Exercise-based Cardiac Rehabilitation for patients with Angina Pectoris - a CaReMATCH Individual Participant Data Meta-analysis

Iris A. De Koning[1*], Joyce. M. Heutinck[1,2*], Benjamin J.R. Buckley[3,4], Grace O. Dibben [5], Gianluca Campo[6], Arto J. Hautala[7], Johan A. Snoek[8,9], Ralph Maddison[10], Núria Santaularia[11,12,13], Scott A. Lear[14,15], Julie Houle[16], Gregory Y.H. Lip[3,17], Robert Jan M. Van Geuns [18], Tom Vromen[19], Hareld M.C. Kemps[2,19], Rod S. Taylor[5,20**], Niels A. Stens[1,18**], Dick H.J. Thijssen[1,4**], CaReMATCH collaborators

* shared first co-authorship

** shared last co-authorship

[1] Department of Medical BioSciences, Radboud University Medical Center, Nijmegen, the Netherlands

[2] Department of Industrial Design, Eindhoven University of Technology, Eindhoven, the Netherlands

[3] Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool John Moores University, and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom

[4] Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, United Kingdom

[5] Primary Care and General Practice, University of Glasgow, Glasgow, United Kingdom

[6] Cardiology Unit, Azienda Ospedaliero Universitaria di Ferrara, Ferrara, Italy

[7] Faculty of Sport and Health Sciences, University of Jyvaskyla, Jyvaskyla, Finland.

[8] Isala Heart Center, Zwolle, the Netherlands

[9] Sports Medicine Department Isala, Zwolle, the Netherlands

[10] Institute for Physical Activity and Nutrition, Deakin University, Geelong, Victoria, Australia

[11] Cardiac Rehabilitation Integrated Practice Unit, Althaia Xarxa Assistencial Universitària de Manresa, Manresa, Spain

[12] Faculty of Health Sciences at Manresa, Universitat de Vic - Universitat Central de Catalunya (UVic-UCC), Manresa, Spain

[13] Central Catalonia Chronicity Research Group (C3RG), Institut de Recerca i Innovació en Ciències de la Vida i de la Salut a la Catalunya Central (IRIS-CC), Vic, Spain

[14] Faculty of Health Sciences, Simon Fraser University, Burnaby, Canada

[15] Division of Cardiology, Providence Health Care, Vancouver, Canada

[16] Nursing Department, Université du Québec à Trois-Rivières, Trois-Rivières City, Québec, Canada

[17] Danish Center for Clinical Health Services Research, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

[18] Department of Cardiology, Radboud University Medical Center, Nijmegen, the Netherlands

[19] Department of Cardiology, Maxima Medical Centre, Veldhoven, The Netherlands

[20] Robertson Centre for Biostatistics, University of Glasgow, Glasgow, United Kingdom

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Author for correspondence: Dick H.J. Thijssen, Department of Medical BioSciences (928), Radboud University Medical Center, P.O. Box 9101, 6500 HB Nijmegen, the Netherlands. Phone: +31 24 361 4273, Email: Dick.Thijssen@radboudumc.nl

Statement of authorship (CRediT): IdK, JMH, BJRB, GOD, GYHL, RJMvG, TV, HMCK, RST, NAS and DHJT conceptualized and designed the study. NAS and BJRB wrote the protocols, with feedback from IdK, JMH, GOD, GYHL, RST, and DHJT. GC, AJH, JAS, RM, NS, SAL and JH acquired and contributed individual participant data from their respective trial. Formal analyses, programming of code, data curation and visualization

of results were performed by NAS. Validation of data were performed by IdK, JMH and NAS. Interpretation of results were performed by IdK, JMH, BJRB, GOD, RST, NAS and DHJT. The first version of the manuscript was drafted by IdK and JMH, and feedback was provided by all other authors (BJRB, GOD, GC, AJH, JAS, RM, NS, SAL, JH, GYHL, RJMvG, TV, HMCK, RST, NAS, DHJT). All authors have approved the final manuscript. Those involved in the CaReMATCH collaborators were involved in the design and conduct of the respective trial included in CaReMATCH, and have been listed in the Supplemental Material.

INTRODUCTION

Angina pectoris (AP) is a common condition in Western society. Contemporary treatment of AP includes optimal medical therapy, which comprises preventive and anti-anginal medication to reduce morbidity and mortality, and improve health-related quality of life (HRQoL). When symptoms persist, revascularisation should be considered. However, trials have questioned the benefits of revascularisation on morbidity and mortality in patients with stable AP (1), highlighting the need to explore other therapeutic strategies. Interestingly, retrospective evidence showed lower risks for morbidity and mortality following ExCR compared to revascularisation (2). Randomised controlled trials (RCTs) on the contemporary benefits of ExCR in patients with AP are scarce, and are limited by small sample sizes and/or heterogeneity in design (3). Therefore, we aimed to provide contemporary estimates on the effect of ExCR in patients with AP.

METHODS

This study represents a secondary analysis of The Cardiac Rehabilitation Meta-Analysis of Trials in patients with coronary heart disease (CHD) using individual participant data (CaReMATCH) study. The main results of CaReMATCH have been described elsewhere (4). The ethics committee of the Radboudumc (Nijmegen, The Netherlands) waived the requirement for ethical approval (2022-15847). Included trials were approved by their local ethics committee.

For the present study, we exclusively selected individuals diagnosed with angina pectoris. RCTs were eligible if they 1) were published since 2010, 2) had a minimum of 6-months follow-up, and 3) compared ExCR to usual care without any structured exercise prescription. ExCR was supervised or non-supervised, either with or without additional psychosocial or educational intervention, and managed in an outpatient, community- or home-based setting. AP was defined as both stable and unstable angina, with most trials being unable to differentiate between the two. The primary outcome was HRQoL, and was measured using one of four validated questionnaires, including the Euro Quality of Life questionnaire (EQ-5D), Short Form 36-item health survey (SF-36), 15-dimensional quality of life questionnaire (15D), and Quality of Life Index – cardiac version. To combine

questionnaires, primary analyses on HRQoL were based on calculating standardized scores (i.e., Z-scores). To ease interpretation of HRQoL effect sizes, we performed secondary analyses by pooling data from questionnaires reporting HRQoL as utility indices (UIs).

Secondary outcomes included composite outcomes of 1) all-cause mortality and rehospitalisation, and 2) cardiovascular-related mortality and rehospitalisation. Time to event data were defined as the interval between randomisation and event or right censoring, whichever occurred first. We adopted one-stage linear and Cox mixed effects models as our primary analysis to quantify the overall effect of ExCR on HRQoL and time-to-event outcomes in the intention-to-treat population with complete follow-up data, respectively. Given the variation in trial follow-up timings, we pooled HRQoL data from the last follow-up timing with a maximum follow-up of 12 months. To evaluate the robustness of our results, we performed: 1) two-stage meta-analyses using random effects, and 2) omitted the largest trial from the analyses (Snoek et al.; **Supplemental References**). Data were presented as means and standard errors (SE), medians (interquartile range (IQR)) or frequencies (%) as appropriate. Reporting were performed in line with the Preferred Reporting Items for Systematic Review and Meta-Analyses of Individual Participant Data (PRISMA-IPD) statement (**eTable 1**).

RESULTS

Seven out of eight trials included in CaReMATCH involved individuals with AP (**Supplemental References**, **eFigure 1**, **eTable 2**), comprising 286 participants. Baseline characteristics were well-balanced across groups. Participants were frequently male (n=229, 80.1% men) and had a mean age of 68±8.9 years. Comorbidities were frequently present (hypertension: n=189, 66.1%, diabetes: n=62, 21.7%). Trials were published between 2012 and 2020, and were frequently performed in Europe (n=4). Delivery of ExCR was often home-based (n=4), or combined with center-based sessions (n=2), with all trials including aerobic exercise (**eTable 2**).

Compared to controls, participation in ExCR significantly increased HRQoL measured as Z-scores (standardised mean difference (SMD): 0.252, 95% confidence interval (CI): 0.037 to 0.467) (**Figure 1***).*

Comparable inferences were made when pooling questionnaires reporting UIs, although 95%CI's were wider (mean difference (MD): 0.031, 95% CI: -0.004, 0.067) (**eFigure 2**). During a median follow-up of 12.5 months (IQR: 11.3, 17.6), 38 events occurred related to mortality or hospitalisation (ExCR: n=16, control: n=22), with 29 events being cardiovascular-related (ExCR: n=10, control: n=19). Participation in ExCR did not significantly reduce the risk for all-cause (HR 0.60, 95% CI; 0.29 to 1.26) or cardiovascular-related mortality and hospitalisation (HR: 0.81, 95% CI; 0.41 to 1.62, **Figure 1**). observations were consistent across secondary analyses (**eTable 2**, **eFigure 3-4**).

DISCUSSION

In patients with AP, participation in ExCR significantly improved HRQoL compared to non-ExCR controls up to 12-month follow-up. The 2018 Cochrane review found no beneficial effects of ExCR on HRQoL compared to non-ExCR controls (3). Importantly, six out of the seven RCTs included in the 2018 Cochrane-review were published more than two decades ago. This may be explained by the observation that studies published in the past decade typically included a case-mix of patients with CHD rather than a specified population of AP. Pooling IPD from multiple trials bypasses this limitation, as we exclusively included trials conducted since 2010 and selected participants with AP only. Consequently, this led to a sample size of 286 participants that is substantially larger than previous RCTs, which varied between 24 to 113 participants (3). This enabled us to demonstrate that contemporary ExCR significantly improved HRQoL in patients with AP. This observation has significant clinical importance, especially since improving patients' HRQoL is one of the main goals in the treatment of chronic coronary syndromes (5).

Following our secondary aim, we did not observe significant effects of ExCR on all-cause or cardiovascular-related mortality or hospitalisation risk across 12-month follow-up. Potential explanations for this observation include the relatively low event rate in patients with AP, combined with the relatively small sample size and short follow-up. Supporting this, effect sizes of ExCR on all-cause and cardiovascular-related

hospitalisation and mortality observed in our IPD meta-analysis are comparable to those presented in meta-analyses on the effects of ExCR in patients with heart failure or CHD (6, 7). Therefore, ExCR may have the potential to reduce mortality and hospitalisation risk in patients with AP, although further research using a sufficiently powered sample size is needed.

Our study has some limitations. First, we were unable to distinguish between patients with stable and unstable AP in several included trials. Since the majority of included trials excluded conditions that interfere with performing physical activity, we expect that the majority of patients included stable AP. Second, no data on timing of revascularisation prior to ExCR was available, so we could not evaluate the clinically relevant question whether the timing of ExCR affected our outcomes. Future studies are recommended to specifically focus on the timing of ExCR in relation to the revascularisation procedure, as one may adopt ExCR as a post-revascularisation treatment, but also as a first-line approach prior to potential need for revascularisation.

CONCLUSION

This CaReMATCH IPD meta-analysis found contemporary ExCR participation to significantly improve HRQoL in patients with AP, although we did not observe significant effects on all-cause and cardiovascular-related mortality and hospitalisations over a 12-month follow-up. The improvement in HRQoL confirms the benefit of participating in ExCR, highlighting the need to further study the potential wider clinical effects of ExCR in patients with AP.

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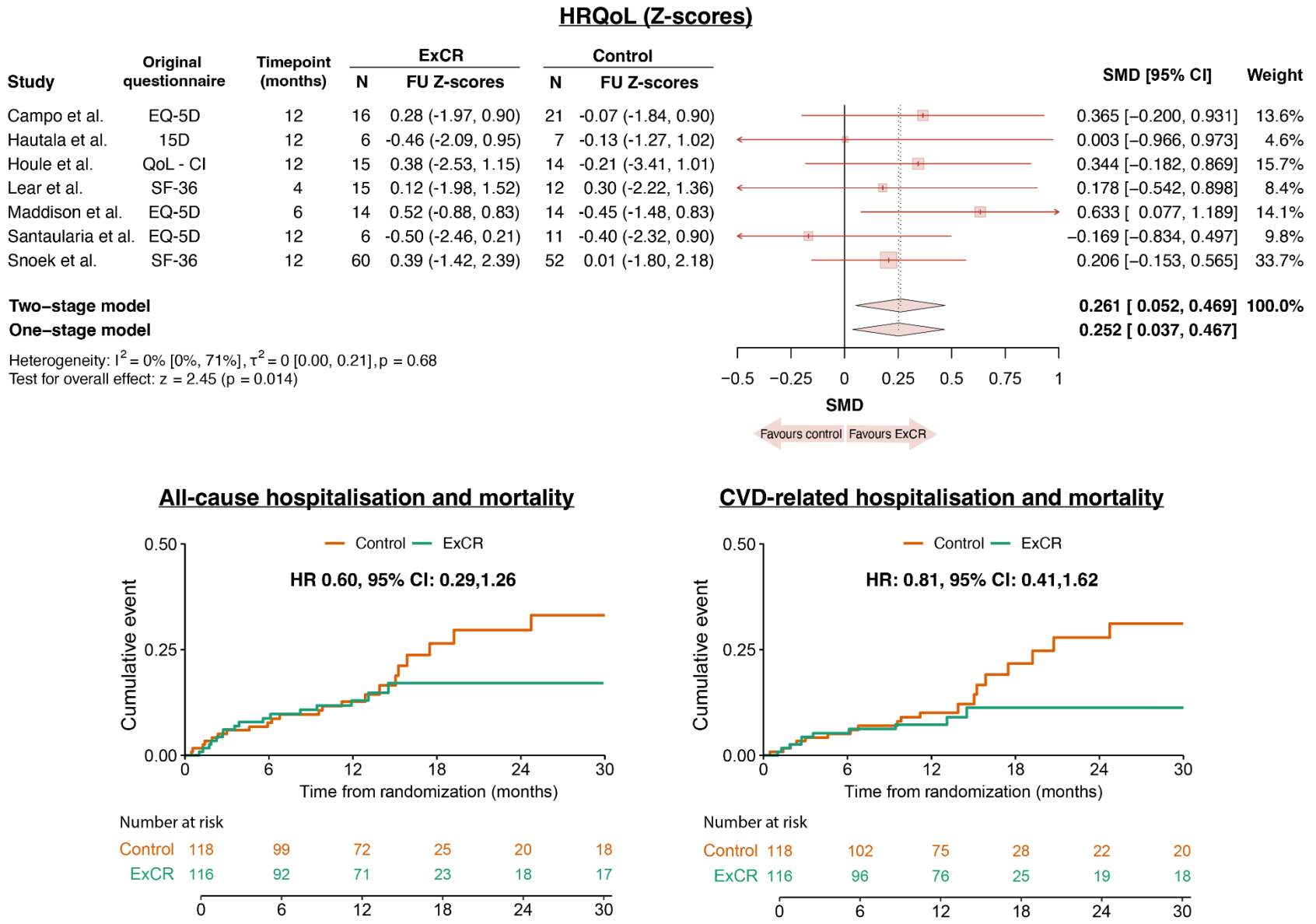
Table 1. Baseline characteristics of patients with angina pectoris randomized to either ExCR or non-ExCR controls.

	ExCR (n = 143)	**Controls (n = 143)**
Age, years (SE)	68.1 (0.74)	68.3 (0.85)
Sex, n women (%)	31 (21.7)	26 (18.2)
BMI, kg/m^2 (SE)	28.1 (0.37)	28.1 (0.41)
LVEF, % (SE)	53 (1.7)	57 (1.5)
Current smoker, n (%)	12 (8.4)	8 (5.6)
Medication use, n (%)		
Betablockers	94 (65.7)	100 (69.9)
ACE-inhibitors	64 (44.8)	68 (47.6)
ARB	14 (17.9)	16 (19.0)
Antilipids	132 (92.3)	128 (89.5)
Diuretics	45 (31.5)	29 (20.3)
Antithrombotics	139 (97.2)	136 (95.8)
Hypertension, n (%)	101 (79.5)	88 (68.2)
Dyslipidaemia, n (%)	103 (81.1)	99 (76.7)
Diabetes, n (%)	37 (26.1)	25 (17.5)
Revascularisation		
PCI, n (%)	71 (49.7)	72 (61.0)
CABG, n (%)	23 (24.2)	25 (21.2)
PCI + CABG, n (%)	6 (4.2)	4 (2.8)
No revascularisation, n (%)	20 (14.0)	26 (18.2)
Unknown, n (%)	23 (16.1)	25 (17.5)

Data were presented as means (mean difference (MD)) and standard errors (SE), medians (interquartile range (IQR)) or frequencies (%) as appropriate. ACE-inhibitors angiotensin-converting enzyme inhibitors, ARB angiotensin receptor blocker, BMI body mass index, ExCR exercise based cardiac rehabilitation, LVEF left ventricular ejection fraction, PCI percutaneous coronary intervention, CABG coronary artery bypass graft.

Figure 1. Effect of ExCR on HRQoL and time-to-event outcomes.



Multipanel figure presenting the effect of participation in ExCR on HRQoL (upper panel) and all-cause and cardiovascular-related hospitalisation and mortality (bottom panels). Compared to non-ExCR controls, participation in ExCR resulted in an increased HRQoL up to 12 months (SMD 0.252 [95% CI: 0.037, 0.467]). Additionally, participation in ExCR did not reduce the risk of all-cause or CVD-related hospitalisation and mortality (HR 0.60, 95%CI 0.29, 1.26; 0.81, 0.41, 1.62, respectively), although 95%CI were wide. Results were derived from linear and Cox mixed effects models respectively. Given the variation in trial follow-up timings, we pooled HRQoL data from the last follow-up timing with a maximum follow-up of 12 months. All models on HRQoL were corrected for the baseline HRQoL. HRQoL was expressed as standardized scores (i.e. Z-scores). CI confidence interval, CVD cardiovascular disease, EQ-5D Euro Quality of Life with 5 dimensions, ExCR exercise-based cardiac rehabilitation, FU follow-up, HRQoL health-related quality of life, HR hazard ratio, QoL CI quality of life – cardiac index, SF-36 Short Form 36-item health survey, SMD standardized mean difference, UI utility index, 15D 15-dimensional quality of life questionnaire.

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A CaReMATCH Individual Participant Data Meta-analysis

Supplemental material

CaReMATCH collaborators

Name	Affiliations
Alun D. Hughes, MD	- MRC Unit for Lifelong Health and Ageing at University College London, London, United Kingdom
Ajay S. Vamadevan, PhD	- Centre for Chronic Disease Control, New Delhi, India - Public Health Foundation of India, New Delhi, India
Ambalam M Chandrasekaran, MSc	- Centre for Chronic Disease Control, Public Health Foundation India, New Delhi, India.
Ambuj Roy, MD, DM	- All India Institute of Medical Sciences, New Delhi, India
Andrea Raisi, MSc	- Center for Exercise Science and Sport, University of Ferrara, Ferrara, Italy.
Anil R Jain, MS	- SAL Hospital and Medical Institute, Ahmedabad, India
Arnoud W.J. van't Hof, MD, PhD	- Department of Cardiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM), Maastricht, the Netherlands
Bhaskara Rao, MD	- CARE Hospital Heart institute, Vishakapatnam, India
Bishav Mohan, MD	- Dayanand Medical College, Ludhiana, India
Davinder S Chadha, MD	- Command Hospital, Bengaluru, India
Dimple Kondal, PhD	- Centre for Chronic Disease Control, New Delhi, India
Divya Soni, MSc	- Centre for Chronic Disease Control, New Delhi, India
Dorairaj Prabhakaran, MD, DM	- Centre for Chronic Disease Control, Public Health Foundation India, New Delhi, India. - Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK
Ed P. de Kluiver, PhD	- None
Elisabetta Tonet, MD	- Cardiology Unit, Azienda Ospedaliera Universitaria di Ferrara, Ferrara, Italy
Gianni Mazzoni, MD	- Center for Exercise Science and Sport, University of Ferrara, Ferrara, Italy.
Giovanni Grazzi, MD	- Center for Exercise Science and Sport, University of Ferrara, Ferrara, Italy.
Ian Roberts, PhD	- London School of Hygiene and Tropical Medicine, London, United Kingdom
Jabir Abdullakutty, DM	- Lisie Hospital, Kochi, India
Kalpana Singh, PhD	- Centre for Chronic Disease Control, New Delhi, India
Kaushik Chattopadhyay, MSc	- London School of Hygiene and Tropical Medicine, London, United Kingdom - University of Nottingham, Nottingham, United Kingdom.
Kavita Singh, PhD	- Centre for Chronic Disease Control, New Delhi, India
Kolli S Reddy, DM	- Public Health Foundation of India, New Delhi, India
Kushal Madan, PhD	- Sir Ganga Ram Hospital, New Delhi, India
Manjunath C Nanjappa, DM	- Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bengaluru, India
Nagamalesh U Madappa, DM	- M S Ramaiah Medical College and Hospital, Bengaluru, India
Nagraj Desai, DM	- JSS Medical College, Mysuru, India
Narsimhan Calambur, DM	- CARE Hospital, Hyderabad, India
Natrajan KU, DM	- Amrita Institute of Medical Sciences, Kochi, India
Nikhil Tandon, DM	- All India Institute of Medical Sciences, New Delhi, India
Nishi Chathurvedi, MD	- MRC Unit for Lifelong Health and Ageing at University College London, London, United Kingdom

	- Imperial College London, London, United Kingdom.
Paul Poirier, MD, PhD	- Faculty of Pharmacy, Université Laval - Institut universitaire de cardiologie et de pneumologie de Québec
Poppy Malinson, MSc	- London School of Hygiene and Tropical Medicine, London, United Kingdom.
Prabhavathi Bhat, DM	- Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bengaluru, India.
Pradeep A Praveen, PhD	- Centre for Chronic Disease Control, New Delhi, India - All India Institute of Medical Sciences, New Delhi, India
Prakash C Negi, DM	- Indira Gandhi Medical College, Shimla, India
Prasad MR, DM	- KLE Academy of Higher Education & Research/ College/university, Belgaum, India
Raghava Sarma, DM	- Lalitha Super Specialities Hospital, Kothapeta, India
Raji Devarajan, MSc	- Centre for Chronic Disease Control, New Delhi, India.
Ravindra K Tongia, DM	- Escorts Fortis Hospital, Jaipur, India
Rita Pavasini, MD	- Cardiology Unit, Azienda Ospedaliera Universitaria di Ferrara, Ferrara, Italy.
Sadananda S Kanchanahalli, DM	- Sri Jayadeva Institute of Cardiovascular Sciences and Research, Mysuru, India
Sanjay Kinra, MD, PhD	- Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK
Satish Patil, MD	- SRI BM.Patil medical college, Vijayapura, India.
Shah Ebrahim, MD	- London School of Hygiene and Tropical Medicine, London, United Kingdom.
Shankar Patil, MD	- SRI BM.Patil medical college, Vijayapura, India.
Sharad Chandra, DM	- King George's Medical University, Lucknow, India
Srikumar Swaminathan, DM	- Frontier Lifeline Hospital, Chennai, India
Srinivas Mallya, MS	- SAL Hospital and Medical Institute, Ahmedabad, India
Stefano Volpato, MD, MPH	- Department of Medical Science, University of Ferrara, Ferrara, Italy
Stuart Pocock, PhD	- London School of Hygiene and Tropical Medicine, London, United Kingdom
Subhash C Manchanda, DM	- Sir Ganga Ram Hospital, New Delhi, India
Subramaniam Natarajan, DM	- G.Kuppuswamy Naidu Memorial Hospital, Coimbatore, India
Sudhir R Naik, DM	- Apollo Hospital, Jubilee Hills, Hyderabad, India
Sunil Kumar, DM	- JSS Hospital, Mysuru, India

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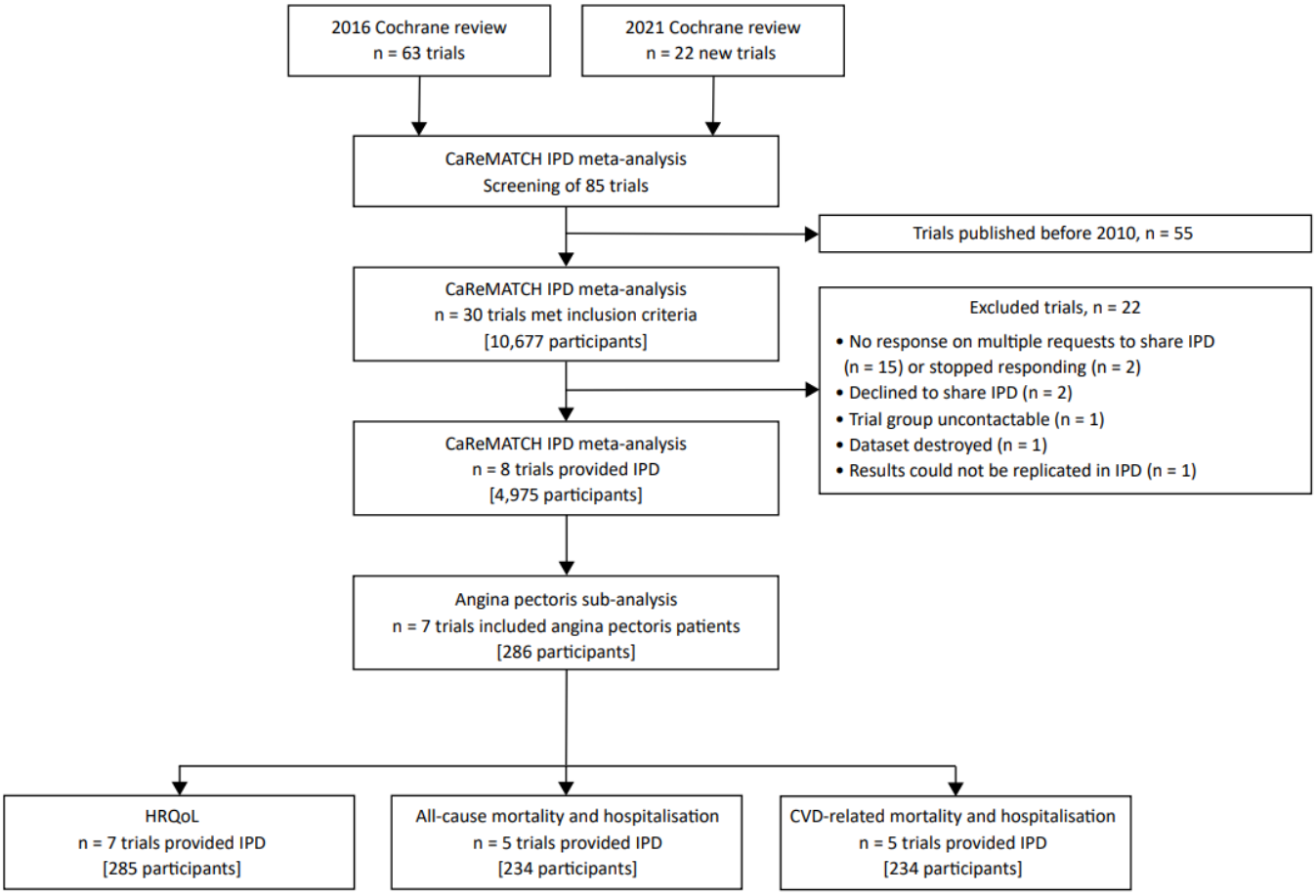
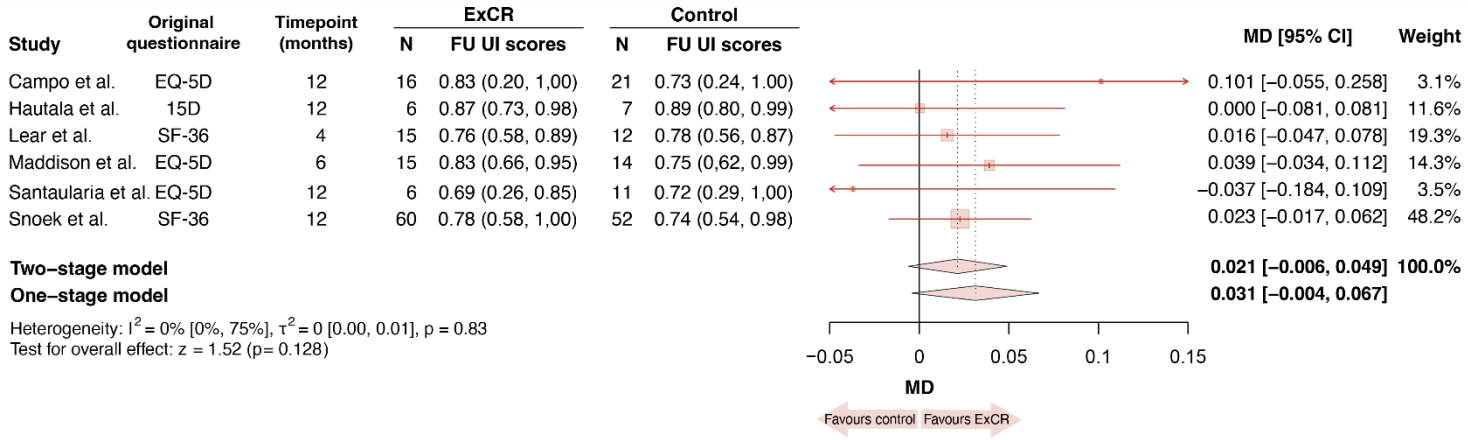
eFigure 1. PRISMA flowchart of search results and study selection.



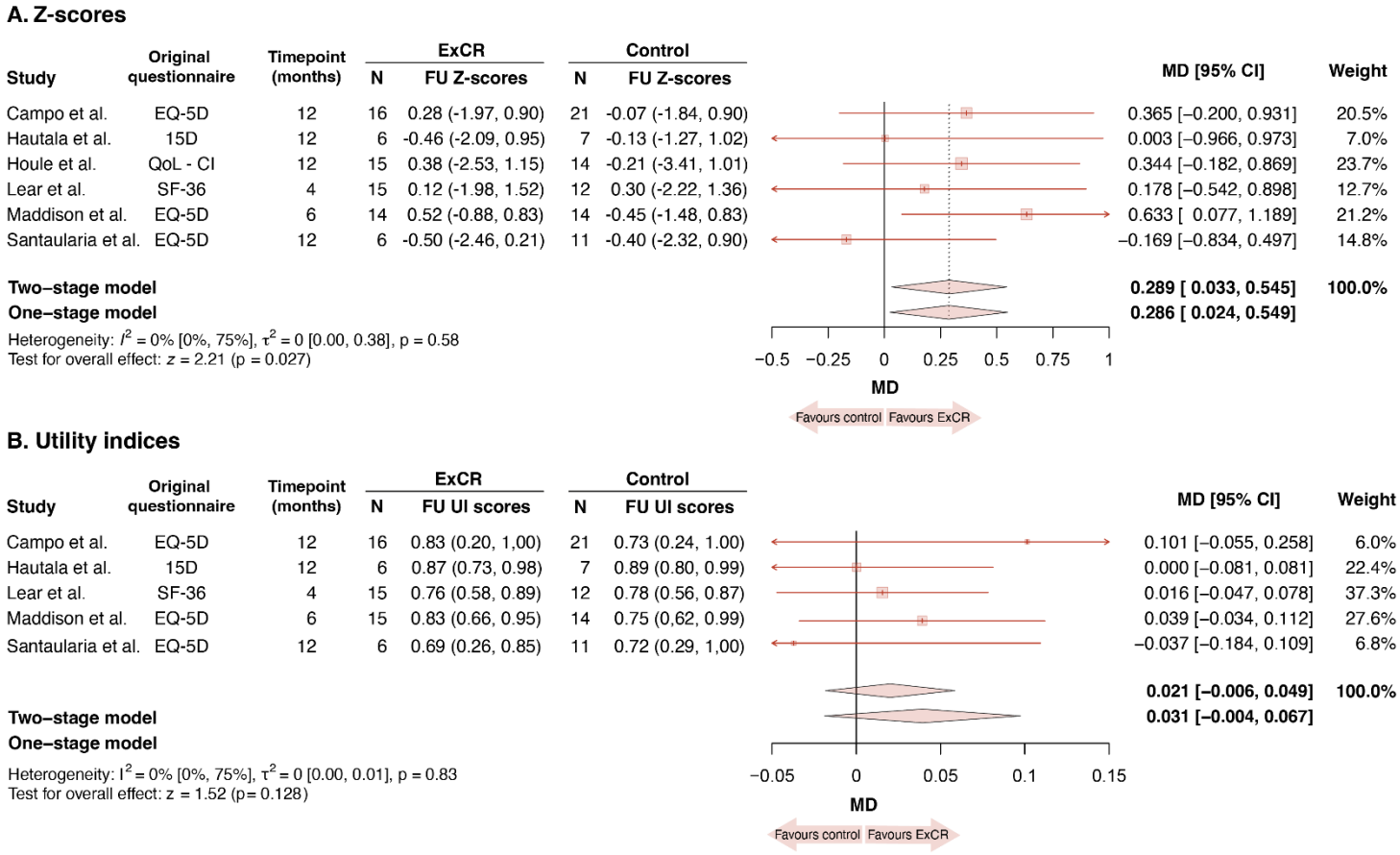
Out of 85 trials, 30 trials (n: 10,677) were eligible. IPD from 7 trials were analysed, comprising 286 participants. CVD cardiovascular disease, HRQoL health-related quality of life, IPD individual participant data.

eFigure 2. Effect of exercise-based cardiac rehabilitation on HRQoL up to 12 months of follow-up, expressed as utility indices.



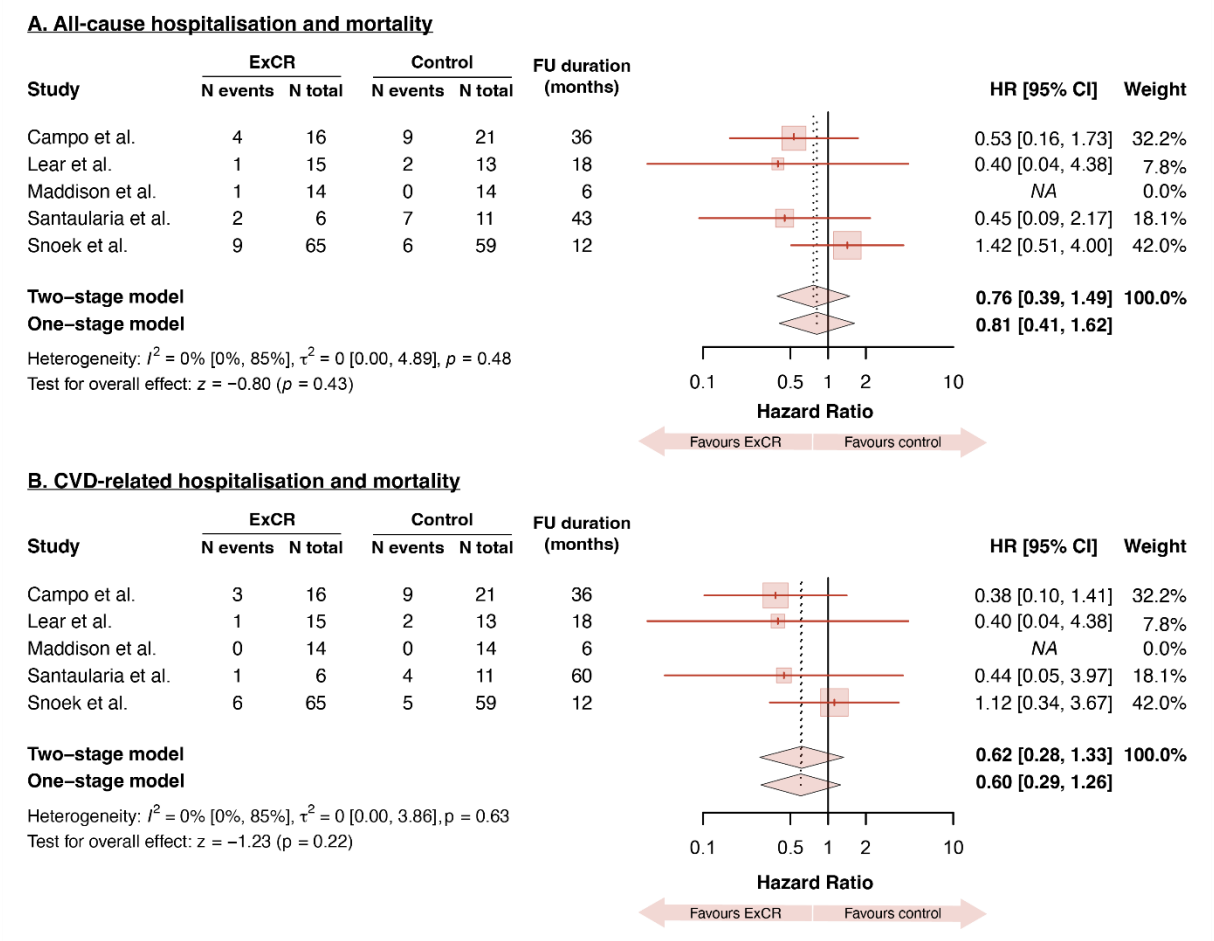
Forest plot highlighting that participation likely increases HRQol compared to controls, although 95% confidence intervals were wide. Given the variation in trial follow-up timings, we pooled HRQoL data from the last follow-up timing with a maximum follow-up of 12 months. All models were corrected for the baseline HRQoL. For each study, red horizontal lines represent the effect estimate and 95% confidence interval. Study weights were obtained via a random-effects meta-analysis and are presented as shaded squares and percentages. The red diamond represents the pooled estimate and its 95% confidence interval. CI confidence interval, EQ-5D Euro Quality of Life with 5 dimensions, ExCR exercise-based cardiac rehabilitation, FU follow-up, HRQoL health-related quality of life, MD mean difference, SF-36 Short Form 36-item.

eFigure 3. The effect of ExCR on HRQoL up to 12 months of follow-up, excluding Snoek et al.



Forest plot highlighting that, after excluding Snoek et al., participation in ExCR increased HRQol compared to controls. The forest plot is stratified for HRQoL as expressed by Z-scores (panel A) and UI-scores (panel B). Given the variation in trial follow-up timings, we pooled HRQoL data from the last follow-up timing with a maximum follow-up of 12 months. All models were corrected for the baseline HRQoL. For each study, red horizontal lines represent the effect estimate and 95% confidence interval. Study weights were obtained via a random-effects meta-analysis and are presented as shaded squares and percentages. The red diamond represents the pooled estimate and its 95% confidence interval. CI confidence interval, EQ-5D Euro Quality of Life with 5 dimensions, ExCR exercise-based cardiac rehabilitation, FU follow-up, HRQoL health-related quality of life, MD mean difference, SF-36 Short Form 36-item, UI utility index..

eFigure 4. Pooling effects of ExCR on all-cause and cardiovascular-related mortality and hospitalisation using two-stage models.



Forest plots on the effects of ExCR on all-cause (panel A) and CVD-related (panel B) hospitalisation and mortality. Effects were pooled using a two-stage framework and are presented alongside pooled effects from one-stage models as documented in our main results. In the two-stage framework, a Cox proportional hazards regression model was applied to each trial individually, and resulting ln-transformed hazard ratios were pooled in a random effects meta-analysis. As hazard ratios cannot reliably be computed in studies with zero events in one or both treatment groups, effect sizes for some individual trials could not be determined using two-stage models. For each study, red horizontal lines represent the effect estimate and 95% CI. Study weights were obtained via a random-effects meta-analysis and are presented as shaded squares and percentages. The red diamond represents the pooled estimate and its 95% CI. Heterogeneity and tests for the overall effect belong to the two-stage models. CI confidence interval, ExCR exercise-based cardiac rehabilitation, FU follow-up, HR hazard ratio, NA not applicable.

eTable 1. PRISMA-IPD Checklist of items to include when reporting a systematic review and meta-analysis of individual participant data (IPD)

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	Page 1
Abstract			
Structured summary	2	Provide a structured summary including as applicable:	NA
		Background: state research question and main objectives, with information on participants, interventions, comparators and outcomes.	
		Methods: report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias.	
		Results: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice.	
		Discussion: state main strengths and limitations of the evidence, general interpretation of the results and any important implications.	
		Other: report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	Pages 4
Methods			
Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	Main paper of CaReMATCH
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	Page 4, eFigure 1 Main paper of CaReMATCH

Identifying studies - information sources	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	eFigure 1 Main paper of CaReMATCH
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Main paper of CaReMATCH 2016 and 2021 Cochrane review
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	Page 4 Main paper of CaReMATCH 2016 and 2021 Cochrane review
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study). If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	Main paper
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardizing or translating variables within the IPD datasets to ensure common scales or measurements across studies.	Main paper
IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	Main paper
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	Main paper
Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	Pages 4-5

Synthesis methods	14	Describe the meta-analysis methods used to synthesize IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): • Use of a one-stage or two-stage approach. • How effect estimates were generated separately within each study and combined across studies (where applicable). • Specification of one-stage models (where applicable) including how clustering of participants within studies was accounted for. • Use of fixed or random effects models and any other model assumptions, such as proportional hazards. • How (summary) survival curves were generated (where applicable). • Methods for quantifying statistical heterogeneity (such as I^2 and τ^2). • How studies providing IPD and not providing IPD were analyzed together (where applicable). • How missing data within the IPD were dealt with (where applicable).	Page 5 Main paper of CaReMATCH
Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analyzed as potential effect modifiers, and whether these were pre-specified.	Main paper of CaReMATCH
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	Main paper of CaReMATCH 2016 and 2021 Cochrane reviews
Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	Page 5, Figure 1, eFigures 2-4, eTable 3
Results			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	eFigure 1
Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	eTable 2
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	Main paper of CaReMATCH
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	Main paper of CaReMATCH

Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot.	Figure 1
Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.	Figure 1
		When exploring variation in effects due to participant or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.	Main paper of CaReMATCH
		Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.	Pages 5-7
Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	Main paper of CaReMATCH
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarize the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	Page 6, Figure 1, eFigures 2-4, eTable 3
Discussion			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome.	Page 6
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	Page 6
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	Page 7
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	Page 7
Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	Page 7

eTable 2. Trial-level characteristics of the seven trials included in the CaReMATCH study that included patients with angina pectoris.

				ExCR							Control
First author (year) ***Acronym***	**Main study location**	**N Total**	**N Angina pectoris (N ExCR)**	**Primary exercise mode(s)**	**Resistance training**	**Reported components**	**Setting**	**Duration (weeks)**	**Frequency (sessions per week)**	**Intensity**	**Usual care definition**
Campo (2020) *HULK (1-3)*	ITA	235	37 (16)	Walking and calisthenics	No	Exercise, health education	Hybrid	26	≥3-4	RPE 11-13	To underline the importance of aerobic physical activity, participants had a 15-minute visit with a study doctor and received a detailed brochure on the benefits of physical activity.
Hautala (2017) *EFEX-CARE (4, 5)*	FIN	204	13 (6)	Walking, running, cycling or cross-country skiing	1-2x/week	Exercise, dietary counselling, check-up by physical therapist	Hybrid	Total: 52 Home: 52 Center: 26	4-5	RPE 12-15 (aerobic), RPE 13 (resistance)	Participants randomized to usual care did not receive any individually-tailored exercise prescriptions.
Houle (2012) (6)	CAN	65	34 (17)	Walking	No	Pedometer-based exercise, education and socio-cognitive intervention	Home	52	7	30 min walking at moderate intensity (~100 steps/min) or RPE 11-14	Participants received recommendations regarding physical activity, diet and medication, and had no restrictions to participate in a structured ExCR program or related healthcare professional. Participants received a blinded pedometer to assess exercise behavior every three months.
Lear (2014) (7-9)	CAN	78	30 (16)	Participants were able to choose their preferred mode of exercise	No	Exercise, education on health, exercise and diet	Home	16	3-5	50-80% of heart rate reserve	Participants received care from their primary care physician, and were provided internet-based resources and simple guidelines on safe exercising and healthy diet.

Maddison (2015) *HEART (10-12)*	NZL	171	31 (17)	Walking[a]	No	Exercise, SMS texts and pedometer to improve exercise adherence	Home	24	≥5	RPE 11-13 (early stages of program), RPE 13-15 (later stages of program)	All participants were free to participate in any other ExCR service or support that they wished to use, as well as encouragement to by physically active.
Santaularia (2017) (13-15)	ESP	85	17 (6)	Cycle ergometry	3x/week for 10 weeks	Exercise only	Centre	10	3	75-90% of peak HR, RPE 11-15 (aerobic) RPE 11-14 (resistance)	Participants received information on CVD risk factors. Participants were provided guidance on how to return to physical activity, and were provided instruction on breathing exercises and exercises to regain mobility, maintain muscle tone and peripheral circulation.
Snoek (2020) *EU-CaRe (16, 17)*	NL	179	124 (65)	Walking[a]	No	Exercise only	Home	26	5	RPE 12-13	Participants in the control group did not receive any form of cardiac rehabilitation but received locally-defined standard of care.

[a] *Walking was the primary exercise mode, but participants were allowed to deviate from walking and chose their preferred mode of exercise (e.g. cycling, swimming). ExCR exercise-based cardiac rehabilitation, HR heart rate, RPE rating of perceived exertion*

eTable 3. Baseline characteristics of patients with angina pectoris randomized to either ExCR or non-ExCR controls, Snoek et al. excluded.

	ExCR (n = 78)	Controls (n = 84)
Age, years (SE)	64.61 (11.12)	64.60 (12.13)
Sex, n women (%)	16 (20.5)	16 (19.0)
BMI, kg/m^2 (SE)	28.36 (0.52)	28.66 (0.54)
LVEF, % (SE)	53.56 (17.0)	56.87 (15.4)
Current smoker, n (%)	6 (7.7)	9 (10.7)
Medication use, n (%)		
Betablockers	54 (69.2)	54 (69.2)
ACE-inhibitors	42 (53.8)	42 (53.8)
ARB	14 (17.9)	14 (17.9)
Antilipids	72 (92.3)	72 (92.3)
Diuretics	26 (33.3)	26 (33.3)
Antithrombotics	74 (94.9)	74 (94.9)
Hypertension, n (%)	45 (72.6)	46 (65.7)
Dyslipidaemia, n (%)	46 (74.2)	51 (72.9)
Diabetes, n (%)	18 (23.4)	14 (16.7)
Revascularisation		
PCI, n (%)	31 (56.4)	29 (49.2)
CABG, n (%)	21 (38.2)	19 (32.2)

Data were presented as means (mean difference (MD)) and standard errors (SE), medians (interquartile range (IQR)) or frequencies (%) as appropriate.

ACE-inhibitors angiotensin-converting enzyme inhibitors, ARB angiotensin receptor blocker, BMI body mass index, ExCR exercise based cardiac rehabilitation, LVEF left ventricular ejection fraction, PCI percutaneous coronary intervention, CABG coronary artery bypass graft.

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