for those patients with myocardial infarction, although the number of such subjects was quite small.

In addition, the “healthy adherer effect” could have caused a favourable outcome for rehabilitation participants – especially in the

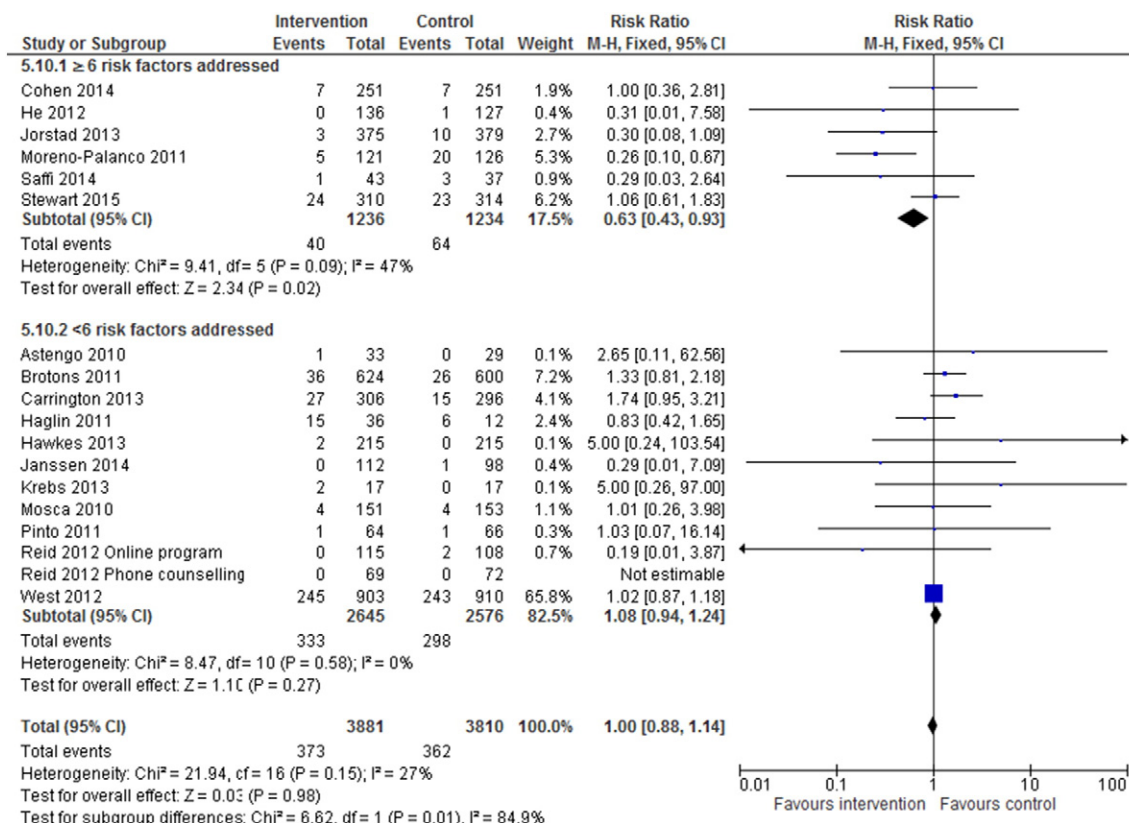


Fig. 6. Number of risk factors addressed (≥6 vs <6).

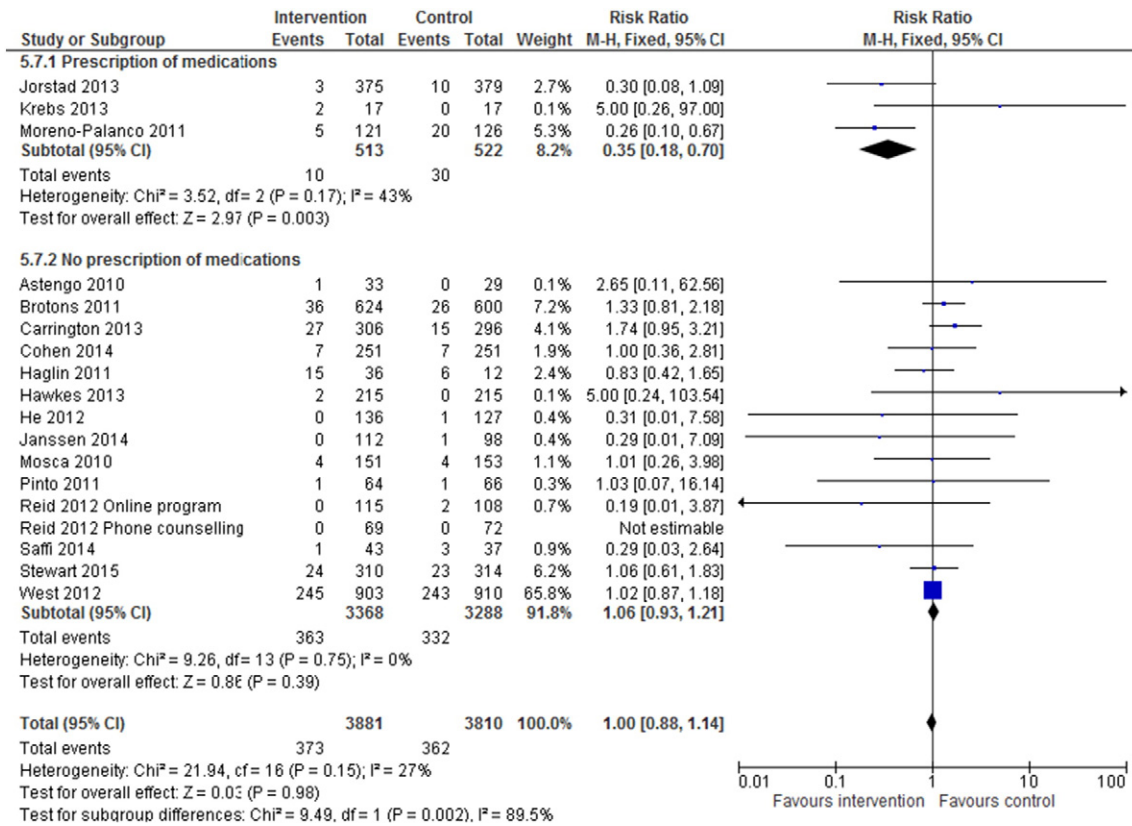


Fig. 7. Effect of medical risk factor management on all-cause mortality.

past [35]. The studies that we considered included – on average – more patients than in earlier meta-analyses. Therefore, publication bias is less likely to have played a role in our results compared with older meta-analyses.

The favourable effect we observed on cerebrovascular events has not been reported previously. An earlier study, the GOSPEL trial, which randomised 3241 patients with a recent MI to a lifestyle programme or usual care, found a non-significant reduction in non-fatal stroke during 3-year follow-up (RR 0.84, 95% CI 0.38, 1.88) [36]. Of note, a meta-analysis of lifestyle based rehabilitation for stroke patients reported a reduction in cardiac events (OR 0.38, 95% CI 0.16, 0.88), but not for death or recurrent cerebrovascular events [37].

The mean age of the patients included in the studies in the current meta-analysis varied from 56 to 70 years. Also, all studies that we analysed included women (16–30% of the study population). Therefore

the studies included in our analysis are more representative than previous meta-analyses as we included older patients and more women [3,5].

4.3. Strengths and limitations

The studies we included suffered from several potential biases common to all studies in this field of research. Loss to follow-up was the most important one, which is a well-recognised problem in all programmes, and could exaggerate the benefits of prevention and rehabilitation. Other forms of bias, such as allocation bias and selective outcome reporting, were less important but could have affected the results as well. The low mortality in the contemporary CHD population decreases the power of some of our analyses, especially the mortality analyses. Future trials should therefore have larger patient samples and have a longer follow-up.

Cardiovascular mortality was presented in just four reports with a combined total of only 32 deaths. These numbers are small and could be biased by selective reporting. Cardiovascular mortality, MI and CVA outcomes were all significant outcomes of our analysis. Of note, the four studies that analysed cardiovascular mortality also reported significantly lower all-cause mortality. The study by Moreno-Palanco et al. in particular influenced this outcome. Two of these four studies also included prescribing and monitoring of medications within programmes which could have played an important role in the overall reduction in MI and cerebrovascular events we observed.

Although highly significant ($p = 0.002$), the sub-group analysis on prescribing and monitoring of medications within programmes was based on just three studies, two studies made up 98.3% of the total weight, while one study – by Krebs et al. – made up only 1.7% of weight, and a relatively small number of events. On the other hand, such a major effect is entirely plausible given the reduction in all cause mortality shown by many drug trials – anti-platelet therapies, beta-blockers, ACE inhibitors – in secondary prevention. There is also internal consistency in our analyses in that those programmes prescribing cardioprotective

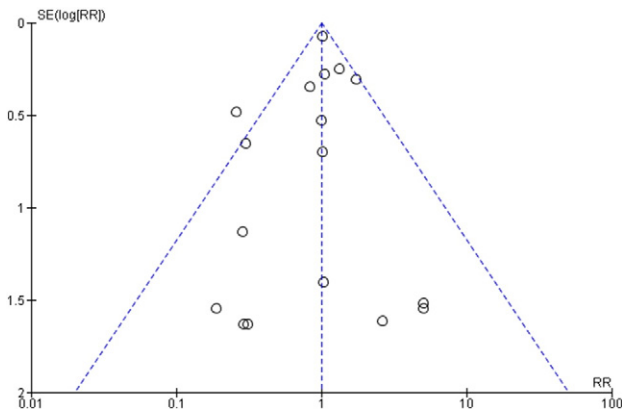


Fig. 8. Funnel plot all-cause mortality.

medications also contributed to the reduction in all-cause mortality in those managing six or more risk factors. This reinforces the importance of taking a comprehensive approach beyond exercise based rehabilitation by treating all aspects of lifestyle and associated risk factors and, in particular, prescribing and monitoring medications as an integral part of cardiovascular prevention and rehabilitation protocols rather than deferring this responsibility externally to other physicians.

5. Conclusions

Improving patient survival has been a hall mark of cardiac rehabilitation since the first meta-analyses [38,39]. The challenge now for the cardiac rehabilitation professions from our systematic review and meta-analysis of contemporary trials of cardiovascular prevention and rehabilitation programmes, and that reported for trials of exercise based cardiac rehabilitation, both show no overall benefit for total mortality [16]. However, we have shown in our meta-analysis that comprehensive prevention and rehabilitation programmes addressing six or more risk factors, and those prescribing and monitoring medications within programmes, are still effective in reducing all-cause mortality. Cardiovascular mortality, myocardial infarction and, for the first time, cerebrovascular events were also significantly reduced. In contrast exercise based cardiac rehabilitation, whilst reducing cardiovascular mortality, did not reduce myocardial infarction and stroke was not reported. Reduction of stroke should now be considered a target for prevention and rehabilitation programmes and included as an endpoint of trials and meta-analyses.

The distinction between exercise based cardiac rehabilitation and secondary prevention is artificial. As evidenced by our meta-analysis, integrating prevention and rehabilitation to provide truly comprehensive programmes is critical to achieving best patient outcomes; reducing myocardial infarction, stroke, cardiovascular and all-cause mortality. A comprehensive prevention and rehabilitation programme uses a behavioural approach to address all aspects of lifestyle – smoking cessation, diet and weight management, physical activity and psychosocial factors – together with in-programme management of all other risk factors – blood pressure, lipids and glucose – and prescribing, monitoring and maximising adherence with cardioprotective medications [40,41]. Yet the reality of clinical practice as described by the EUROASPIRE surveys is that adverse lifestyle trends in coronary patients are countering slow improvements in risk factor management, illustrating the pressing need for comprehensive prevention and rehabilitation [42,43]. Across Europe only 44.8% of coronary patients are advised to participate in any form of rehabilitation, and with an attendance rate of 81.4% only 36.5% of all eligible patients currently access any programme [12]. For those who do so the prevalence of smoking more than a year after hospitalisation is significantly lower than in those who do not attend. However, there is no impact on the prevalence of obesity and central obesity. About half of all patients attending rehabilitation still have uncontrolled blood pressure and lipids at follow-up. Diabetes control is no better either [12]. So the opportunity to improve patient outcomes through a comprehensive cardiovascular prevention and rehabilitation programme is enormous.

The challenge for exercise based cardiac rehabilitation is that all-cause mortality is no longer reduced in the era of acute revascularisation and cardioprotective medications. However, we have shown that comprehensive programmes managing six or more risk factors, and those prescribing and monitoring medications within programmes, still reduce all-cause and cardiovascular mortality, myocardial infarction and stroke. There are many deficiencies in conventional cardiac rehabilitation and secondary prevention services which need to be addressed in order to achieve truly comprehensive care and hence the recent call to reinvestigate our specialty [42]. All the professions involved – physicians, nurses, dietitians, physiotherapists and physical activity specialists, occupational therapists, psychologists, pharmacists – must face this new challenge. We must take the opportunity to evolve cardiac

rehabilitation by integrating secondary prevention and rehabilitation to provide truly comprehensive preventive cardiology programmes which are fit for purpose in the modern management of atherosclerotic cardiovascular diseases.

Authorship

D.W. and K.K. conceived the study. G.H. wrote the protocol draft, performed the statistical analysis and wrote the article draft. G.H. and H.T. performed the literature search and extracted the data. D.W., J.D. and K.K. participated in writing and reviewing the study protocol draft and the article draft. R.D. participated to the data analysis and article draft. All authors approved the final version of the article.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ijcard.2016.12.125>.

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