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Effectiveness of Comprehensive Cardiac Rehabilitation in Coronary Artery Disease Patients Treated According to Contemporary Evidence Based Medicine – Update of the Cardiac Rehabilitation Outcome Study (CROS-II)

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Abstract

Background: Despite numerous studies and meta-analyses the prognostic effect of cardiac rehabilitation (CR) is still under debate. This update of the Cardiac Rehabilitation Outcome Study (CROS II) provides a contemporary and practice focused approach including only CR interventions based on published standards and core components to evaluate CR delivery and effectiveness in improving patient`s prognosis.

Design: Systematic review and meta-analysis

Methods: Randomized controlled trials (RCT) and retrospective and prospective controlled cohort studies (rCCS, pCCS) evaluating patients after acute coronary syndrome (ACS), coronary bypass grafting (CABG) or mixed populations with coronary artery disease (CAD) published until Sep 2018 were included.

Results: Based on CROS inclusion criteria out of 7,096 abstracts 6 additional studies including 8,671 patients were identified (2 RCT, 2 rCCS; 2 pCCS). In total, 31 studies including n=228,337 patients were available for this meta-analysis (3 RCT, 9 pCCS, 19 rCCS; patients after ACS: n=50,653, after CABG: n=14,583, mixed CAD populations: n=163,101; follow-up periods ranging from 9 months up to 14 years).

Heterogeneity in design, CR delivery, biometrical assessment and potential confounders was considerable. CCS showed a significantly reduced total mortality (primary endpoint) after CR participation in patients after ACS [pCCS: hazard ratio (HR) 0.37, 95% confidence interval (CI): 0.20-0.69; rCCS: HR 0.64, 95% CI 0.53-0.76; pCCS: odds ratio (OR) 0.20, 95% CI 0.08-0.48], but the single RCT fulfilling the CROS inclusion criteria showed neutral results. CR participation also was associated with reduced total mortality in patients after CABG (rCCS: HR 0.62, 95% CI 0.54-0.70, one single RCT without fatal events), and in mixed CAD populations (rCCS: HR 0.52, 95% CI 0.36-0.77; 2 out of 10 CCS with neutral results).

Conclusion: CROS II confirms the effectiveness of CR participation after ACS and after CABG in actual clinical practice by reducing total mortality under the conditions of current evidence-based CAD treatment. The data of CROS II, however, underscore the urgent need to define internationally accepted minimal standards for CR delivery as well as for scientific evaluation.

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Keywords. cardiac rehabilitation, cardiac rehabilitation delivery, acute coronary syndrome, coronary bypass grafting, coronary artery disease, mortality

Introduction

Within the past 25 years, cardiovascular morbidity and mortality after acute coronary syndromes (ACS) showed remarkable decrease which is associated with the implementation of acute coronary revascularizations as well as the application of effective acute and long-term pharmacotherapy.1 Supporting these results from the United States1 the French FAST-MI registry revealed a mortality reduction six months after ST-elevation myocardial infarction (STEMI) and Non-ST-elevation myocardial infarction (NSTEMI) from 17.2% to 5.3% and 6.3% respectively.2 Moreover, on the basis of the SWEDEHEART registry a marked improvement of 2-years survival was found, but strictly associated with the use of acute coronary interventions and evidence-based long-term secondary prevention.3 Accordingly, current evidence-based treatment modalities of ACS and CAD do have a large impact on acute and long-term success of care delivered to these patients. Against this background the effects of special treatment modalities like cardiac rehabilitation (CR) need to be re-evaluated in light of their added short and long-term clinical and prognostic benefit. The Cardiac Rehabilitation Outcome Study (CROS) aimed to evaluate the prognostic effect of CR after ACS and coronary artery bypass grafting (CABG) in the modern era of cardiovascular treatment modalities. On the basis of predominantly controlled observational studies including a large amount of patients, CROS confirmed a beneficial effect of CR (i.e. reduced all cause mortality after ACS and after CABG).4 However, with CROS it became apparent that minimal requirements for CR delivery (based on published standards and core components)5–8 had to be fulfilled to reach effectiveness. These minimal requirements have been addressed by other recent meta-analyses9–13 with a focus on volume and intensity of exercise sessions and treatment of CV risk factors during CR. Not meeting these minimal requirements may explain in part the negative results of some recent studies and meta-analyses.14–16

Against this background, the aim of this CROS-update was to critically re-evaluate the results of CROS I in the light of newly published CR studies meeting the strict CROS inclusion criteria. Moreover, the aim of this update was to further elucidate the CR-effect on secondary and non-fatal clinical endpoints representing a heterogeneous field in clinical CR research. By evaluating controlled observational studies the CROS data finally reflect everyday clinical care thereby allowing an estimation of how guideline standards are actually translated into clinical practice.

Methods

This review was conducted and reported according to the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), and the MOOSE statement (Meta-analysis Of Observational Studies in Epidemiology).17,18 The core methods used were essentially unchanged compared to the 2016 publication. The study protocol was prospectively published in PROSPERO (CRD42014007084).19

Study eligibility criteria

Randomized controlled trials (RCT) as well as prospective and retrospective controlled cohort studies (pCCS, rCCS) of multi-component CR versus usual care, with a follow-up period of at least six months, were investigated. We included men and women of all ages after hospitalization for ACS or CABG, respectively. In addition, we included studies enrolling mixed populations of patients after ACS and/or after CABG as basic requirement, as well as patients with chronic stable coronary artery disease (CAD) with or without elective percutaneous coronary intervention (PCI). Patient enrolment had to be carried out by 1995 or later. The primary endpoint was total mortality. Secondary endpoints mainly included non-fatal cardiovascular events, hospital readmissions and mixed endpoints. The detailed study selection criteria were previously presented (see LINK TO SUPPLEMENTAL MATERIAL, Table SM 1).4

Search methods and identification of studies

For the previous review4 highly sensitive search strategies were developed to identify two types of studies: RCT and CCS regardless of the studies´ current status (published, unpublished, finished or ongoing). A detailed description of the elaboration of the search strategy is available in the previous review.4

For this update, we restricted our search to the following four databases: PubMed, Embase, Cochrane Central Register of Controlled Trials and the World Health Organization´s International Clinical Trials Registry Platform (ICTRP). Databases, which did not contribute studies for inclusion in the previous review, were no longer deployed. The search informing this update comprised the period 23 December 2015 – 4 September

2018. No language restrictions were applied. Details of all search strategies are documented in supplemental material (LINK TO SUPPLEMENTAL MATERIAL, Table SM 2). In addition to searching electronic databases, the references of recent systematic reviews were screened.

Study selection

The titles and abstracts of all references were independently evaluated by at least two members of the reference selection board (AS, CHD, BR). Abstracts of potential interest were re-evaluated and selected for full text evaluation (FTE) and structured study evaluation (SSE), respectively, consented within the whole board. FTE for assessing main inclusion criteria and SSE with quality assessment was performed and consented within an extended reference selection board (AS, CHD, BR, PD) including a biometrician (KJ). The primary reasons for study exclusion are given in Table SM 4 (online version, supplemental material).

For the meta-analysis, the studies resulting from the SSE process of the current update were merged with the selected studies from the 2016 publication. The study selection process is outlined in Figure 1.

Study evaluation process

The study evaluation included design, data sources, information on population, interventions, controls, calculation and presentation of outcomes and handling of bias. For RCT the Cochrane risk of bias table (http://tech.cochrane.org/revman/download), and for the CCS the checklists of methodological issues on non-randomized studies,20,21 and the Newcastle Ottawa Scale (NOS) were used.22 To facilitate the study evaluation with respect to management of confounding, age, gender, smoking, diabetes, history of stroke, history of acute myocardial infarction (AMI), reduced left ventricular ejection fraction and acute or early PCI during AMI have been pre-specified as potential confounders.

Data extraction

Data extraction was performed by two biometricians independently (KJ, MH), using a standardized extraction form. Disagreements were solved by consensus. We extracted the following information from each eligible article: name of first author, year of publication, study location (country), study design, data source, number of participants, population (ACS, CABG or mixed), inclusion period, inclusion criteria, follow-up time, mean age of participants, proportion of men, intervention characteristics, control characteristics, reported outcomes, information on outcomes, data on outcomes, covariates included in the adjusted models.

Statistical analysis

The analyses were separated with regard to population (AMI, CABG or mixed) and study design (RCT, pCCSand rCCS). For time-to-event outcomes, the hazard ratio (HR) with its 95% confidence interval was chosen as effect measure per study. If possible, log HRs and their standard errors were extracted directly, preferably from an adjusted model and matched-group analysis. If they were not reported but adequate univariate analyses were available, an indirect estimation method was used.23,24 In some study publications, instead of HR adjusted odds ratios (OR) at the end of follow-up or only absolute numbers of events to calculate ORs were reported. HRs and ORs were reported and pooled separately in the present review.25 For dichotomous outcomes, the OR with its 95% confidence interval was used as the effect measure per study. If no event occured in one or in both arms, a continuity correction of 0.5 per cell was applied. For consistency, we re-calculated the treatment effect to be in the same direction, as necessary, with an HR or OR above 1 indicating a higher risk for CR with respect to each outcome. HRs were combined using the generic inverse-variance method. ORs were pooled using the Mantel-Haenszel method or the generic inverse-variance method. The latter one was used when at least one study reported an adjusted OR. Random-effects models were used to calculate overall effect estimates and confidence intervals because we assumed heterogeneity between the ‘true’ effects of the different CR programs used in the studies. All results were investigated for statistical heterogeneity by I2 statistics with 0-30% representing no or only small, 30-60% moderate, 50-90% substantial and 75-100% considerable heterogeneity.26 A statistical investigation of potential publication bias based on a test of funnel plot asymmetry could not be done because of too few studies per single meta-analysis.26 Nevertheless, sensitivity analyses for the outcome total mortality have been performed with respect to extracted results of alternative analysis techniques (e.g.

independent groups instead of matched groups). There are some deviations from the review protocol published in PROSPERO.19 ORs instead of RRs were used as effect measure for dichotomous outcomes because in some studies adjusted ORs and no absolute numbers are reported. Furthermore, it was not possible to undertake the planned subgroup analyses due to the small number of studies in each subgroup. R version 3.5.1 (R Foundation for Statistical Computing, 2015) and the R "meta" package version 4.9-2 (developed by Guido Schwarzer) was used for all statistical analyses.

Results

Study characteristics

Study characteristics (design, population, interventions, controls and primary results) of the newly identified studies are presented in Table 1. With respect to the design, only 2 RCT (n=240 patients) fulfilled the CROS criteria increasing the total number of RCT to 3 (n=2,053 patients). In addition, 2 rCCS (n=5,238 patients) and 2 pCCS (n=3,193 patients) were newly identified. Thus, a total of 18 rCCS (n=211,334 patients) and 9 pCCS (n=15,386 patients) were considered for final analysis.

Three new studies enrolled 4,315 patients after ACS (total of 15 studies; n=50,653 patients), one additional study included 36 patients after CABG (total of 10 studies; n=14,583 patients), while 2 newly identified studies recruited 4,320 patients in "mixed populations" (total of 11 studies; n=163,101 patients).

CR setting was "out-patient" in all new studies (total of 27) and CR duration varied from 12 weeks to 12 months, thereby not changing the range of 3-4 weeks up to 12 months identified in the previous CROS study. Moreover, the previously reported "CR intensity" ranging from 2 up to more than 5 exercise sessions per week plus motivation, information, education, and psychosocial interventions with variable intensities and combinations remained unchanged.

Notably, the included studies reveal a considerable heterogeneity not only with respect to the predefined study designs (RCT, pCCS, rCCS), and populations (after ACS, after CABG, mixed CAD populations), but also with respect to study endpoints and biometrical evaluation (Tables 2, 3a/b and Fig. 2). For this reason, the majority of the secondary endpoints predefined by CROS could not be integrated into a meta-analysis (Table 2, Figure 2).

Primary endpoint “total mortality”

A summary of the clinical outcomes is shown in Table 2. The primary endpoint “total mortality” was evaluated in 27 studies, one of them evaluating both, mortality after ACS and after CABG (Figure 2).[27] Participation in CR was associated with a significant reduction of total mortality in all but 6 studies.[14,28–32]

After ACS a significant reduction of total mortality was confirmed by the newly added pCCS (4 studies, HR 0.37, 95% CI 0.20-0.69; I^2=28%) and even strengthened by the newly added rCCS (4 studies; HR 0.64, 95% CI 0.53-0.76; I2=33%).

After CABG, the newly identified single RCT was small, only enrolling n=36 low risk patients. During a follow-up period of one year, no deaths occurred, and the risk of “underpowering” has to be regarded as high in this study (see Table 3b, Figure 2).. No additional rCCS or pCCS were identified; consequently, the previous positive results on mortality reduction remained unchanged in this population.

In “mixed populations” the addition of one more pCCS confirmed the significant mortality reduction in CR participants (2 studies; HR 0.66, 95% CI 0.55-0.79) with zero heterogeneity. No additional rCCS calculating HR within the mixed populations could be included by the current search (HR 0.52, 95% CI 0.36-0.77, I^2=84%). The single rCCS newly added within the group calculating OR did not change the neutral result reported before in this group (3 studies, OR 0.68, 95% CI 0.34-1.37) but heterogeneity was high (I2=94%). Sensitivity analyses did not change the overall results.

Secondary endpoints

The results of CROS II with respect to the secondary endpoints are listed in Table 2, differentiating between the various study designs, populations and biometrical approaches. These results are summarized as follows:

Regarding the secondary endpoints “CV mortality” (3 additional studies, 7 studies in total) and “MACCE” (3 studies, unchanged) all selected studies considerably differed with respect to populations and designs, and a “matching” of these studies for meta-analysis was not possible (Table 2). Focusing on the endpoint “CV mortality” and based on the two large controlled observational studies (pCCS, rCCS) there might be a trend in favor of CR participation after ACS and after CABG. With regard to the endpoint MACCE, however, the selected studies do not allow a final conclusion on the effect of CR-participation (Table 2).

The outcomes “non-fatal MI” (total 7 studies) and “non-fatal stroke” (total 3 studies) also did not show a clear trend, but all studies varied in design and population thus hindering a further evaluation by meta-analysis.

The same is true for studies investigating the variably predefined endpoints for “hospital readmission” (endpoints 6-9, see Methods). Most of these studies had heterogeneous designs, and matching of the studies for meta-analysis was not possible (Table 2).

In a descriptive way the results on “hospital readmission” may be summarized as follows: all studies included in CROS either showed a reduction of hospital readmissions in favor of CR-participation, or there was a neutral result. In 12 studies, combined endpoints with various components were evaluated. One more RCT has been identified showing a statistically reduced combined end-point (death, recurrent acute coronary events, or hospitalization for HF) after CR participation compared to usual care (HR=0.26, 95% CI 0.09–0.73).33

Quality evaluation of the studies:

The sum of positive adjudications estimated by NOS is presented in Table 3a (for details see online version, supplemental material: Table SM 5). Four additional studies were graded within a range of 5-7. In total, 5 out of 28 studies (18%) were graded with 5 points or less. Limitations were found with respect to representativeness (6 studies), comparability of the cohorts (3 studies), adequacy of follow-up (5 studies), and the assessment of outcomes (2 studies).

On the basis of the checklist of methodological issues on non-randomized studies the following limitations were identified (Tables 3a/b):

Three studies were based on a secondary analysis of original studies with different original objectives

In 3 studies, either time or location differences between the study groups were apparent.

In most studies, the group formation was potentially influenced by health care decision makers and patient's preferences.

The majority of the studies had unclear study protocols and a consort flow diagram was presented only in seven out of 28 studies

Management of confounding was not reported in 3 studies, whereas the description of potential confounding domains remained unclear or has not been reported in 16 studies.

Predefinition and calculation of all confounding domains as pre-specified by CROS (see Materials and Methods) were performed to various degrees. In only 4 studies all 8 predefined confounders were considered for adjustment. Moreover, 6 studies only considered 3 or even less confounders as predefined by CROS. In general, adjustment for confounding was performed in 24 CCS with 4 studies not applying adequate biometrical methods.

BothRCT evaluating the primary endpoint "total mortality" do have a considerable risk of being underpowered (Table 3b).[14,30,33]

Discussion

This update of the Cardiac Rehabilitation Outcome Study (CROS II) confirms the beneficial prognostic effect of CR in CAD patients by significantly reducing the primary endpoint "total mortality" especially after ACS or CABG. However, the effects of CR-participation on secondary endpoints like "CV-mortality", "non fatal myocardial infarction", "non fatal stroke", "combined endpoints" and various forms of "hospital readmission” remain less clear. This at least in part - is due to a considerable heterogeneity of the selected studies with respect to design, populations, predefined endpoints and biometry. Inconsistent results may be due to the kind of selected endpoints including “weak” endpoints with increased risks of confounding. This is particularly true for the variable forms of “hospital re-admission”, which may be influenced by local routines in medical services, individual comorbidities not necessarily associated with CV diseases, and the individual`s disease perception. Moreover, a longer survival of patients after AMI/CABG may reveal other diseases that primarily determine the number of hospital admissions during prolonged follow-up.

With regard to the secondary endpoint “non-fatal AMI” an overall “neutral” effect also has been reported by Cochrane (Anderson et al. 2016). As AMI and death are closely interrelated clinical events one might speculate that CR-participation effectively prevents death initiated by AMI, but also reduces the incidence of AMI (fatal + non-fatal) per se, resulting in an apparent “neutral effect” with respect to non-fatal AMI occurrence. Unfortunately, the data sources presently available for CROS do not allow to further evaluate this hypothesis.

One of the major strengths of this study is its robust approach to CR intervention aligned with published national CR standards and core components.5–7 Our strict definition of a comprehensive multi-component CR underscores the importance of the amount of physical exercise provided, the adherence to exercise intervention and the adherence to non-exercise components on the patients’ prognosis. The results of recently published meta-analyses (some of them including studies of the modern era of novel medication and interventions) seem to support this approach and somehow elucidate our results. Thus, van Halewijn et al. have shown that a significant reduction in all-cause mortality was feasible in CAD patients only under the condition of a comprehensive CR program managing six or more CV risk factors,10 while the recently published EU-CaRE study showed positive effects of comprehensive CR in 58% of older patients with three or more uncontrolled risk factors before CR.34 These findings, coupled with CROS II results, strengthen clinical recommendations that comprehensive CR is preferable to standalone exercise based CR in reducing total and cardiac mortality, in post-MI patients.13 The effectiveness of a comprehensive CR program is increased by the patient's adherence and by the shared effort to consequently assess and treat the majority of all individual CV risk factors.

With regards to the importance of the CR dose, Santiago de Araujo Pio et al. established that total mortality reduction was only possible in cardiovascular disease patients experiencing medium and high doses of CR.12 Similar CR dose and volume related effects on mortality have been published.9,35 Finally, in a systematic review of multi-component CR, applying almost all CROS inclusion criteria, the study by Sumner et al. carried out a meta-analysis of observational studies published after the year 2000, concluding that all-cause and cardiac mortality were reduced in AMI patients following a CR program.36

Still, one has to keep in mind that this beneficial effect of CR-participation as shown in CROS may not apply to special subgroups like elderly and frail patients who need a particularly personalized approach.37 According to Deaton C et al.38 however, the average age of the CROS study population reflects actual clinical reality. Likewise, CR participation of patients with severe systolic heart failure may not result in mortality reduction as shown in previous meta-analyses.39–41

Apart from these limitations, CROS II presents a timely account of the effectiveness of CR when delivered to agreed published standards including scientifically proven CR core components.5–7 Utilizing a strict approach to CR intervention study inclusion we can report a significant benefit (Table 2 and figure 2) in favor of CR with respect to all-cause mortality. However, at the same time this approach might be viewed as a significant weakness as it makes our findings almost incompatible with previous reviews which have been much more inclusive of CR interventions often defined by innovations in CR being evaluated as part of clinical trials rather than informed by interventions based on published CR program standards and core components. Only three RCT were selected for CROS II compared to 63 in the most recent Cochrane review which reported a significant reduction in cardiovascular mortality but not in all-cause mortality.9 We are not suggesting that previous trial based reviews are erroneous. On the contrary, we agree that robust trials-based reviews remain top of the evidence base hierarchy. What we are prosing is that, the CROS II approach differs to the extent that it should be viewed as an additional form of evidence that utilizes registry-based research reflecting a broader population in the modern cardiology era from 1995 onwards.

For a critical estimation of the CROS II results, the following aspects have to be emphasized:

Cardiac rehabilitation participation after ACS or CABG is associated with reduced total mortality if delivered on top of the current evidence-based treatment modalities (medication and acute coronary interventions). Cardiac rehabilitation participation therefore may contribute to treatment adherence and further add effective individual life style changes necessary to significantly reduce patient`s cardiovascular risk.42–46

This positive effect of CR participation obviously works in current clinical practice of different countries provided a minimum of CR volume and intensity is delivered. This especially refers to the individually adapted and supervised exercise training and a rigorous treatment of all individual cardiovascular risk factors. 9,12,13,47

Unfortunately, these prerequisites of successfully delivered CR - although outlined in detail in many position papers - are not necessarily followed in clinical practice. As noted in CROS II, these prerequisites are not sufficiently described in many clinical studies evaluating CR effectiveness. Therefore, there is an urgent need to effectively translate these well-known and evidence-based minimal standards into all day clinical practice wherever CR is offered. Moreover, these clinical standards need to be the adamant basis of future CR outcome studies. To this end, minimal standards for CR interventions in clinical practice and clinical trials should be based on robust published guidelines and research. We offer the CROS II definition and criteria as a useful guide for optimal CR intervention content and delivery; including multi-disciplinary and multi-component programs with structured, supervised exercise training delivered at least twice per week in combination with motivational techniques, risk factor modification education, dietary advices, psychosocial and vocational support delivered at least once per week. The CR setting could be in-, out-patient or mixed but the time between hospital discharge and CR initiation should be as low as possible, preferably within three months.

From this background it is one of the CROS study's aim not only to evaluate the results and clinical outcomes of the studies included, but also to critically evaluate strengths and deficiencies in detail of each single study included into the meta-analysis (see Table 3). As in the first evaluation in CROS, this update uncovers considerable deficits in current CR studies that need to be addressed and prevented in future. These deficits include predominantly insufficient description of CR content (e.g. applied components), frequency and volume of exercise sessions, CR initiation (i.e. after hospital stay for an acute cardiac event) and duration, absence of CR adherence at follow up as well as methodological issues such as the inadequate consideration of confounding parameters at the stage of study and statistical analysis design.

Clinical implications

Together with the results of other recent reviews, minimal requirements for a successful CR after ACS or CABG are apparent and need to be ensured in clinical practice:[4,9,10,12,13,45]

- Cardiac rehabilitation is multi-component including consequent treatment of the individual`s cardiovascular risk factors, individually adapted physical exercise, information, motivation as well as individualized psychosocial support.[4]
- The individualized approach also reflects gender, age, frailty, heart failure, concomitant diseases, psychosocial background and effectors of the individual`s health and capabilities.
- Cardiac rehabilitation is supervised and carried out by adequately trained health professionals including cardiologists.[4]
- During CR the "dose" of exercise training (number of weeks of exercise training × average number of sessions/week × average duration of session in minutes) exceeds 1.000.[9]
- The number of CR sessions (including physical exercise, information, education and psychosocial support) needs to exceed 36.[12]
- During CR all individually recognized cardiovascular risk factors need to be addressed and treated.[10]

Consequently, future studies on the effect of CR need to report in detail whether these minimal requirements were rigorously followed by the participating CR centres.

Conclusions

CROS II confirms the effectiveness of CR participation after ACS and after CABG in actual clinical practice by reducing total mortality under the conditions of current evidence-based CAD treatment. The CROS approach to more strictly predefined CR intervention and to include controlled registry based studies represents a valid hybrid approach that has clear utility in clinical decision-making.

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PROSPERO International prospective register of systematic reviews (registration number: CRD42014007084): http://www.crd.york.ac.uk/prospero/review_print.asp?RecordID=7084&UserID=5736

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Author contribution

All authors participated in designing the study, generating hypotheses, interpreting data, and critically reviewing the report. The special responsibilities were as follows:
Initiation, organization and leading of the project: BR, CHD, PD, JPS, HV; literature search and search strategies: MIM, BR; study selection: AS, CHD, PD, BR; study evaluation: AS, CHD, BR, KJ; statistical and biometrical analyses: KJ, MH; writing: AS, HV, CHD, PD, KJ, MIM, BR; internal reviewing: JPS, BR, HV, AS, PD, CHD, and the nucleus members of the Secondary Prevention and Rehabilitation section of the European Association of Preventive Cardiology (EAPC).

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Tables

Table 1. Newly identified studies selected for quantitative analysis; baseline study characteristics and overall results

Study Publication year Country	Study design	Population (P): **a.** Data sources **b.** Number of included participants (N) **c.** Index events **d.** Inclusion period **e.** Other inclusion criteria and characteristics **f.** Age (y, mean±SD or as stated) **g.** Gender (male, %)	Intervention (I): **a.** Number (n) **b.** Structured and multi-component CR (SMC-CR)? **c.** Start after index event **d.** Duration (time period and/or total number of CR sessions) **e.** Frequency (CR exercise sessions per wk) **f.** CR-setting	Control (C): **a.** Number (n) **b.** Treatment, characteristics	Outcome (O): **a.** Follow-up period **b.** Outcomes according to the CROS criteria (numbers according to table 1) **c.** Other outcomes not predefined by CROS II	Overall results, with respect to endpoints 1–10 as defined by CROS. Definitions are given at the end of the table*	Remarks
Espinosa Caliani S et al. 200448 Spain	pCCS	a. Institutional, Hospital Clínico Universitario Virgen de la Victoria, Málaga, Spain. b. N=153 c. AMI d. not stated; after 1995 e. control group did not accept CR program f. 49.9±8.4 (CR+) 53.5±9.5 (no CR) g. 93.5	a. n=113 b. SMC-CR c. Immediately after discharge (phase I) d. 12 wk (phase II) at least 9 mo (phase III) e. n=3 (24 sessions) + educational talks, dietary and nutritional advice, psychological support (3mo, phase II). Maintenance phase III until 12 mo f. primary care centre (phase II, III)	a. n=40 b. CR non-attenders	a. 1 y1 y post AMI b. (10) c. Quality of life, exercise capacity, body mass index	Event rate (%CR+/noCR)) Endpoint 10 (angina, hospitalization, re-infarction, cardiac insufficiency and/or death): 6.7/ 6.7 (p=NS)	- Only patients with low-risk MI - CR by patients' decision - CR supervised by "family doctor" not by cardiologist - CR program accredited by Cardiology Spanish Society

Lee JY et al. 201649 Canada	pCCS	a. Data linkage: ASAN Medical Center-Left MAIN Revascularization registry (single-center retrospective database) b. N=3,040 c. mixed population: patients with unprotected LMCA stenosis >50% with subjective or objective ischemia; ACS (64.2%), silent ischemia (8%), stable AP (27.8%) d. 01/01/1995–31/12/2010 e. Patients treated with PCI (37.7%), CABG (49.1%) or medically (13.2%); end of follow-up 31/08/2014 f. 60.8±10.3 (CR+) 62.4±10.5 (no CR) g. 76.2 (CR+) 72.9 (no CR)	a. n=596 n=507 (matched pairs) b. SMC-CR c. Within 3 mo after index hospitalization (phase II) d. 3 mo (36 sessions) e. n=3 f. outpatient	a. n=2,444 n=507 (matched pairs) b. CR non-attenders	a. Mdn 7.3y (IQR, 4.4- 10.2y) b. (1),(2),(4),(5),(8) c. Risk factors' modification, exercise capacity, QoL, return to work, psychological results	Event rate (%CR+/noCR)) Endpoint 1: 13.3/ 18.5 Endpoint 2: 10.4/ 15.5 Endpoint 4: 3.0/ 6.7 p<0.001 for all Endpoint 5: 2.0/ 3.4 p=0.07 Endpoint 8: 7.3/ 10.9 p=0.006 HR (95% CI) after multivariate analysis Endpoint 1: 0.70 (0.49–1.00); p=0.05 Endpoint 2: 0.69 (0.48–0.97); p=0.03 Endpoints 4, 5, 8: p=NS HR (95% CI) propensity-matched pairs Endpoint 1: 0.62 (0.43–0.89); p=0.009 Endpoint 2: 0.54 (0.36–0.80); p=0.002 Endpoints 4, 5, 8: p=NS	- participation in CR was defined as attending at least one outpatient CR session (phase II) within 3 mo after index hospitalization
Aronov DM et al. 201730 Russia	RCT	a. Institutional Moscow Centre of Interventional Cardioangiology. b. N=36	a. n=18 b. SMC-CR (educational program + physical training) c. 2–8 wk after CABG (mean 7.8±1.6 wk)	a. n=18 b. CR non-attenders; only educational	a. 1 y b. (1), (6), (8), (10) c. Exercise and echocardiography parameters, lipd levels, QoL,	Event (nr CR+/nr no CR) Endpoint 1: 0/0 Endpoint 6: 1/3 Endpoint 8: 1/1 Endpoint 10 (AP, MI, re-vascularization,	- publication in Russian language (translations received from Cochrane Russia

		c. patients with IHD who had undergone CABG d. not stated; after 1995 e. -- f. 58.6±7.0 (CR+) 55.9±7.0 (no CR) g. 100	d. 4 mo e. n=3 f. monitored (medical supervision) or not-monitored (home based)	program available	AP attacks, return to work	hospitalization for IHD exacerbation): 2/7	and a private agency) - no statistical analyses of the results - CR had educational component only - contact to author not successful
Hautala AJ et al. 201733 Finland	RCT	a. EFEX-CARE (Effectiveness of Exercise Cardiac Rehabilitation) database of the Finnish Health care setting b. N=204 c. ACS d. 02/2011–05/2014 e. Exclusion criteria: NYHA ≥III, scheduled or emergency CABG, UA, severe peripheral atherosclerosis, diabetic retinopathy or neuropathy, inability to perform regular home-based exercises (i.e. severe musculoskeletal problems)	a. n=109 (drop-out, n=31) b. SMC-CR c. within 1 wk after hospital discharge d. 1 y e. n=4-5 (1 in hospital session per wk and home-based sessions for 6 mo; thereafter home based only) + information, motivation, education, social and vocational support f. outpatient	a. n=95 (drop-out, n=25) b. UC	a. 1 y b. (10) c. Health care costs, quality-adjusted life years, cost-effectiveness	Event rate (%CR+/no CR) Endpoint 10 after 1y: (combination of death, recurrent acute coronary event, or hospitalization for HF) 4.6/16.8, p=0.004	- Center-based CR under supervision of cardiologists and physiotherapists, all components of SMC-CR were available to most of the patients, no information about psychological support (information provided by the author)

		f. 60±11 (CR+), 62±9 (no CR) g. 73 (CR+), 71 (no CR)					
Doimo S et al. 201832 Italy	rCCS	a. Patients discharged from two tertiary hospitals b. N=1,280 c. mixed population; STEMI (n=378), NSTEMI (n=265), CABG with or without valve surgery (n=353) or planned PCI (n=284) d. 01/01/2009–31/12/2010 e. Non-residents in the region or with severe non-cardiac comorbidities (i.e. end-stage tumors), dementia, or immobilized patients, were excluded from the CR group. 13% of eligible patients did not attend CR f. 68±11 (CR+), 66±12 (no CR) g. 68 (CR+), 75 (no CR)	a. n=839; STEMI (n=251), NSTEMI (n=162), CABG (n=243), PCI (n=183) b. SMC-CR c. 89 d (average) d. 5 mo (average) e. 1st part (10 sessions of 45min of cyclette training 2 times/wk for 5 wks); 2nd part (18 sessions of 45min of gym training 3 times/wk for 6wks) supervised by trained nurse and physiotherapist. Other components: Lifestyle counseling at every visit + nutritional advice once/mo + psychological support a. outpatient	a. n=441; STEMI (n=127), NSTEMI (n=103), CABG (n=110), PCI (n=101) b. CR non-attenders receiving all other components of CR	a. Mdn 82 mo (IQR 60 – 89 mo) b. PEP: (9) SEP: (1), (2), (6) c. effect of CR in various subgroups	Event rate (%CR+/no CR) Endpoint 1: 17/18 (p=0.861) Endpoint 2: 6/6 (p=0.623) Endpoint 6: 15/27 (p<0.001)) Endpoint 9: 18/30 (p<0.001)) HR (95% CI) Endpoint 9: 0.578 (0.432–0.773); p<0.001 Event rate, propensity matched analysis (%CR+/ no CR) Endpoint 1: 10/19 (p=0.002) Endpoint 2: 2/7 (p=0.008) Endpoint 6: 25/11 (p<0.001)) Endpoint 9: 29/13 (p<0.001))	- Group allocation by different hospitals - Multivariable regression model and propensity score matching analysis (covariates: age, sex, hypertension, LVEF, DM, smoking, CKD, dyslipidaemia, previous PCI, previous ACS, BB, ACEi/ARB, statins/ezetimibe) - statistical analysis does not address cardiovascular mortality adequately - 5-year composite endpoint as primary outcome (hospitalization for cardiovascular causes and cardiovascular mortality)

Sunamura M et al. 201850 The Netherlands	rCCS	a. Patients from Erasmus Medical Centre (no CR), Rotterdam were propensity score matched with patients from Capri Cardiac Rehabilitation Cater, Rotterdam (CR+) b. N=3,958 c. ACS followed by primary PCI d. 2003 - 2011 e. Excluded: patients with cardiogenic shock (2.3%) and with early (within 60 d post-PCI) death (5.2%) f. 59.0±9.9 (CR+), 58.8±11.83 (no CR) g. 77 (CR+), 78 (no CR)	a. n=1,159 b. SMC-CR c. Mdn 4-6 wk d. 12 wk e. n=2 (1.5h group exercise session). Other components: verbal and written instructions on how to deal with exercise, diet, smoking cessation, and stress management. Individual consultations with psychiatrist, psychologist, and social workers was available if necessary. Complete CR if attended at least 75% of the physical program f. outpatient	a. n=1,159 b. no CR participants	a. Mdn 10 y 4-12 y (range) b. (1) c. Mortality rates of CR completion vs non-completion	Cumulative rates (% CR+/no CR) Endpoint 1 at 5 y: 6.4/10.4 Endpoint 1 at 10 y: 14.7/23.5 HR (95% CI) Endpoint 1 at 10y: (unadjusted) 0.56 (0.43-0.73) (adjusted) 0.61 (0.46-0.81); p<0.001	- Propensity score matching analysis 1:1 (covariates: age, sex, STEMI, current smoking, family history of CAD, HTN, hypercholesterolemia, DM, prior MI, prior history of PCI or CABG, proximal LAD lesion, socioeconomic status)

Descriptive values of metric variables are given in mean or mean plus standard deviation (SD), if applicable. Other calculations are noted in the table. Mdn, median; N, number of total population, n, number of subpopulation; d, days; wk, week(s); mo, month(s); y, year(s)

ACEi, angiotensin converting enzyme inhibitors; (A)MI, (acute) myocardial infarction; AP, angina pectoris; ARB, angiotensin receptor blockers; CABG, coronary artery bypass grafting; BB, beta-blockers, ACEi/ARB CAD, coronary artery disease; CKD, chronic kidney disease; CR, cardiac rehabilitation; DM, diabetes mellitus; HF, heart failure; IHD, ischemic heart disease; IQR, interquartile range; LAD, left anterior descending coronary artery; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction; pCCS, prospective controlled cohort trial; PCI, percutaneous coronary intervention; PEP, primary endpoint; QoL, quality of life; rCCS, retrospective controlled cohort trial; RCT, randomized controlled trial; SEP, secondary endpoint; SMC-CR, structured and multi-component CR; (N) STEMI, (non) ST-elevation myocardial infarction; UC, usual care including ambulatory supervision by family doctor and/or cardiologist, and may also include advise to exercise at home

Table 2. Summary of results

Outcome	Population (number of Studies)	Design (number of Studies)	Events/number of patients (CR)	Events/number of patients (control)	HR (95% CI)	OR (95% CI); pooling method	Heterogeneity: I2; tau2; p-value
Total mortality	ACS (11)	RCT (1)	82/903	84/910	1.01 (0.85-1.21)		NA
		pCCS (4)	NO/3,519	NO/2,063	0.37 (0.20-0.69)		18%; 0.092; p = 0.30
		rCCS (4)	NO/12,033	NO/24,266	0.64 (0.53-0.76)		33%;0.011; p = 0.22
		rCCS (2)	109/2,901	241/1,846		0.20 (0.08-0.48); MH	60%; 0.288; p = 0.11
	CABG (6)	RCT (1)	0/18	0/18		1.00 (0.02-53.12); NA	NA
		pCCS (1)	1/149	5/89		0.11 (0.01-0.99); NA	NA
		rCCS (4)	NO/5,109	NO/7,889	0.62 (0.54-0.70)		0%; 0; p = 0.71
	Mixed (10)	pCCS (2)	254/3,407	398/2,939	0.66 (0.55-0.79)		0%; 0; p = 0.72
		rCCS (5)	NO/2,606	NO/3,577	0.52 (0.36-0.77)		84%;0.145; p < 0.01
		rCCS (3)	1,700/71,674	3,806/71,160		0.68 (0.34-1.37); NA	94%; 0.339; p < 0.01
Cardiovascular mortality	ACS (2)	pCCS (1)	18/2,505	32/1,042	0.44 (0.24-0.82)		NA
		pCCS (1)	0/37	1/37		0.32 (0.01-8.23); NA	NA
	CABG (2)	pCCS (1)	0/18	0/18		1.00 (0.02-53.12); NA	NA
		rCCS (1)	NO/527	NO/4,747	0.64 (0.51-0.81)		NA
	Mixed (3)	pCCS (1)	37/507	75/507	0.54 (0.36-0.80)		NA
		rCCS (1)	34/719	46/719	0.67 (0.44-1.03)		NA
		rCCS (1)	48/839	28/441		0.90 (0.55-1.45); NA	NA
MACCE	ACS (2)	pCCS (1)	81/2,376	81/971	0.55 (0.39-0.77)		NA
		rCCS (1)	212/2,756	281/1,791		0.70 (0.35-1.40); NA	NA
	Mixed (1)	rCCS (1)	158/785	206/1,224	0.85 (0.74-0.98)		NA
Non-fatal myocardial infarction	ACS (3)	RCT (1)	7/162	8/115		0.60 (0.21-1.72); NA	NA
		pCCS (1)	43/2,362	27/946	0.75 (0.45-1.26)		NA
		pCCS (1)	0/37	0/37		1.00 (0.02-51.73); NA	NA

	CABG (1)	pCCS (1)	3/343	13/334		0.22 (0.06-0.77); NA	NA
	Mixed (3)	pCCS (1)	15/507	23/507	0.65 (0.34-1.26)		NA
		rCCS (1)	NO/785	NO/1,224	1.01 (0.74-1.37)		NA
		rCCS (1)	14/795	26/679		0.45 (0.23-0.87); NA	NA
Non-fatal stroke	ACS (2)	RCT (1)	0/162	1/115		0.23 (0.01-5.81); NA	NA
		pCCS (1)	10/2,364	13/954	0.35 (0.14-0.85)		NA
	Mixed (1)	pCCS (1)	8/507	13/507	0.92 (0.24-3.52)		NA
Hospital readmission for any reason	ACS (3)	pCCS (2)	794/2,447	351/1,035		0.96 (0.81-1.13); IV	0%; 0; p = 0.32
		rCCS (1)	NO/878	NO/824	1.00 (0.82-1.22)		NA
	CABG (1)	RCT (1)	3/18	1/18		3.40 (0.32-36.27); NA	NA
	Mixed (2)	pCCS (1)	NO/2,900	NO/2,432	0.77 (0.71-0.84)		NA
		rCCS (1)	253/795	258/679		0.76 (0.61-0.94); NA	NA
Unplanned readmission for any cardiovascular event	ACS (2)	RCT (1)	23/162	16/115		1.02 (0.51-2.04); NA	NA
		pCCS (1)	17/74	20/54		0.51 (0.23-1.10); NA	NA
	Mixed (2)	pCCS (1)	32/2,900	109/2,432	0.68 (0.55-0.84)		NA
		rCCS (1)	122/839	119/441		0.46 (0.35-0.61); NA	NA
Unplanned coronary revascularization	ACS (1)	pCCS (1)	4/69	7/72		0.57 (0.16-2.05); NA	NA
	CABG (1)	pCCS (1)	44/343	49/334		0.86 (0.55-1.33); NA	NA
	Mixed (1)	pCCS (1)	44/507	33/507	1.38 (0.88-2.16)		NA
		rCCS (1)	33/795	37/679		0.75 (0.46-1.22); NA	NA
Cardiovascular mortality and readmission	ACS (1)	pCCS (1)	0/74	4/54		0.08 (0.00-1.43); NA	NA
	Mixed (1)	rCCS (1)	155/839	133/441	0.58 (0.43-0.77)		NA
Combined endpoints	ACS (8)	RCT (1)	5/109	16/95	0.26 (0.09-0.73)		NA
		RCT (1)	24/162	25/115		0.63 (0.34-1.15); NA	NA
		pCCS (1)	NO/521	NO/522	0.65 (0.30-1.41)		NA
		pCCS (4)	47/620	69/567		0.58 (0.33-1.00); MH	21%; 0.080; p = 0.28
		rCCS (1)	183/2,756	263/1,791		0.41 (0.34-0.50); NA	NA
	CABG (2)	RCT (1)	2/18	7/18		0.20 (0.03-1.13); NA	NA
		pCCS (1)	44/343	68/334		0.58 (0.38-0.87); NA	NA
	Mixed (2)	rCCS (1)	NO/785	NO/1,224	0.77 (0.65-0.91)		NA
		rCCS (1)	259/795	263/679		0.73 (0.59-0.91); NA	NA

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; NO, sum of events has not been calculated, if one study of a specific subgroup did not report the number of events; MH, Mantel-Haenszel pooling; NA, not applicable; IV, inverse variance pooling; RCT, randomised controlled trial; rCCS, retrospective controlled cohort study; pCCS, prospective controlled cohort study; HR, hazard ratio; CI, confidence interval; OR, odds ratio.

617 Table 3a. Quality evaluation of cohort studies included into meta-analysis20,21

					Were groups formed by:												Management of confoun-ding (design stage)				
Study	Basic design	NOS, sum of positive adjudications	Reporting of CR-characteristics ╤	Specific actions to select and compare the groups *	Time differences?	Location differences?	Health care decision makers?	Patient`s preferences	On the basis of outcome?	Protocol pre-specifying study outcomes?	Was the intervention`s effect a pre-specified study objective?	Were outcomes, as specified in the CROS protocol, measured and analyzed? †	Consort flow diagram available?	Potential selection bias?	Potential reporting bias (selectively reporting outcomes according to statistical significance?	Potential reporting bias (selectively reporting multiple adjusting	General control for confounding	Have selection criteria for potential confounding domains been described?	Did researchers pre-specify and calculate confounding domains as specified by CROS? ‡	Adjustment for confounding? (analysis)	Method (adjustment for confounding) §
Boulay 200451	R	3	+	1	Y	N?	Y?	Y?	N	Y?	Y	4,7	N	Y	N	NA	Y	N	1,2,7	N	NA
Norris 200452	R	8	(+)	2	N	N	Y	N?	N	Y?	Y	1	N	Y	N	N	Y	Y	1,2,4-7	Y	a,c,d
Kutner 200653	R	7	↓	3	N	N	NC	NC	N	Y?	Y	1,2	N	Y	N	N	Y	Y	1,2,4,6	Y	a,d
Milani 200754	R	6	+	4	N	N	Y	NC	N	Y	Y	1	N	N	N	N	Y	N	1,2,4,7	Y	a,d
Nielsen 200855	R	8	+	5	N	N	NC	NC	N	Y?	Y	1,4	N	Y	N	N	Y	N	1,2	Y	a
Alter 200956	R	8	+	6	N	N	Y	Y	N	Y?	Y	1	Y	Y	N	N	Y	Y	1,2,4,6	Y	a,d,e
Hansen 200957	P	6	+	7	N	Y	Y	NC	N	N	Y	1,4,8,10	N	Y?	N	N	Y	N	1,2-4,8	Y	a,d
Suaya 200958	R	7	(+)	6	N	N	Y?	Y?	N	NC	Y	1	N	Y	N	N	Y	Y	1,2,4-7	Y	a,b,d
Jünger 201059	R	7	(+)	8	N	N	Y	Y	N	Y	Y	1,3,10	Y	Y	N	N	Y	N	1-8	Y	a,c,d
Goel 201160	R	7	(+)	6,15	N	N	Y	Y	N	Y?	Y	1,2,4,8,10	N	Y	N	N	Y	Y	1-8	Y	b,c,d
Kim 201128	P	4	(+)	9	N	N	NC	Y	N	NC	Y?	1,6,8,10	N	NC	NC	NA	Y	N	1,2,4,7	N	NA
Schwaab 201131	R	6	(+)	10	N	NC	Y	Y	N	NC	Y?	1,4,6,8	N	NC	N	N	Y	N	1,2,7	Y	a
Martin 201261	P	7	(+)	11	N	N	Y	Y?	N	Y?	Y?	1,6,7	Y	Y	N	N	Y	NC	1-8	Y	a,b
Beauchamp 201362	R	7	(+)	12	N	N	Y	Y	N	NC	N?	1	N	N	N	NC	N	N	1,2,4	Y	a
Lee 201363	P	8	(+)	13	N	N	Y	Y	N	NC	Y	2,4,10	N	N	N?	N	N	N	N	N	NA
Marzolini 201364	P	8	↓	14	N	N	Y	Y	N	Y	Y?	1,10	Y	Y	N	N	Y	Y	1-4	Y	a,c
Pack 201365	R	7	+	15	N	N	Y	Y	N	Y?	Y	1	N	N	N	N	Y	Y	1-7	Y	a-d
Coll-Fernandez 201466	P	8	↓	16	N	N	Y	Y?	N	NC	Y	1,10	N	N	N	N	Y	Y	1-4,8	Y	a,d

Prince 201467	R	6	↓	17	N	N	Y	Y	N	Y?	Y	1	N	N	N	N	Y	N	1,2	Y	a
Rauch 201468	P	8	+	18	N	N	Y	Y	N	Y	Y	1-6,8	Y	Y	N	N	Y	Y	1-8	Y	a,c,d
Goel 201369	R	7	(+)	15	N	N	Y	Y	N	Y?	Y	1	N	N	N	N	Y	Y	1-3,5	Y	a,c,d
De Vries 201527	R	7	+	19	N	N	Y	Y	N	Y	Y	1	Y	N	N	N	Y	Y	1,2,4,5,7	Y	a,c,d
Meurs 201570	R	5	(+)	20	N	N	Y	Y	N	Y	Y	1,6	N	Y	N	N	Y	Y	1,2,6,7	Y	a,d
Schlitt 201571	R	4	(+)	21	N	N	Y	Y	N	NC	Y	1	N	Y	N	NC	Y	N	1-7	Y	a,d
Lee 201649	P	7	+	22	N	N	Y	NC	N	Y?	Y	1,4,5,8	Y	N	N	N	Y	N	N	Y	a,b
Espinosa Caliani 200448	P	6	+	23	N	NC	NC	Y	N	NC	NC	10	N	N	N	N	N	N	N	N	NA
Doimo 201832	R	5	+	6, 24	N	Y	NC	NC	N	Y?	Y	1,7,9,10	N	N	N	N	Y	N	1-4,6,7	Y	a,d
Sunamura 201850	R	7	+	7	N	NC	NC	NC	N	NC	Y	1	N	N	N	N	Y	N	1-4,6	Y	a-d

Ŧ Reporting of CR-characteristics: +, sufficient; (+), information obtained by author or other sources; ↓, information limited

* specific actions to compare groups: (1) prospectively evaluated intervention group versus retrospectively evaluated control group; (2) linkage of Canadian APPROACH and NACPR registry; (3) data extracted from the United States renal data System, USRDS; (4) retrospective identification of groups by questionnaires within a predefined study cohort; (5) retrospective identification of groups in a population surviving AMI for at least 30 d; (6) retrospective evaluation and formation of matched pairs; (7) groups were formed by two hospitals following different CR referral policies; (8) retrospective identification of groups by questionnaires and personal contact to relatives of deceased patients; (9) groups were formed prospectively according to predefined inclusion and exclusion criteria; (10) retrospective definition of the study groups out of an independent pre-existing study cohort on the basis of medical records;72 (11) propensity score matching; (12) retrospective evaluation of a pre-existing cohort of another study evaluating CR attendance after automatic referral; (13) predefinition of inclusion and exclusion criteria, but final group formation by patient`s preferences and health care decision makers; (14) selection of CAD-patients with musculoskeletal disease in addition. (15) retrospective definition of the groups; CR+ group was defined as attending at least one session within 6 mo after the index event; (16) prospective definition of the groups out of the FRENA registry;73 (17) patients referred to CR but not attending served as control; (18) groups were pre-specified from the OMEGA-trial cohort;74 (19) 180 days survival after index event required; (20) study population has been extracted from two pre-existent studies (DepeMI, MIND-IT);75,76 (21) retrospective recruitment of study population from two previous RCT not investigating CR or prognostic CAD outcomes;71,77 (22) data extracted from ASAN Medical Center-Left MAIN Revascularization registry and ASAN Medical Center cardiac rehabilitation database; (23) control group was formed of patients who did not accept CR program; (24) matching pairs from the Capri Cardiac Rehabilitation database and Erasmus Medical Centre database (control)

† Outcomes under investigation: the numbers refer to the predefined outcomes as outlined in Table 1.

‡ Confounding domains as specified by CROS: 1, age; 2, sex; 3, smoker; 4, diabetes; 5, history of stroke; 6, history of acute myocardial infarction; 7, reduced left ventricular ejection fraction; 8, acute/early

percutaneous coronary intervention during acute myocardial infarction.

§ Biometrical methods to manage confounding: (a) multivariable regression analysis; (b) propensity score matching; (c) propensity score-adjusted multivariable regression analysis; (d) confounders described; (e) retrospective matched pairs. Adjusting only for age and gender has been regarded as insufficient for the limitation of confounding.

APPROACH, Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease; NACRP, Northern Alberta Cardiac Rehabilitation Program; FRENA, Risk Factors and Arterial Disease registry (Factores de Riesgo y ENfermedad Arterial); OMEGA, Randomized, Placebo-Controlled Trial to Test the Effect of Highly Purified Omega-3 Fatty

Acids on Top of Modern Guideline-Adjusted Therapy after Myocardial Infarction; DepreMI, Depression after Myocardial Infarction study; MIND-IT, Myocardial Infarction and Depression Intervention Trial.

R, retrospective cohort control study; P, prospective cohort control study; Y, yes; Y?, probably yes; N, no; N?, probably no; NC, not clear, not reported; NA, not applicable;
green → adjudication is in favor to reliability of results and reporting;
yellow → item potentially increases risk of limited reliability of results and reporting;
red → item increases risk of reliability of results and reporting.

Table 3b. Quality evaluation of randomised controlled trials included into meta-analysis (according to the Cochrane risk of bias table)

Risk	West 2012[14]	Aronov 2017[30]	Hautala 2017[33]
Under-powering	High risk	High risk	Unclear risk
Selection bias	Unclear risk	Unclear risk	Low risk
Random sequence selection bias	Unclear risk	High risk	Low risk
Allocation concealment	Low risk	High risk	Unclear risk
Confounding variables	Unclear risk	High risk	Low risk
Performance bias	Low risk	Unclear risk	Low risk
Detection bias	Low risk	Unclear risk	Low risk
Attrition bias (incomplete outcome data)	Low risk	Low risk	Low risk
Groups balanced at baseline	Low risk	Unclear risk	Low risk
Groups not receiving the same baseline treatment	Unclear risk	Low risk	Low risk
Intention to treat analysis	Low risk	Low risk	Low risk
Reporting bias	Low risk	Low risk	Low risk
Comments	Low recruitment (22.5% CR arm; 22.7% control arm), study participation influenced by patient`s preferences, random sequence generation is not reported, per protocol centrally organized randomization and blinded with respect to baseline characteristics, confirmation of exposure sufficient, CR status has been blinded before outcome assessment, follow-up reporting was completed in 95% of surviving patients, baseline treatment with respect to medication and medical supervision has to be assumed; control group may also have received life style support to a variable extend	No primary endpoint defined; no pre-estimation of sample sizes and effect sizes were described with respect to any endpoint measured), exclusively low risk patients, no randomization method described, potential confounding variables were not assessed, no allocation concealment, interactions between the study groups confounding performance cannot be excluded, Baseline values were presented in a descriptive way without statistical evaluation. At least in n=3 relevant clinical characteristics a balance between groups was not achieved	Primary endpoint: Cost / quality-adjusted life year of a cardiac patient (QALY) Secondary endpoint: Major Adverse Cardiac Event (MACE) Statistical power of the study has not been reported with respect to either of the presented endpoints

green → adjudication is in favour to reliability of results and reporting; yellow → item potentially increases risk of limited reliability of results and reporting; red → item increases risk of reliability of results and reporting.

Figure legends

Figure 1. Study selection flow chart

a Other reasons PS level: reviews, letters, study protocol, only abstract available, b Other reasons FTE level: referral only, referral only, no information about CR enrollment and adherence available. ICTRP: International Clinical Trials Registry Platform; PS: primary selection of extracted studies; FTE: full-text evaluation; SSE: structured study evaluation and quality analysis according to the checklist of methodological issues on non-randomized studies.[20]

Figure 2. Analysis of total mortality

Forest plots presenting the evaluation of the endpoint “total mortality”. HR, Hazard ratio; OR, Odds ratio; MH, Mantel-Haenszel pooling method; CR, cardiac rehabilitation; no CR, no cardiac rehabilitation (control); CI, confidence interval; Events, number of events in the evaluated group; Total, number of patients in the evaluated group; Start (w), start of cardiac rehabilitation after hospital discharge in weeks; Follow-up, follow-up in years.