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ORIGINAL ARTICLE
Interventional cardiology and cardiac surgery

Beneficial effects of cardiac rehabilitation after acute coronary syndrome and coronary artery bypass grafting: Real-world evidence from the Cardiac Rehabilitation Outcome Study update (CROS-III)

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Aims To review the effects of cardiac rehabilitation (CR) in patients with acute coronary syndrome (ACS), coronary artery bypass grafting (CABG) and in mixed populations treated with contemporary interventional, surgical and pharmacological therapy.

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Methods and results

A systematic review and meta-analysis (PROSPERO CRD42025630588) including randomized controlled trials (RCT) and prospective/retrospective controlled cohort studies (pCCS/rCCS) was performed with total mortality as main endpoint. Additional endpoints were cardiovascular mortality, non-fatal cardiovascular events, and hospital readmissions. Subgroup analysis was performed for age and sex. From 40 included studies, 29 studies encompassing 308 514 patients were eligible for this meta-analysis, including 5 newly identified (published between 11/2018–09/2025) studies with 92 571 patients. In pCCS and rCCS, CR-participation was associated with significantly reduced total mortality in patients with ACS (n = 41 740; pCCS: HR 0.33, 95% CI 0.15–0.69; rCCS: HR 0.64, 95% CI 0.55–0.75) and with CABG (n = 17 998; rCCS: HR 0.65, 95% CI 0.56–0.76). The effects regarding total mortality were similar in sex and age subgroups. Cardiovascular mortality and non-fatal stroke were decreased in ACS and CABG patients. In mixed populations, CR was associated with reduced hospital readmissions for any reason and for any cardiovascular event. Methodological and structural heterogeneity and low patient numbers prevented robust results.

Conclusion

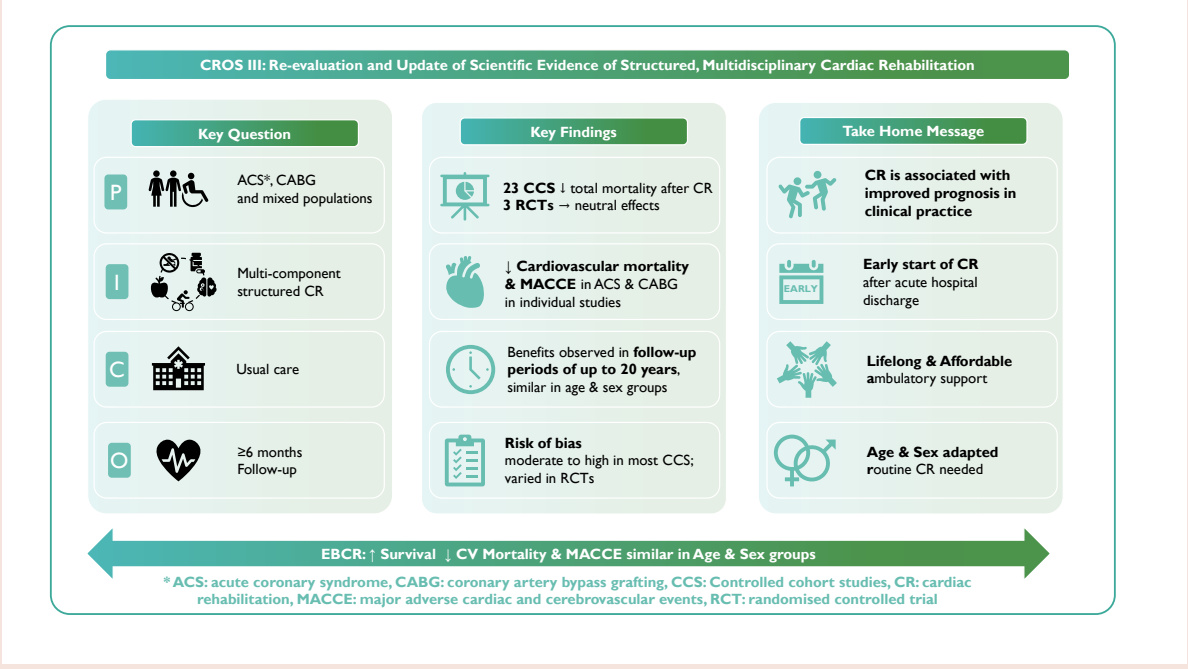
Based on observational data, participation in CR is associated with an improved prognosis in current patients after ACS, CABG and mixed populations, similarly for sex and age subgroups. Hence, CR should be an integral part of secondary prevention in those patients. Nevertheless, high-quality studies are needed to increase the CR evidence base further.

Lay summary

This review, which includes information from 29 studies, shows that taking part in cardiac rehabilitation after a heart attack or heart bypass surgery can significantly improve long-term survival and reduce future health problems.

- Patients who attended cardiac rehabilitation had lower overall and cardiovascular-related death rates, regardless of age or sex.
- Cardiac rehabilitation also helped reduce strokes and hospital readmissions in people recovering from heart attacks or bypass surgery.

Graphical Abstract



Keywords Cardiac rehabilitation • Acute coronary syndrome • Coronary bypass grafting • Mortality • Age • Sex

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Introduction

Prevalence and burden of cardiovascular diseases (CVD), especially coronary artery disease (CAD), remain high in Europe and globally[1,2] Over the past decades, the clinical prognosis for patients surviving an acute coronary syndrome (ACS) has markedly improved, mainly driven by the implementation of rapid and complete acute coronary revascularization, specific medication and the adoption of evidence-based long-term secondary prevention strategies, including regular physical exercise, risk factor control and further lifestyle modifications.[3,4]

However, an ongoing increase in CVD-related deaths is expected as a result of a continuously aging population.[5] Moreover, an evident heterogeneity in age-standardized mortality is observed across countries and regions, attributed to a varying prevalence of modifiable risk factors and availability of appropriate secondary prevention strategies within different healthcare systems.[2,5]

Exercise-based cardiac rehabilitation (CR), defined as an integrative, individualized therapeutic approach—thereby including professional medical supervision, cardiovascular risk factor management, lifestyle modification, and psychosocial counselling—is highly recommended to improve patients' long-term clinical and prognostic outcomes, especially after atherosclerotic cardiovascular events like an ACS and coronary bypass grafting (CABG).[6] Nevertheless, the availability and content of CR services considerably vary across or even within different countries.[7] Furthermore, in clinical practice, CR referral and attendance are inadequate, particularly concerning women and patients of advanced age.[8–10]

The present update of the Cardiac Rehabilitation Outcome Study (CROS) series was conducted to re-evaluate the clinical and scientific evidence of structured, multidisciplinary CR as defined by the European Society of Cardiology in being effective by improving clinical outcomes of patients after ACS, CABG, or in mixed populations with CAD.[6,11,12] As there is still a considerable knowledge gap concerning the evidence of CR in women and patients of advanced age,[13,14] we decided to enrich this systematic review by corresponding subgroup descriptions and analyses. This update was performed using contemporary methodological approaches and perspectives, including a corresponding re-evaluation of formerly included studies.

Methods

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statements.[15,16] The core methods used remained largely unchanged compared with the 2016 and 2020 publications.[17,18] The study protocol was prospectively published in PROSPERO (CRD42025630588).[19]

Study eligibility criteria

We included randomized controlled trials (RCTs) as well as prospective and retrospective controlled cohort studies (pCCSs, rCCSs) investigating multi-component CR vs. usual care, with a follow-up period of at least 6 months. The populations of interest comprised adults after hospitalization for an ACS or CABG, respectively. Studies enrolling mixed populations with a proportion of patients after an ACS and/or after CABG of more than 50% were also included. The patients' index event must have occurred in 1995 or later.

Total mortality was defined as the main endpoint, while additional endpoints included cardiovascular mortality, non-fatal cardiovascular events, hospital readmissions, and combined endpoints. The detailed study selection criteria were previously published.[17]

Search methods and identification of studies

For the baseline review and its first update,[17,18] highly sensitive search strategies were developed to identify two types of studies:

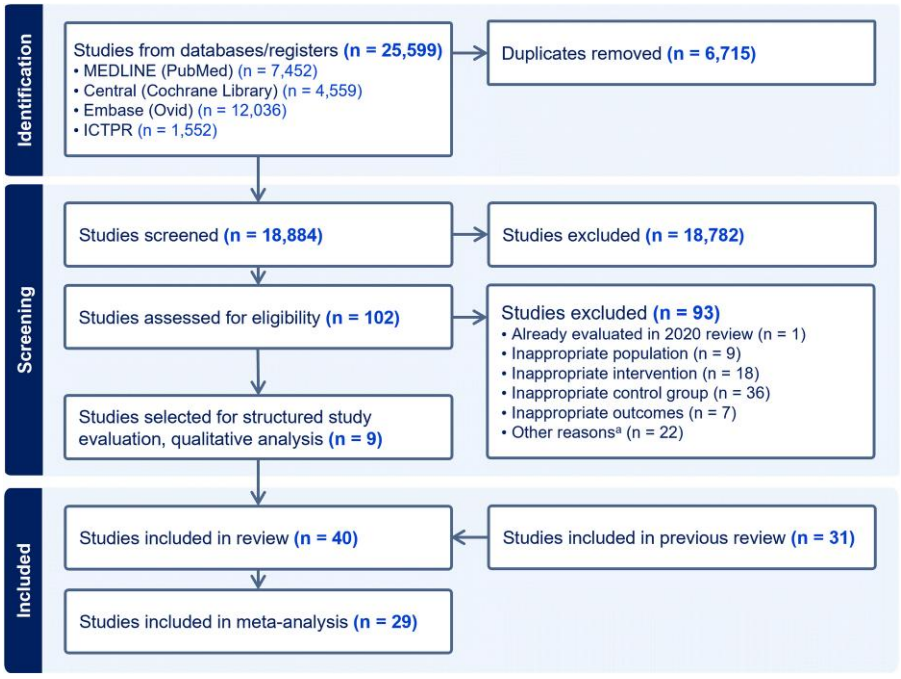


Figure 1 Study selection flow chart. [a]Other reasons: no study publication available (abstract only), inappropriate study design, inappropriate follow-up duration, no investigation of uptake/attendance in cardiac rehabilitation (referral only).

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RCTs and CCSs, regardless of the studies' current status (published, unpublished, finished or ongoing). A detailed description of the search strategy is available in the baseline review.[17] As for the first update,[18] we restricted our search for the current update 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). The search informing the current update comprised the period 1 September 2018 to 5 September 2025. No language restrictions were applied. Details of all search strategies are documented in the Supplementary material online, Supplementary material. In addition to searching electronic databases, the references of recent systematic reviews were screened.

Study selection

Titles and abstracts were independently screened by two reviewers using a systematic review management software (Veritas Health Innovation. Covidence systematic review software. Melbourne, Australia: Veritas Health Innovation; Available from: https://www.covidence.org). Conflicts were resolved by consensus and with third-party involvement (GP, GH, DN). Subsequently, full-text articles were assessed for eligibility. Unpublished studies or Studies not meeting the predefined inclusion criteria were excluded (DN, GP) (*Figure 1*; Supplementary material). A structured study evaluation was then conducted from an extended reference selection board (AS, BR, BBW). For the current update, studies identified through the structured evaluation process were integrated with those published in 2020.

Risk of bias assessment

We assessed the risk of bias for each former and newly included study specifically for the endpoint of total mortality using the Risk of Bias in Non-randomized Studies of Interventions version 2 (ROBINS-I V2)[20] tool for CCSs and the revised Cochrane Risk of Bias tool for randomized trials (RoB-2)[21] for RCTs, respectively. Three researchers (MS, DN, GP) independently divided and assessed the studies using the respective tools, guided by the ROBINS-I V2 or RoB-2 signalling questions across all domains. Discrepancies were resolved through discussion and, when necessary, by consultation with a fourth reviewer.

Data extraction

Data extraction was carried out by a team consisting of a clinician (AxS or BR) and a biometrician (ACR or JAV) using Covidence. Discrepancies were resolved through discussion and consensus with a third reviewer. The following information from each eligible article were extracted: 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, baseline characteristics (age, sex), intervention characteristics, control characteristics, information on outcomes, data on outcomes, information on the statistical approach and covariates included in the regression models to adjust for.

Sex and age subgroups evaluation

As these subgroup analyses have not been conducted in CROS and CROS II,[17,18] all included studies were screened for results of the endpoints total mortality and major adverse cardiovascular and cerebrovascular events (MACCE) within sex- and age-specific subgroups. The corresponding effect measures and the cut-off used to define age subgroups were extracted independently by two clinicians (ET and GH) and validated by a biometrician (ACR).

Statistical analysis

The analyses were separated with respect to population (ACS, CABG, mixed) and study design (RCT, pCCS, rCCS). All outcomes were preferably considered as time-to-event outcomes, and hence the hazard ratios (HRs) and their 95% confidence intervals (CIs) were used as effect measures. For outcomes reported as binary, the odds ratios (ORs) and their 95% CIs were utilized. For RCTs, unadjusted effect measures were used, whereby the HR and its 95% CI were estimated from other reported statistics using the methods described by Tierney *et al.*[22] when not directly reported by the study. For RCTs reporting binary outcomes, the ORs and their 95% CIs were estimated by the absolute numbers of events and participants per group, and in case of zero events, the continuity correction of 0.5 was applied. Since the non-randomized cohort studies (pCCSs and rCCSs) do not account for confounding by design, only adjusted effect measures ideally derived by propensity score matching or a multiple regression model were used. For consistency, the treatment effects were recalculated to be in the same direction, with an HR or OR below 1 indicating a beneficial effect of CR. In the study by Junger *et al.* 2010,[23] the population was divided into STEMI and NSTEMI groups, hence, the reported results were first pooled by the inverse-variance method using the common effect model.

The (adjusted) HRs and ORs with their 95% CIs were separately pooled using the inverse-variance method. Random-effects models were utilized to calculate the overall effect estimate since clinical heterogeneity between the studies was expected. Heterogeneity was assessed by the I^2 statistic and the between-study variance τ^2. Funnel plots were not generated due to the limited number of included studies for each outcome. A sensitivity analysis was conducted regarding the risk of bias assessment.

Where available, subgroup results reported as adjusted HR and OR with their 95% CIs for sex (male and female) and age groups (most commonly defined by a cut-off of 65 years) were pooled using the same method as in the main analyses. Statistical analyses were performed in R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/) using the 'meta' package.

Results

Study characteristics of newly identified studies

This update identified 9 new studies[24–32] including $n = 107\,916$ patients, with study characteristics (design, population, interventions, controls, and primary results) summarized in *Table 1*. Overall, 40 studies comprising 330 333 patients were included in this systematic review.

With respect to the design, one RCT[31] ($n = 512$ patients) fulfilled the CROS criteria, increasing the total number of RCTs to four ($n = 2565$ patients). In addition, seven rCCSs ($n = 107\,038$ patients)[24–29,32] and one pCCS[30] ($n = 366$ patients) were newly identified. Thus, a total of 25 rCCSs ($n = 314\,881$ patients) and 11 pCCSs ($n = 12\,887$ patients) were considered for this systematic review.

Patients after ACS ($n = 15,\,857$) were enrolled in five new studies[25,29–31] (total of 20 studies with $n = 64\,857$ patients), while patients after CABG ($n = 5000$) were evaluated in one new study[28] (total of seven studies, $n = 18\,272$ patients). Mixed populations ($n = 87\,059$) were evaluated in three newly identified studies[24,26,27] (total of 14 studies with $n = 247\,204$ patients).

The CR setting was 'outpatient' in seven new studies[24–28,30,32] (total of 34), with a duration varying between 3 weeks and 6 months, being exactly within the range known from previous CROS publications.[17,18] Among the newly included studies, only one study[29] ($n = 13\,540$ patients) evaluated an in-patient setting with a duration of 3 weeks.

In the nine newly included studies,[24–32] the number of exercise sessions ranged from two to three per week. Thus,

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

Author name year of publication, 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 multicomponent CR (SMCCR)? (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 III	Overall results, with respect to endpoints 1–10 as defined by CROS. Definitions are given at the end of the table*	Remarks
Graham HL *et al.* 2019,[27] USA	rCCS	(a) Electronic medical records from accredited hospitals, Rocky Mountain Region, USA, and State Health Department Records (b) *N* = 361 (*N* = 207 for readmission) (c) MI, PCI, CABG, (d) Nov 2001-Feb 2003 (e) residing <50 miles from the hospital (f) 67.5 ± 11.6 (total) 66.8 ± 11.1 y (CR+) 68.2 ± 12.3 y (no-CR) (g) 72%	(a) *n* = 188 (*n* = 127 for readmission) (b) SMC-CR (exercise and education) (c) referred to CR prior to hospital discharge (d) up to 3 months (e) 3 sessions/wk (f) outpatient	(a) *n* = 173 (*n* = 79 for readmission) (b) UC, follow-up visit within 3 months	(a) From the time of the index event to 14 years (b) (1), (7) (c) None	**Endpoint 1:** PFP: 122 deaths (total) CR: *n* = 41 vs. no-CR: *n* = 81; adjusted OR 0.22 (95% CI 0.12–0.39), *P* < 0.05 **Endpoint 7:** SEP: CR 21.1% vs. no-CR 39.2%; adjusted OR 0.48 (95% CI 0.24–0.96), *P* < 0.05	No-CR Group; standard care from physician, including a follow-up visit within 3 months of discharge and medication management
Thomas E *et al.* 2019,[30] Australia	pCCS	(a) ADVENT-study (b) *N* = 416 (50 were discharged within 1 month) (c) ACS (d) Jan 2013-Jun 2014 (e) admission to Monash Heart (metropolitan hospital in Melbourne, Australia) (f) 58.4 ± 9.9 y (CR+) 60.1 ± 11.3 y (no-CR) (g) 70.7% (CR+)	(a) *n* = 267 (b) SMC-CR (exercise training, educational component, vocational support to assist return to work, support for family/ caregivers) (c) median 36 days (d) 6–12 weeks (e) not stated (f) outpatient (hospital or community-based)	(a) *n* = 99 (b) UC, CR non-attenders	(a) 24 months post-index event admission (b) (6) (c) Number of hospital readmissions, length of stay	**Endpoint 6:** PEP: CR: 141 vs. no-CR 61, *P* = 0.183 **additional:** number of hospital readmissions: Common OR 0.53 (95% CI, 0.31–0.91), *P* = 0.022	Unadjusted analysis of endpoint 6; Adjusted regression model using the number of hospital readmissions as ordinal outcome; endpoints not eligible for meta-analysis

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Table 1 *Continued*

Author name year of publication, 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 multicomponent CR (SMCCR)? (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 III	Overall results, with respect to endpoints 1–10 as defined by CROS. Definitions are given at the end of the table*	Remarks
Eijsvogels TMH *et al.* 2020,[24] Netherlands	rCCS	(a) VGZ health insurance database, national statistical office (Statistics Netherlands), Dutch Population Register (b) *N* = 83 687 (c) ACS = STEMI, NSTEMI, or unstable AP; CABG; 'mixed', including ACS, CABG, stable AP, PCI, either with or without heart failure.; stable AP; CABG, valve replacement; PCI (d) 1 Jul 2012–31 Dec 2017 (e) within 90 days (f) 67 ± 12 (total) 64 ± 11 y (CR+) 69 ± 12 y (no-CR) (g) 60.4%	(a) *N* = 26 171 (b) SMC-CR (exercise, mental health and stress relief, social health; cardiovascular risk management, relaxation therapy, lifestyle modification therapy, education) (c) Not reported (d) 6–12 wk (e) Not reported (f) outpatient	(a) 57 516 (b) UC, CR-non-participants	(a) 92 months (max); mean: 4.7 ± 1.8 y, 56 months (b) (1)	**Endpoint 1**: PEP: Number of deaths (Total): 15 409 CR: 1966 vs. no-CR: 13 443 adjusted HR 0.68 (95% CI 0.65–0.71) **STEMI:** adjusted HR 0.59 (95% CI 0.52–0.68) **NSTEMI** adjusted HR 0.64 (95% CI 0.58–0.70) **stable AP** adjusted HR 0.69 (95% CI 0.63–0.76) **unstable AP** adjusted HR 0.75 (95% CI 0.67–0.85) **acute PCI;** adjusted HR 0.64 (95% CI 0.57–0.72) **elective PCI;** adjusted HR 0.82 (95%CI, 0.74–0.91) **CABG:** adjusted HR 0.75 (95%CI 0.63–0.90)	
Soldati S *et al.* 2021,[29] Italy	rCCS	(a) Health Information Systems of the Lazio Region, Italy (b) *N* = 13 540 (c) AMI with hospitalizations for AMI or related causes (d) 1 Jan 2013–31 Dec 2015 (e) discharged in a hospital from the Lazio region, Italy (f) median age: 67 y (total) 69 y (CR+) 67 y (no-CR) (g) 66%	(a) *n* = 1101 (b) SMC-CR (daily activity and program for preventing deconditioning, exercise therapy and patient education) (c) 30 days following hospital discharge from the index admission (d) 20–22 days (median) (e) not stated (f) inpatient	(a) *n* = 12 439 (b) UC, CR-non-participants	(a) From the 30th day after hospital discharge to max 3 years (b) (1), (7) (c) First admission to emergency department; adherence to evidence-based therapies	**Endpoint 1:** SEP: NSTEMI-NO-PCI: IRR 0.76 (95% CI 0.60–0.95), *P* = 0.021 **Endpoint 7:** SEP: NSTEMI-NO-PCI: IRR 0.78 (95% CI 0.65–0.94), *P* = 0.011) **Additional results**: admission to emergency department. NSTEMI-NO-PCI: IRR 0.80 (95% CI 0.70–0.91), *P* < 0.0001; first hospital readmission due to major adverse cardio-vascular and cerebrovascular events (MACCE) NSTEMI-NO-PCI: IRR 0.78 (95% CI 0.65–0.94). *P* < 0.001	Poisson regression models (counts divided by person time) providing IRRs; endpoints not eligible for meta-analysis

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Table 1 *Continued*

Author name year of publication, 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 multicomponent CR (SMCCR)? (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 III	Overall results, with respect to endpoints 1–10 as defined by CROS. Definitions are given at the end of the table*	Remarks
Karkhanis R *et al.* rCCS 2021,[28] Canada	rCCS	(a) CorHealth Ontario Cardiac Registry, Canadian Immigration Database, ICES ethnic database, Registered Persons Database, ICES hypertension and diabetes databases (b) *N* = 5000 (c) CABG (d) 1 Jan 1996–30 Sep 2008 (e) Adult patients identified from the CorHealth Ontario Cardiac Registry (f) 62.6 ± 9.5 y (CR+) 64 ± 10.5 y (no-CR) (g) 85%	(a) *n* = 3685 (b) SMC-CR (exercise; dietary counselling, stress management, health education, smoking cessation, additional home-based physical activities) (c) Median discharge-to referral time 32.5 days (d) 6–12 wk, 24–36 sessions (e) 1 session/wk (f) Outpatient	(a) *n* = 1315 (b) UC, CR referred but did not attend CR	(a) 20 y (b) (1), (3), (4), (5)	**Endpoint 1:** SEP: adjusted survival at 15 years HR 0.76 (95% CI 0.68–0.84), *P* < 0.001) **Endpoint 3:** PEP: adjusted HR 0.83 (95% CI 0.75–0.91), *P* < 0.001 **Endpoint 4:** SEP: adjusted HR 0.84 (95% CI 0.71–1.01), *P* = 0.06 **Endpoint 5:** SEP: adjusted HR 0.76 (95% CI 0.60–0.96), *P* = 0.02	No-CR group: patients were referred but did not attend CR
Gonzalez-Jaramillo *N et al.* 2022,[26] Switzerland	rCCS	(a) CARDIOBASE Bern PCI registry, hospital administrative records (b) *N* = 3011 (c) PCI (d) 1 Jan 2009–31 Oct 2018 (e) Patients who were alive 30 days after PCI (f) 67 ± 12 y (total) 62 ± 12 y (CR+) 71 ± 11 y (no-CR) (g) 67%	(a) *n* = 1058 (b) SMC-CR (exercise, education, psychological counselling, social medical care, smoking cessation) (c) Not reported (d) 12 wk (e) 2–3 sessions/wk (f) Outpatient	(a) *n* = 1953 (b) UC, CR-non-participants	(a) One y after PCI (b) (1), (2), (3) (c) Non-cardiovascular mortality	**Endpoint 1**: 96 deaths (total) CR: 5 vs. no-CR: 91; adjusted HR 0.12 (95% CI 0.03–0.37) **Endpoint 2**: CR: 1 vs. no-CR: 38; adjusted HR 0.1; (95% CI 0.02–0.7) **Endpoint 3**: CR: 118 vs. no-CR: 218; adjusted HR 1.1 (95% CI 0.86–1.5)	Mortality within 30 days after PCI was excluded

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Table 1 *Continued*

Author name year of publication, 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 multicomponent CR (SMCCR)? (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 III	Overall results, with respect to endpoints 1–10 as defined by CROS. Definitions are given at the end of the table*	Remarks
Gambó Ruberte EP *et al.* 2023,[25] Spain	rCCS	(a) Medical records from Hospital de Nuestra Señora Gracia, Zaragosa, Spain (b) *N* = 230 (c) ACS and PCI (d) Jan 2015-Jun 2015 (e) mal gender, age ≤65 y (f) 53.3 y (total); 52.8 y (CR+) 53.9 y (no-CR) (g) 100%	(a) *n* = 115 (b) SMC-CR (exercise, psychological, and educational program, occupational, smoking cessation, dietary consulting and more) (c) **c.** referred to CR unit at hospital discharge (d) 8 wk (e) 3 sessions/wk (f) outpatient	(a) *n* = 115 (b) UC, conventional outpatient care	(a) 5 y (b) (1), (3), (5) (c) Reinfarction, readmission for HF	**Endpoint 1:** SEP: 9 deaths (total) CR: 1 vs. no-CR: 8, *P* = 0.017; OR 0.12 (95% CI 01–0.94), *P* = 0.01) **Endpoint 3:** PEP: CR: 9 vs. no-CR: 31, *P* < 0.0001; OR 0.23 (95% CI 0.10–0.50), *P* < 0.0001) **Endpoint 5**: SEP: CR: 0 vs. no-CR: 6; *P* = 0.013 **Additional results:** reinfarction rate: CR: 10 vs. no-CR: 1, *P* = 0.010; OR 0.29 (95% CI 0.11–0.77), *P* = 0.007)	Publication in Spanish language (translated into English) Only unadjusted analysis; endpoints not eligible for meta-analysis
Agam *et al.* 2025,[32] Denmark	rCCS	(a) Medical records from Regional Hospital in Hjorring, Denmark; Danish National Patients Registry; The Regional Cardiac Rehabilitation Database, Denmark (b) *N* = 1209 (c) (A)MI; (*n* = 965 with revascularization) (d) Jan 2017-Dec 2021 (e) Patients surviving 3 months post-MI (f) 67.83 ± 12.67 y (total); (g) 67.4%	(a) *n* = 1078 (923 with revascularization) (b) SMC-CR (exercise, psychosocial support, anxiety and depression screening, pat. education, vocational advice, smoking cessation and nutritional consulting, optimization of pharmacological treatment, clinical follow-up and maintenance of goals) (c) Referred to CR unit at hospital discharge (d) 12 wk (e) 2 sessions/wk (f) Outpatient	(a) *n* = 131 (42 with revascularization) (b) UC	(a) 90 d—1 y (b) (1)	**Endpoint 1:** 90 d—1y 56 deaths (total) CR vs. no-CR: *P* = 0.132	Different definition of endpoint and no suitable effect measure reported; endpoint not eligible for meta-analysis

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Table 1 *Continued*

Author name year of publication, 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 multicomponent CR (SMCCR)? (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 III	Overall results, with respect to endpoints 1–10 as defined by CROS. Definitions are given at the end of the table*	Remarks
Tonet *et al.* 2025,[31] Italy	RCT	(a) PIpELINe-trial; Patients across seven sites in the Italian Emilia-Romana Region; University Hospital of Ferra, Italy (b) *N* = 512 (c) (A)MI (d) Mar 2020—Nov 2023 (e) Age ≥65 y; admitted with STEMI or NSTEMI; successful coronary revascularization; scored 4–9 in SPPB (f) Mdn 80 (75–84) (CR+); Mdn 80 (76–83) (no-CR) (g) 64.3% (CR+) 62,4% (no-CR)	(a) *n* = 342 (b) SMC-CR (exercise, management of cardiovascular risk factors, dietary consulting) (c) Referred to CR unit 30 days after hospital discharge (d) 1 y (e) 4 sessions/wk (f) home-based with six on-site supervised exercise sessions (30 d; 60 d; 90 d; 180 d; 270 d; 360 d)	(a) *n* = 170 (b) UC; single in-person visit; 30-min counselling session and educational materials	(a) 1 y (b) (1) (2) (6) (7) (c) Cardiovascular death or unplanned hospitalization for cardiovascular causes (PEP) unplanned (d) unplanned Hospitalization for heart failure (e) Myocardial infarction (f) coronary revascularization (g) Cerebrovascular accident (h) Unplanned hospitalization for non-cardiovascular causes	**Endpoint 1:** SEP: 32 deaths (total) CR+: 19 vs. no-CR: 13; HR 0.72 (95% CI 0.35–1.45) **Endpoint 2:** SEP: 24 deaths (total) CR+: 14 vs. no-CR: 10; HR 0.69 (95% CI 0.31–1.55) **Endpoint 6:** SEP: 95 events (total) CR+: 56 vs. no-CR: 39; HR 0.67 (95% CI 0.44–1.01) **Endpoint 7:** SEP; 61 events (total) CR+: 31 vs. no-CR: 30; HR 0.48 (95% CI 0.29–0.79) **Additional results:** **Cardiovascular death or unplanned hospitalization for cardiovascular causes (PEP)** 78 events (total) CR+: 43 vs. no-CR: 35; HR 0.57 (95% CI 0.36–0.89); $P < 0.01$ **Unplanned hospitalization for heart failure** 17 events (total) CR+: 5 vs. no-CR: 12; HR 0.20 (95% CI 0.07–0.56) **Myocardial infarction** 23 events (total) CR+: 13 vs. no-CR: 10; HR 0.63 (95% CI 0.28–1.44) **Coronary revascularization** 21 events (total) CR+: 13 vs. no-CR: 8; HR 0.80 (95% CI 0.33–1.93) **Cerebrovascular accident** 5 events (total) CR+: 3 vs. no-CR: 2; HR 0.74 (95% CI 0.12–4.43) **unplanned hospitalization for non-cardiovascular causes** 41 events (total) CR+: 28 vs. no-CR: 13; HR 1.06 (95% CI 0.55–2.02)	

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 694 subpopulation; d, days; wk, week(s); mo, month(s); y, year(s).

(A)MI, (acute) myocardial infarction; (N)STEMI, (non) ST-elevation myocardial infarction; AP, angina pectoris; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI, confidence interval; CR, cardiac rehabilitation; DM, diabetes mellitus; endpoint 1, total mortality; endpoint 2, cardiovascular mortality; endpoint 3, MACCE, major adverse cardiac and cerebrovascular events; endpoint 4, non-fatal MI, myocardial infarction; endpoint 5, non-fatal stroke; endpoint 6, hospital readmission for any reason; endpoint 7, unplanned hospital readmission for any cardiovascular event; HF, heart failure; HR, hazard ratio; IHD, ischaemic heart disease; IQR, interquartile range; IRR, incidence rate ratio; no-CR, no participation in cardiac rehabilitation; OR, odd ratio; 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; SPPB, Short Physical Performance Batterie; UC, usual care including ambulatory supervision by family doctor and/or cardiologist, and may also include advise to exercise at home.

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Table 2 Summary of results

Outcome	Population	Design	Events/ number of patients (CR)	Events/ number of patients (control)	HR (95% CI)	OR (95% CI)	Heterogeneity: I^2; τ^2; *P* value
Total mortality	ACS (10)	RCT (2)	101/1245	97/1080	0.99 (0.83–1.18)		0%; 0; *P* = 0.37
		pCCS (3)	NO/3450	NO/1991	0.33 (0.15–0.69)		38%; 0.175; *P* = 0.20
		rCCS (4)	NO/12033	NO/24266	0.64 (0.55–0.75)		33%; 0.003; *P* = 0.22
		rCCS (1)	105/2756	229/1791		0.47 (0.37–0.6)	
	CABG (6)	rCCS (5)	NO/8794	NO/9204	0.65 (0.56–0.76)		48 %; 0.013; *P* = 0.10
		RCT (1)	0/18	0/18		1.00 (0.02–53.12)	
	mixed (12)	pCCS (2)	254/3407	398/2939	0.66 (0.55–0.79)		0%; 0; *P* = 0.72
		rCCS (7)	NO/29535	NO/62875	0.43 (0.25–0.72)		85%; 0.438; *P* ≤ 0.01
		rCCS (3)	1620/70598	3862/70583		0.38 (0.26–0.54)	60%; 0.067; *P* = 0.08
Cardiovascular mortality	ACS (3)	RCT (1)	14/342	10/170	0.69 (0.31–1.54)		
		pCCS (1)	18/2505	32/1042	0.44 (0.24–0.82)		
		pCCS (1)	0/37	1/37		0.32 (0.01–8.23)	
	CABG (2)	rCCS (1)	NO/527	NO/4747	0.64 (0.51–0.81)		
		RCT (1)	0/18	0/18		1.00 (0.02–53.12)	
	mixed (4)	pCCS (1)	37/507	75/507	0.54 (0.36–0.80)		
		rCCS (2)	35/1777	84/2672	0.25 (0.02–2.53)		81 %; 2.365; *P* = 0.02
		rCCS (1)	9/370	25/370		0.34 (0.16–0.75)	
MACCE	ACS (2)	pCCS (1)	81/2376	81/971	0.55 (0.39–0.77)		
		rCCS (1)	212/2756	281/1791		0.70 (0.57–0.86)	
	CABG (1)	rCCS (1)	NO/3685	NO/1315	0.83 (0.75–0.91)		
	mixed (2)	rCCS (2)	276/1843	424/3177	0.92 (0.75–1.13)		51%; 0.012; *P* = 0.15
Non-fatal myocardial infarction	ACS (3)	pCCS (1)	43/2362	27/946	0.75 (0.45–1.26)		
		RCT (1)	7/162	8/115		0.60 (0.21–1.72)	
		pCCS (1)	0/37	0/37		1.00 (0.02–51.73)	
	CABG (1)	rCCS (1)	NO/3685	NO/1315	0.84 (0.7–1.00)		
	mixed (2)	pCCS (1)	15/507	23/507	0.65 (0.34–1.26)		
		rCCS (1)	NO/785	NO/1224	1.01 (0.74–1.37)		
Non-fatal stroke	ACS (2)	pCCS (1)	10/2364	13/954	0.35 (0.14–0.85)		
		RCT (1)	0/162	1/115		0.23 (0.01–5.82)	
	CABG (1)	rCCS (1)	NO/3685	NO/1315	0.76 (0.6–0.96)		
	mixed (1)	pCCS (1)	8/507	13/507	0.92 (0.24–3.52)		
Hospital readmission for any reason	ACS (3)	RCT (1)	56/342	39/170	0.67 (0.44–1.02)		
		rCCS (1)	NO/878	NO/824	1.00 (0.82–1.22)		
		pCCS (1)	794/2378	349/963		0.96 (0.81–1.13)	
	CABG (1)	RCT (1)	3/18	1/18		3.40 (0.32–36.27)	
	mixed (1)	pCCS (1)	NO/2900	NO/2432	0.77 (0.71–0.84)		
Unplanned readmission for any cardiovascular event	ACS (2)	RCT (1)	31/127	30/79	0.48 (0.29–0.79)		
		RCT (1)	23/162	16/115		1.02 (0.51–2.04)	
	mixed (3)	pCCS (1)	32/2900	109/2432	0.68 (0.55–0.84)		
		rCCS (2)	69/497	125/449		0.40 (0.28–0.56)	0%; 0; *P* = 0.55
Unplanned coronary revascularization	ACS (1)	RCT (1)	13/342	8/170	0.80 (0.33–1.93)		
	mixed (1)	pCCS (1)	44/507	33/507	1.38 (0.88–2.16)		

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Table 2 *Continued*

Outcome	Population	Design	Events/ number of patients (CR)	Events/ number of patients (control)	HR (95% CI)	OR (95% CI)	Heterogeneity: I^2; τ^2; *P* value
Cardiovascular mortality and readmission	ACS (1) mixed (1)	RCT (1) rCCS (1)	43/342 155/839	35/170 133/441	0.57 (0.36–0.9) 0.58 (0.43–0.77)		
Combined endpoints	ACS (6)	RCT (1)	5/109	16/95	0.26 (0.09–0.73)		
		pCCS (1)	NO/521	NO/522	0.65 (0.30–1.41)		
		RCT (1)	24/162	25/115		0.63 (0.34–1.16)	
		pCCS (2)	34/461	50/464		0.46 (0.11–1.96) 0.64 (0.52–0.79)	52%; 0.691; *P* = 0.15
		rCCS (1)	183/2756	263/1791		0.64 (0.52–0.79)	
	CABG (1)	RCT (1)	2/18	7/18		0.20 (0.03–1.13)	
	mixed (2)	rCCS (1)	NO/785	NO/1224	0.77 (0.65–0.91)		
		rCCS (1)	259/795	263/679		0.73 (0.59–0.91)	

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio; NO, sum of events has not been calculated, if at least one study of a specific subgroup did not report the number of events; OR, odds ratio; pCCS, prospective controlled cohort study; rCCS, retrospective controlled cohort study; RCT, randomized controlled trial.

considering all included studies, CR volume ranges from two up to more than five exercise sessions per week in addition to motivational counselling, teaching, education, and psychosocial interventions with variable intensities and combinations.

The newly included studies revealed the same considerable heterogeneity with respect to study designs (RCT, pCCS, rCCS), populations (ACS, CABG, mixed CAD populations), study endpoints, and statistical evaluation, as seen in CROS and CROS II.[17,18]

In contrast to the previous CROS reviews,[17,18] studies were considered eligible for inclusion in the meta-analysis only if appropriate adjustment for confounding was performed for the respective outcomes. As a consequence, 11 studies (seven of the previous review, four newly identified) were excluded from this meta-analysis.[33–39]

Main endpoint 'total mortality'

Endpoints are displayed in *Table 2*, differentiating between the various study designs, populations, and effect measures. After stratification by population, study design, and effect measure, only a single study was available for almost all endpoints (*Table 2*).

The main endpoint 'total mortality' was evaluated based on a total of 26 studies, and the results of the meta-analyses are depicted in *Figure 2*.

In ACS patients (*n* = 48 612), one new RCT[31] could be added, resulting in a total of two RCTs[31,40] with an HR of 0.99 (95% CI 0.83–1.18), three pCCSs[41–43] studies were left unaltered, exhibiting an HR of 0.33 (95% CI 0.15–0.69), four rCCS[44–47] studies revealed an HR of 0.64 (95% CI 0.55–0.75), being unchanged to CROS II, and just one rCCS[23] showed an OR of 0.47 (95% CI 0.37–0.60).

For patients after CABG surgery (*n* = 18 034), one new rCCS[28] could be added to a total of five,[28,45,48–50] resulting in an HR of 0.65 (95% CI 0.56–0.76), one remaining RCT[51] showed an OR of 1.00 (95% CI 0.02–53.12), which is identical to CROS II and the only pCCS[33] had to be removed from statistical analysis. In mixed populations (*n* = 239 937), pCCS[52,53] data base was unchanged to CROS II, with two studies resulting in an HR of 0.66 (95% CI 0.55–0.79). Three new rCCSs[24,26,27] were added, while one previously included study[36] was removed, resulting in a total of 7 rCCSs,[24,26,27,54–57] exhibiting an HR of 0.43 (95% CI 0.25–0.72). Concerning OR, one new study[27] could be added, and one older study[58] had to be removed, resulting in an OR of 0.38 (95%, CI 0.26–0.54) (*Table 2*).

Sensitivity analyses regarding risk of bias did not change the overall results in all patient cohorts (see Supplementary material online, Figure *S2*).

Additional endpoints

Participation in CR was significantly associated with reduced risk for cardiovascular mortality in patients after ACS in one pCCS (HR 0.44, 95% CI 0.24–0.82)[43] and CABG in one rCCS[48] (HR 0.64, 95% CI 0.51–0.81), while in mixed populations, most of the individual studies reported a beneficial effect for patients attended in CR (*Table 2*; Supplementary material online, Figure *S3*) were non-significant and inconsistent. CR was significantly associated with reduced risk for MACCE in ACS patients in one pCCS[43] (HR 0.55, 95% CI 0.39–0.77) and in one rCCS[23] (OR 0.70, 95% CI 0.57–0.86), and a modest risk reduction in CABG patients in one rCCS[28] (HR 0.83, 95% CI 0.750.91), but not in mixed populations. None of the individual studies across the different designs and populations reported a statistically significant reduction in the risk of non-fatal infarction associated with CR participation. The risk of non-fatal stroke could be reduced significantly in ACS patients in one pCCS[43] (HR 0.35, 95% CI 0.14–0.85) and CABG patients in one pCCS[28] (HR 0.76, 95% CI 0.60–0.96).

None of the individual studies including patients with ACS reported a statistically significant reduction in hospital readmission by CR, but a modest benefit was observed in mixed CAD populations in one pCCS[52] (HR 0.77, 95% CI 0.71–0.84). Participation in CR was significantly associated with a reduction in unplanned readmission for any cardiovascular event in mixed populations in one pCCS[52] (HR 0.68, 95% CI 0.55–0.84) and in two rCCS[27,59] (OR 0.40, 95% CI 0.28–0.56), but not unequivocally in patients after ACS (RCT:[31] HR 0.48, 95% CI 0.29–0.79; RCT:[40] OR 0.12, 95% CI

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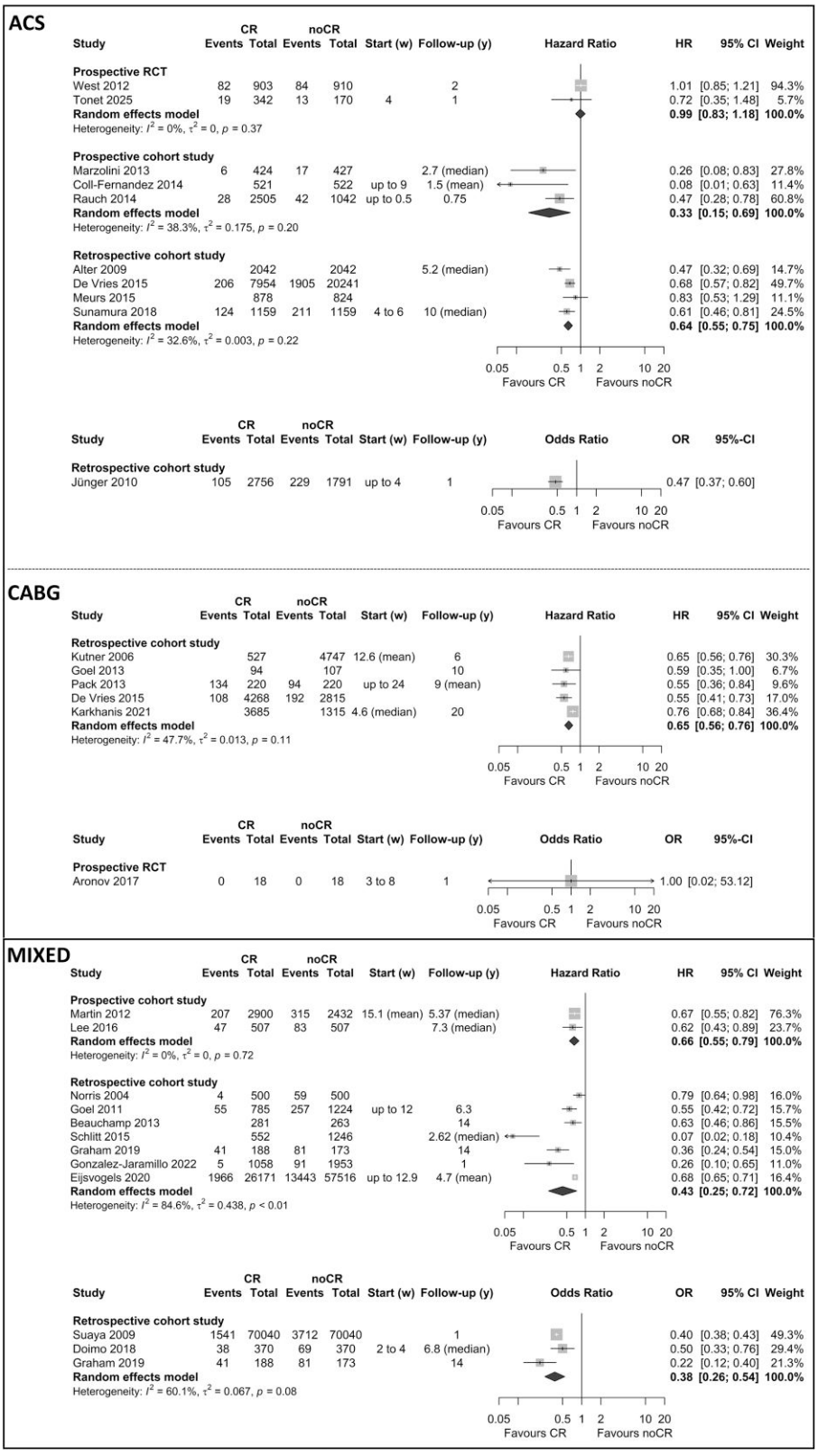


Figure 2 Analysis of total mortality. Forest plots presenting the results of the meta-analyses of the endpoint 'total mortality' stratified by population (ACS, CABG, mixed), study design (RCT, retrospective and prospective controlled cohort study), and effect measure (HR, OR). HR, hazard ratio; OR, odds ratio; CI, confidence interval; CR, cardiac rehabilitation; noCR, no cardiac rehabilitation (control); 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.

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Table 3 Summary of the study results for sex and age subgroups regarding the main endpoint total mortality

Author name year, country	Study design, population	Follow-up	Study subgroup: (a) Sex (f/m) (b) Age (groups)	Total mortality: HR (95% CI) (a) Sex (f/m) (b) Age (groups)	Total mortality: OR (95% CI) (a) Sex (f/m) (b) Age (groups)	Remarks
De Vries *et al.* 2015[45]	rCCS, mixed	25.2 months (median), 48 months max.	(a) f: 13192 m: 22723 (b) ≤70: 20357>70: 15562	(a) 0.79 (95% CI 0.58–1.08) 0.62 (95% CI 0.51–0.74) (b) 0.6 (95% CI 0.45–0.78) 0.68 (95% CI 0.56–0.83)		Reduction of total mortality by CR participation in females was significant at 2 years (HR: 0.67 (95% CI 0.45–0.98)), not at 4 years
Alter *et al.* 2009[44]	rCCS, ACS	5.2 years (median)	(a) n. a. (b) ≤65: 2898>65: 1186	(a) n. a. (b) 0.59 (95% CI 0.35–0.97) 0.31 (95% CI 0.17–0.56)		The effects of CR participation between younger and older patients did not significantly differ, given by a *P*-value of 0.22 of the interaction effect between age and CR participation
Jünger *et al.* 2010[23]	pCCS, ACS	1 year	STEMI: (a) f: 671 m: 1761 (b) ≤70: 1585 >70: 847 NSTEMI: (a) f: 693 m: 1422 (b) ≤70: 1142 >70: 973		STEMI (a) 0.35 (95% CI 0.22–0.57) 0.53 (95% CI 0.28–1.02) (b) 0.38 (95% CI 0.21–0.7) 0.44 (95% CI 0.27–0.71) NSTEMI (a) 0.61 (95% CI 0.4–0.95) 0.38 (95% CI 0.2–0.71) (b) 0.64 (95% CI 0.35–1.17) 0.48 (95% CI 0.31–0.74)	
Rauch *et al.* 2014[43]	pCCS, ACS	1 year	(a) f: 589 m: 2866 (b) ≤65: 2515 >65: 1032	(a) 0.64 (95% CI 0.35–1.17) 0.31 (95% CI 0.11–0.91) (b) 0.53 (95% CI 0.15–1.88) 0.51 (95% CI 0.28–0.91)	(a) 0.63 (95% CI 0.34–1.18) 0.31 (95% CI 0.1–0.94) (b) 0.52 (95% CI 0.15–1.89) 0.50 (95% CI 0.27–0.91)	
Eijsvogels *et al.* 2020[24]	rCCS, mixed	4.7 (1.8) years mean (SD), 7.7 years (max)	(a) f: 33175 m: 50512 (b) <50: 6711 50–64 (<65): 25942 65–74 (≥65): 25659	(a) 0.62 (95% CI 0.51–0.74) 0.79 (95% CI 0.58–1.08) (b) 0.43 (95% CI 0.22–0.68) 0.59 (95% CI		

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Table 3 *Continued*

Author name year, country	Study design, population	Follow-up	Study subgroup: (a) Sex (f/m) (b) Age (groups)	Total mortality: HR (95% CI) (a) Sex (f/m) (b) Age (groups)	Total mortality: OR (95% CI) (a) Sex (f/m) (b) Age (groups)	Remarks
			75–84: 19987>85: 5388	0.52–0.67) 0.64 (95% CI 0.59–0.7) 0.72 (95% CI 0.68–0.77) 0.68 (95% CI 0.59–0.78)		

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CI, confidence interval; CR, Cardiac Rehabilitation; HR, hazard ratio; n.a, not available; NSTEMI, non ST elevation myocardial infarction; OR, odds ratio; pCCS, prospective controlled cohort study; rCCS, retrospective controlled cohort study; SD, standard deviation; STEMI, ST elevation myocardial infarction.

0.51–2.04; Supplementary material online, Figure *S8*). No significant difference was observed in unplanned coronary revascularization. One new study[31] revealed a significant reduction in the combined endpoint 'cardiovascular mortality and readmission' (HR 0.57, 95% CI 0.36–0.90). CR was significantly associated with the reduced risk for all combined fatal/non-fatal endpoints in mixed populations in one rCCS[55] (HR 0.77, 95% CI 0.65–0.91) and one rCCS[58] (OR 0.73, 95% CI 0.59–0.91), while effects in patients after ACS and CABG were mostly not statistically significant (*Table 2*; Supplementary material online, Figure *S11*).

Main and additional endpoints for sex and age subgroups

Results from a total of five studies[23,24,43–45] analysing age, and four studies[23,24,43,45] evaluating sex as subgroups in ACS and mixed populations, respectively, were available from the included studies (*Table 3*; Supplementary material online, Figures *S12* and *S13*). CR participation was associated with a significant reduction in the risk of total mortality, both in younger (ACS: OR 0.49, 95% CI 0.33–0.74; mixed populations: HR 0.58, 95% CI 0.52–0.66) and older populations (ACS: OR 0.47, 95% CI 0.35–0.63; mixed populations HR 0.69, 95% CI 0.66–0.72) (see Supplementary material online, Figure *S12*), as well as both, in females (ACS: OR 0.43, 95% CI 0.28–0.65; mixed population: HR 0.70, 95% CI 0.65–0.75) and males (ACS: OR 0.50, 95% CI 0.38–0.67; mixed populations: HR 0.67, 95% CI 0.64–0.71) (see Supplementary material online, Figure *S13*). In one study,[43] participation in CR was related to a significantly lower rate of MACCE not only in male and younger patients, but also in female patients (HR 0.41, 95% CI 0.22–0.77) and in patients older than 65 years (HR 0.55, 95% CI 0.35–0.86).

Risk of bias assessment of the studies

An overview of the risk of bias assessment across the seven prespecified ROBINS-I V2 domains and five prespecified RoB-2 domains for studies newly included in the current updated systematic review is presented in *Figure 3*. The assessment results for studies included in the previous review are provided in the SM. Of the nine newly included studies, six (67%) were judged to be at serious risk of bias, primarily due to insufficient information on the completeness of outcome data and/or the use of inappropriate methods for handling missing data. One study (11%) was rated as having a critical risk of bias due to a lack of information on whether key confounding variables were measured or adjusted for, or because no adjustment was performed. In the ROBINS-I V2 bias due to confounding domain, six studies (67%) were rated as having moderate risk of bias, as not all prespecified confounders, such as age, sex, pre-existing cardiovascular disease, attendance rate in CR, and type of intervention, were adequately measured or controlled for.

Discussion

Summary and clinical relevance of CROS III data

The present update of the Cardiac Rehabilitation Outcome Study (CROS III) confirms that attendance in multidisciplinary exercise-based CR is strongly associated with reduced total mortality in patients after ACS and CABG, as well as in mixed CAD populations (*Figure 2*).

Reflecting the continuously increasing evidence of CR being effective in stabilizing the clinical course of atherosclerosis and thereby improving clinical long-term prognosis,[9,43,47,60–62] these results of CROS III might have been expected. However, the pharmacological control of cardiovascular risk factors and diseases has also continuously been improved, thereby increasing the capability to better control hypercholesterolemia, hypertension, and diabetes.[1,3,4] The added value of guideline-adapted CR, therefore, is to effectively transfer actualized validated clinical and scientific knowledge into the all-day care of patients at cardiovascular risk, especially after ACS and coronary revascularization procedures.

Minimal standards for successful cardiac rehabilitation

Following minimal standards with respect to CR content and delivery represents a prerequisite for substantially improving the

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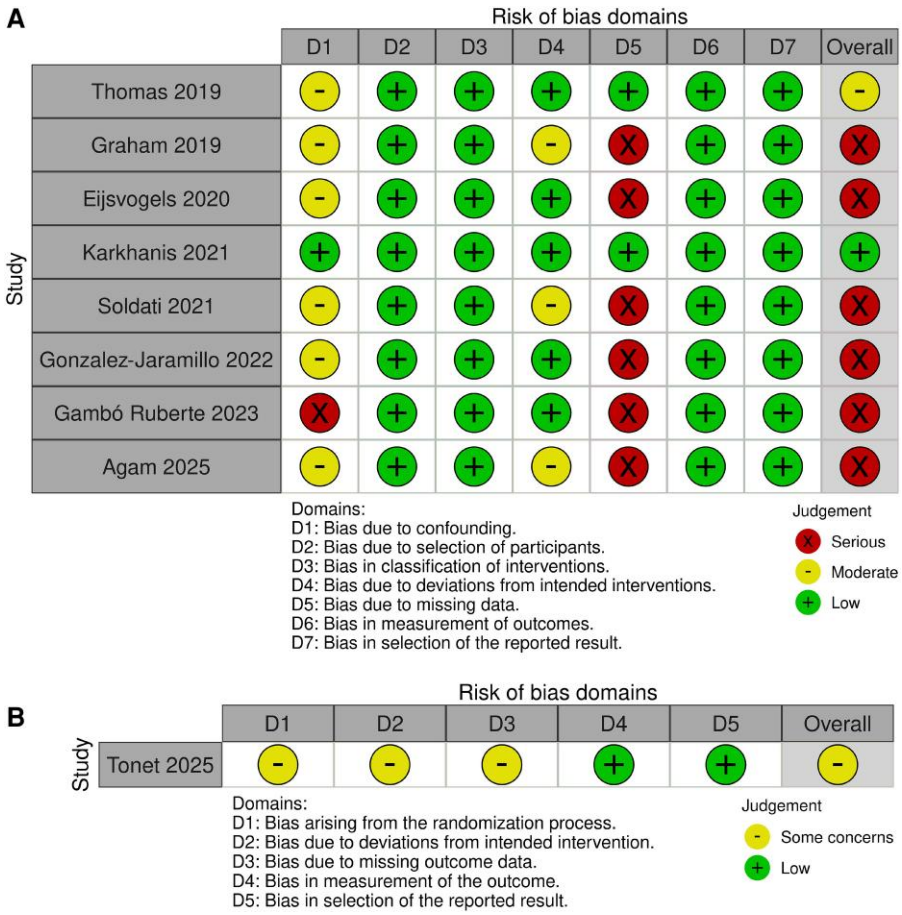


Figure 3 Domain-specific risk of bias assessment for studies included in the meta-analysis using ROBINSI V2 (3a) and ROB-2 (3b).

clinical prognosis of CAD patients.[6,17,18,63,64] Therefore, CR should start as early as possible after hospital discharge and significantly facilitate and support the individual`s lifelong adherence to secondary prevention measures, including healthy lifestyle habits, regular physical activity, adherence to treatment, and psychosocial support.[9,17,18,61,62] Moreover, CR has to guarantee sufficient medical expert supervision by a cardiologist along with structured therapeutic and educational interventions adapted to the individual's diagnoses, comorbidities, age, sex, and potential limitations in everyday skills like frailty.[63–66] Finally, after participating in CR, an individually adapted and supervised ambulatory support in secondary prevention should be offered lifelong in clinically and socioeconomically suitable ways.[63,64]

Methodological considerations

Only recently, the scientific evidence of CR being effective in improving the clinical prognosis of CAD patients has been strongly supported by an RCT.[31] Besides this, the availability of RCTs for the evaluation of effects of CR on clinical and prognostic outcomes in CAD patients remains limited. As a consequence, the scientific evidence generated by CROS is predominantly based on prospective and retrospective CCS. Thus, the risk of bias profile highlights limitations in data completeness and adjustment for confounding, which may affect the robustness of the synthesized results presented in CROS III.

In a recent methodological review of Akbari *et al.* (2023),[67] the variability in statistical approaches among original studies and the importance of accounting for potential confounders have been emphasized. As a consequence, from the CCS included in CROS III, only adjusted effect estimates were considered to reduce confounding bias. However, despite restricting the analysis to adjusted estimates, the selected studies employed different adjustment methods and included varying sets of covariates in their models. This heterogeneity in adjustment strategies may affect the comparability of the reported effect estimates across the studies under evaluation and introduces statistical uncertainty.

Although methodological differences as well as the observational nature of most of the included studies confine causal interpretation, the present meta-analysis remains meaningful. It synthesizes the available evidence, and the consistent direction of effects across the studies being evaluated supports the beneficial effect of CR programs.

Clinical endpoints

All predefined clinical endpoints selected for evaluation have been addressed within the study screening and selection procedure. The main endpoint evaluated in CROS was total

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mortality. Covering data of 26 studies, CROS III confirms CR-attendance to be associated with a reduction of all-cause mortality after ACS, after CABG, and in mixed CAD populations. Moreover, this beneficial effect could be observed along follow-up periods up to twenty years.[27,28,47,56]

In an attempt to better describe the clinical effect of CR-attendance, apart from total mortality, additional endpoints have been evaluated (*Table 2*). As expected, most studies addressing hospital readmissions for any reason did not show a significant effect on long-term survival, as this endpoint may also address diseases of non-cardiovascular origins presenting with high variability in clinical prognosis. In general, studies focusing on non-fatal cardiovascular events predominantly showed a strong tendency towards a better clinical outcome after CR participation.

With respect to the evaluated combined endpoints, careful consideration is required regarding the clinical importance of individual components, as treatment effects on less important components (e.g. non-fatal events) may drive an apparent benefit despite missing effect on more clinically meaningful outcomes (e.g. fatal events). This limitation, however, does not affect the main message of this meta-analysis, which focuses on single-event endpoints.

Although there is an overall trend towards better outcomes in patients attending CR, some of the studies being evaluated showed neutral results. Moreover, referring to the high variability of study characteristics and study size, conclusions must be formulated with caution. No significant effect of CR-attendance after ACS or CABG on hospital readmissions for any reason was detected. This, however, is reasonable as CR is unlikely to have any effect on hospitalizations unrelated to cardiovascular disease.

Sex and age

Notably, in line with a recent individual participant data meta-analysis on exercised-based CR,[68] the beneficial effect of CR attendance was broadly consistent across subgroups defined by sex and age, although sex and age imply specific physiological, pathophysiological, clinical, and socioeconomic aspects that need to be considered by CR implementation and realization.[69–74]

The beneficial results of CROS III also need to be reflected within the context of recent data focusing on women after an ACS-related percutaneous coronary intervention (PCI), who remained at elevated cardiovascular risk during a follow-up of 1 year or even more.[75] Compared with men, women also presented with elevated numbers of atypical symptoms, comorbidities, and increased long-term mortality rates.[76] Despite these adverse cardiovascular risk profiles, women received less guideline-recommended clinical management, thereby signalling the ongoing gap in cardiovascular care between females and males and highlighting the urgent need for age and gender adapted CR contents and delivery.[70]

Against this background, the need for equal, routine CR participation for female and male CAD patients, especially after ACS or CABG, is obvious.

Clinical implications

The significant and stable improvement of a patient`s clinical prognosis represents a prerequisite for regaining the individual`s quality of life and supporting social reintegration despite the existence of a chronic cardiovascular disease. Patients with clinically stabilized CAD, therefore, are strongly recommended to participate in medically supervised, exercise-based cardiac rehabilitation programs,[6,11,12,63,64,77,78] thereby—if feasible—also including home-based programs and tele-rehabilitation.

Of note, CAD patients after an acute ischaemic coronary event also need lifelong professional support, at best within a structured medical network including acute care, routine medical supervision, CR, and long-term maintenance programmes (CR phase III).[6,63,64,79]

Limitations

This updated systematic review and meta-analysis was conducted according to the original inclusion criteria, which included a detailed definition of CR. Consequently, the findings are representative of patients following ACS/CABG who participated in CR programmes, consistent with the CROS definitions. They should not be generalized to other patient groups or different CR settings (e.g. home-based), monomodal, or less frequently applied interventions.

Despite the strict inclusion criteria, the included studies exhibited substantial heterogeneity in CR programmes, study designs, and patient populations. Studies investigating mixed populations may have included not only patients after ACS/CABG (at least 50%), but also patients with any cardiovascular disease. These studies generated the highest, yet least reliable, effects in this updated meta-analysis.

To reflect the potential benefits of CR attendance in real-world conditions and thereby maximize the external validity for this complex intervention, we included observational studies in addition to RCTs.[80] Moreover; the limited number of available RCTs underscores the need to rely on observational data. Given that several guidelines recommend CR after ACS,[6,11,12,63,64,77,78] and that CR is considered an established therapeutic approach in most industrialized countries, conducting RCTs in these settings raises ethical concerns. However, controlling and adjusting for confounding factors in CCS remains a major challenge, particularly within systematic reviews as discussed above. Even after adjusting for predefined confounding factors (mostly age, sex, comorbidities and cardiovascular risk factors), a selection bias is likely to persist, influenced by multiple individual, systemic or contextual aspects.[81]

The subsequent exclusion of CCS without a confounder-adjusted statistical model further reduces the number of studies available for the respective analyses of additional endpoints. Furthermore, only a few studies conducted subgroup analyses by sex and age. In fact, most strata were represented by a single study, which substantially limited the interpretability and robustness of the findings.

Conclusions

In ACS patients treated with modern revascularization approaches (PCI or CABG) and state-of-the-art pharmacotherapy, participation in structured, the attendance in multidisciplinary CR programmes is associated with a significant reduction in prognostically relevant clinical endpoints, including total mortality. Notably, these benefits appear to be largely consistent across age and gender subgroups. This evidence is based on observational data from prospective and retrospective cohort studies, representing a real-world scenario rather than the potentially super-selected patients usually included in RCTs, though generalizability beyond these populations and settings should be interpreted with caution. Despite using adjusted effect estimates, the findings may still be biased due to heterogeneity in confounding adjustment strategies across studies and incomplete reporting of methodological details, particularly regarding the handling of missing data. Additionally, due to heterogeneity across patient cohorts, rehabilitation associated

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interventions, and endpoints, more large-cohort studies with strict methodology and full reporting are needed to strengthen the evidence for CR-related improvement of patients' clinical prognosis. Potentially modulating variables, such as age, sex, frailty, socio-economic status, or mental health, should routinely be assessed and systematically evaluated in future cardiovascular secondary prevention trials.

Data availability

The extracted study characteristics of the included studies are given in *Table 1*, and all data relevant to the meta-analysis are available in the forest plots provided in the manuscript and supplementary materials.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Author contributions

AS, AxS, JAV, M-IM, J-PS, BR, J-CD conceptualized this update study. AxS and AS drafted the protocol, with essential contributions by M-IM and JAV. JAV and ACR performed the statistical analyses and methodically supervised the study. SS provided subgroup data. Study screening and data extraction were done by DN, GH, GP, AS, BB-W, BR, AxS, ET, JAV and ACR. MS and DN assessed the risk of bias in included studies. BR, AS, BBW, AxS, BS, JAV, ET, MS, M-IM drafted parts of the manuscript, and feedback was provided by all authors. AS served as principal investigator. All authors have approved the final manuscript.

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Systematic review registration

PROSPERO International prospective register of systematic reviews (registration number: CRD42025630588): https://www.crd.york.ac.uk/PROSPERO/view/CRD42025630588.

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