Title: Effects of cardiac rehabilitation on the severity of angina, health-related quality of life, and exercise capacity among adults living with microvascular angina: a systematic review and meta-analysis

Corresponding author: Joana Oliveira, j.oliveira@nhs.net

***Author names and affiliations*:**

Joana Oliveira[1], Stephen Paul Hoole[1], Peter Hartley[2,3], Morag Farquhar[4], Christi Deaton[3], Faye Forsyth[3], Allie Welsh[5]

[1]Royal Papworth Hospital, Cambridge, UK

[2]Department of Physiotherapy, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

[3]Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

[4]University of East Anglia, Norwich, UK

[5]Leeds Beckett University, Leeds, UK

Abstract

Aim: To evaluate the effect of exercise-based cardiac rehabilitation (CR) on the severity of angina, health-related quality of life (HRQoL), and exercise capacity in adults living with microvascular angina (MVA).

Methods: 14 online databases were searched to identify randomized controlled trials (RCTs) comparing adults with MVA receiving CR to those receiving a control intervention involving no exercise. Meta-analyses using random-effects models was used to calculate mean differences or standardized mean differences (SMD).

Results: Of 15,873 reports identified, five studies (222 participants) were included. Risk of bias for all outcomes were judged as 'some concerns' or 'high'. Mean ages ranged from 51 to 64 years, and 97.3% were women. Meta-analysis of CR's effect on the severity of angina was not feasible

due to limited data. Meta-analysis on HRQoL was conducted at the domain level of Short Form-36 questionnaire (2 RCTs; n=76) and on exercise capacity measured by peak VO_2 (3 RCTs; n=101). The HRQoL outcome was classified as 'very low certainty', indicating very little confidence in the effect estimates. The meta-analysis on exercise capacity showed a clinically meaningful change in peak VO_2 in favor of CR, with a 4.16mL/kg/min increase in peak VO_2 (SMD of 1.06, 95% CI -0.7 to 2.19, very low certainty).

Conclusions CR may improve exercise capacity in patients living with MVA compared to controls, however the evidence is very uncertain. High-quality RCTs are needed to rigorously determine the impact of CR on the severity of angina, HRQoL, and exercise capacity in patients living with MVA.

Word count: 248 words (max: 250 words)

Lay Abstract:

This review looked at how exercise-based cardiac rehabilitation affects chest pain, quality of life, and fitness levels in adults living with microvascular angina.

- Cardiac rehabilitation might help improve fitness levels in people living with microvascular angina, however, due to the quality of evidence, we are very uncertain about the true effect of cardiac rehabilitation.
- More high-quality studies are needed to better understand how cardiac rehabilitation affects chest pain, quality of life, and fitness levels in adults living with microvascular angina.

Word Count: 80 words (max 250 words)

Key words:

Microvascular angina
Coronary microvascular dysfunction
Syndrome X
ANOCA

INOCA

Angina

Health-related quality of life

Cardiac rehabilitation

Exercise capacity

Physical activity

Word count: 4,608

Introduction

Ischaemic heart disease (IHD) is the leading cause of premature disability and mortality, affecting an estimated 200 million people globally.[1,2] Angina, the most prevalent symptom of IHD, occurs due to a mismatch between myocardial oxygen demand and blood flow to the myocardial muscle, often during physical activity or emotional stress.[3] Historically, it has been linked to obstructive coronary artery disease.[3,4] However, up to 70% of patients undergoing coronary angiography are found to have no blood flow-limiting obstructions in the main coronary arteries.[3-5] Ischemia with non-obstructive coronary artery disease (INOCA) is a prevalent, chronic condition[3,6] associated with an increased risk of major adverse cardiovascular events and all-cause mortality compared to individuals without IHD[7]. Moreover, INOCA is more prevalent in women, with patients experiencing recurrent angina, low health-related quality of life (HRQoL), limited exercise capacity, and high levels of anxiety and depression, leading to frequent visits to healthcare services.[3,7-10]

Microvascular angina (MVA) is a clinical endotype of INOCA and is characterized by myocardial ischaemic symptoms due to structural or functional dysfunction in the coronary microvasculature, leading to impaired coronary flow reserve and/or reduced microcirculatory conductance.[5] Additionally, it can result from abnormal vasoconstriction of the coronary arterioles, causing dynamic arteriolar obstruction.[5] Despite increasing attention from the medical community, MVA remains difficult to diagnose, with no specific disease-modifying therapies and a poor prognosis.[5,11]

Guidelines for the management of stable coronary syndromes like MVA, advocate for lifestyle modifications and preventive strategies.[3,5] Notably, they endorse exercise-based cardiac rehabilitation (CR) programs for their favorable impact on heart health and coronary vasculature, cost-effectiveness, and low incidence of adverse events.[3] Comprehensive CR programs incorporate exercise training, health behavior change, lifestyle modifications, psychosocial health promotion, medical risk management, and long-term strategies.[5,12] These components aim to enhance HRQoL, prognosis, cardiac function, exercise capacity, and reduction of symptom burden.[19] Typically conducted over 10 to 12 weeks by a multidisciplinary team, CR programs can be delivered in various formats, including supervised or unsupervised settings, inpatient or outpatient programs, and home-based or hybrid approaches.[12,13]

Despite the benefits of CR for patients with obstructive coronary artery disease[14], there is limited evidence of its effects on patients living with MVA.[12,15] Scoping searches identified a review without meta-analysis on the effects of CR in patients living with MVA.[16] The review published in 2018, concluded that CR may reduce the severity of angina, improve myocardial perfusion defects as well as improve HRQoL and exercise capacity.[16] However, due to the absence of a systematic approach and the publication of new studies since, we conducted a robust comprehensive contemporary systematic review to synthesize current evidence on the effects of CR, including both exercise-only and comprehensive CR, on the severity of angina, HRQoL, and exercise capacity in adults living with MVA compared to either a control group or an active non-exercise intervention group (e.g., educational, behavioral, or psychological interventions). We also assessed adverse events and adherence to exercise-based CR in this population as secondary outcomes.

Methods

This systematic review was conducted according to the protocol registered on PROSPERO (Ref. CRD420233971119).[17] We undertook this meta-analysis following the Cochrane Handbook for Interventional Reviews, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Synthesis Without Meta-analysis (SWiM) guidelines.[18-20]

Eligibility criteria

We included adults (≥18 years) with a probable or definite diagnosis of MVA according to the COVADIS criteria for the diagnosis of MVA.[21] Participants with non-cardiac chest pain, unstable angina, or those scheduled for revascularization were excluded, as were individuals who had experienced a myocardial infarction, coronary artery bypass graft surgery, or percutaneous coronary intervention within three months before the trial. We excluded trials where less than 50% of the trial sample was composed of participants with probable or definitive diagnosis of MVA. We considered randomized controlled trials (RCTs) of any design, with no restrictions on language or date of publication.

Search strategy and study selection

We identified RCTs through systematic searches of diverse bibliographic databases, as described in our protocol.[17] We also conducted hand searches of references and citations, as per recommendations.[18] Searches were undertaken between January 2024 and February 2024 (all search strategies are provided in Supplementary material online, Table S1).

One reviewer (JO) retrieved, collated, and managed abstracts within the platform EndNote.[22] Two reviewers (JO & AW) pilot-tested the inclusion and exclusion criteria and screened the full-text reports in parallel, assessing them for eligibility. In cases of disagreement, consensus was reached through discussion and consultation with a third reviewer (SPH). Where necessary, authors were contacted via email up to two times, two weeks apart, to request further information.

Data extraction and risk of bias assessment

Study characteristics and outcome data were extracted by one reviewer (JO) using a piloted bespoke data extraction form. Information regarding the study design, methods, participants (baseline characteristics, key inclusion and exclusion criteria), interventions/comparators (including type, frequency, duration, and intensity of exercise training and nature of co-interventions), reported outcomes, outcome measurement details, and all the results compatible with each outcome domain were extracted. The second reviewer (AW) checked the extracted data for accuracy. Any disagreements were resolved by discussion.

We assessed the risk of bias independently, in duplicate, using version 2.0 of the Cochrane risk of bias tool for RCTs and used the risk of bias visualization tool (robvis) to create the risk of bias plots.[18,23,24] To assess the risk of bias due to missing studies or results within studies, we used the Risk Of Bias due to Missing Evidence (ROB-ME) tool to assess the risk of non-reporting.[25]

Data analysis

Data were analyzed following the Cochrane Handbook guidance.[18] We tabulated all reported outcome measures and identified the most frequently reported outcome measure for each outcome. The data available to be included in this systematic review were presented as continuous data, with the exception of one study[26] that reported dichotomous data on the severity of angina. Standard data transformations were performed to enable synthesis. When studies reported the same outcome measure in different ways (e.g. different units), we used the standardized mean difference (SMD) with 95% CI to pool the data. We re-expressed the results from SMD into units of a familiar measure using the formula MD=SMD x pooled standard deviation of the CR groups being compared.[18] For each outcome we used the minimal clinically important difference (MCID) thresholds, or ranges reported in the literature, to aid interpretation of the results. Where ≥2 trials reported the same validated HRQoL measures and domains, the outcomes were pooled separately by domain and reported as MD with 95% CI.

Analysis was undertaken using RevMan, version 5.4.1.[27] We explored heterogeneity by visually inspecting the forest plots, the Chi-Squared test (χ^2) of heterogeneity, and I^2 statistic. Significant heterogeneity was indicated by a p-value of <0.10 and/or an I^2 >50%. We performed random-effects meta-analyses with 95% CIs to account for between-study variability present due to the significant diversity of CR programs around the world.[28] For the outcomes not meta-analyzed, we conducted a narrative synthesis as per the SWiM guidelines, presenting an analysis of the relationships within and between studies, summarizing the effect estimates, and vote-counting.[20]

We planned to conduct subgroup analyses to explore whether the intervention effect estimate varied with different types of CR (exercise-only CR versus comprehensive CR) or with the dose of exercise. We planned to conduct a sensitivity analysis to explore and compare the results of

our meta-analysis when all eligible studies were included versus including only the eligible studies with low risk of bias.[18]

Summary of findings table

We used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework to assess the quality of the evidence.[18] We used GRADEpro GDT[29] to import the data from RevMan to compose the 'Summary of findings' table (Supplementary material online, Table S2) and the GRADE table (Supplementary material online, Table S3.).

Results

Study selection

Figure 1 summarizes the search and screening process. Database and clinical trial register searches yielded 21,132 titles and abstracts, identifying 15,873 unique records. Ten records were identified for full-text review, and five studies (six reports) met the inclusion criteria. Hand searches of reference lists and citations identified a further three articles for full-text review, which were ultimately excluded. Reasons for the exclusion of reports are presented in Supplementary material online, Table S4. No ongoing studies eligible against the criteria were identified in the clinical trial registries.

Study characteristics

Five studies involving 222 randomized participants were included.[26,30-34] Published between 2000 and 2020, the studies were conducted in Sweden,[30,31] UK,[32] Germany[34] and Iran[26,33]. All were single-center RCTs with small sample sizes (mean 44 participants, SD 17.7). Participants had a mean age of 51 to 64 years, and all were diagnosed with definitive MVA. Four studies included only women.[30-34] All studies compared CR to a control group (i.e. usual activities/care). Two studies included additional groups that underwent relaxation training, which involved a modified Jacobson's approach and autogenic training[31,33], with one of these trials, having a fourth group that received both CR and modified Jacobson's approach[33].

The intervention duration varied across the studies, with one study lasting four weeks[26], three studies lasting eight weeks[30-33], and another lasting 24 weeks[34]. Additionally, one study included an eight-week follow-up period after completing the CR program.[32] One study included a weight loss program alongside the CR program.[34] Most of the studies delivered comprehensive CR[30-34] in a clinical setting[26,30-32,34]. All the CR programs utilized aerobic exercise; two studies also used resistance training.[32,34] Each study measured at least one of the primary outcomes of this systematic review.[26,30-34] Regarding our secondary outcomes, three studies reported patient adherence,[31,32,34] and two reported adverse events.[30,31,34] The characteristics of the individual studies included are presented in Table 1.

Risk of bias and GRADE assessment

The risk of bias was judged to be 'some concerns' or 'high risk' (Figure 2.). Randomization methods and allocation concealment were poorly reported in three studies.[30,31,33] Due to the nature of the intervention, neither participants nor the staff delivering the intervention could be blinded, and only two studies reported blinding of outcome assessors.[26,34] Adherence to the intervention was not specified in half of the reports.[26,30,33] Only one study reported complete data for all participants.[33] For the remaining studies, missing data ranged from 6.7% to 12.5%, and all conducted a complete case analysis.[26,30-32,34] While the tool used to measure outcomes were appropriate, the assessment of the severity of angina and HRQoL could have been influenced by participants' knowledge of the intervention. No studies published the statistical analysis plan. Baseline characteristics were balanced across groups, and only one study[34] reported differences in care received besides the intervention (i.e. weight loss intervention in the CR group). The certainty of the evidence for all the primary outcomes was assessed as very low using the GRADE framework (Supplementary material online, Table S3.).

Results of Individual Studies

Results of the individual studies included in this systematic review are presented in (Supplementary material online, Tables S5, S6. and S7.)

Effect of CR on primary outcomes

Severity of angina

The severity of angina was assessed pre- and post-CR intervention in three studies.[26,32,33,35] Of these, only Asbury *et al*[32] and Rahmani *et al*[26] reported outcome data for the severity of angina. Narrative synthesis and vote counting were performed due to incomplete published data. Asbury *et al*[32] (n=58) reported a significant reduction in the severity of angina within the CR group after an eight-week CR program, demonstrating a 16% decrease (baseline: 2.0±0.8; post-intervention: 1.2±1.1, p=0.009). However, the study did not report the post-intervention results for the control group. In contrast, Rahmani *et al*[26] (n=28) observed no changes in the control group and non-significant improvements in the severity of angina scores in the CR group. The effect size between the CR and the control groups was -0.1 (95% CI -0.81 to 0.61), reflecting a non-clinically important difference of 2.5% favoring CR. Of the three studies, only Asbury *et al*[32] and Rahmani *et al*[26] reported outcome data for the severity of angina. Feizi *et al*[33] omitted reporting outcomes related to 'chest pain', despite this being outlined in their study protocol published in the Iranian Registry of Clinical Trials (IRCT201204099422N1)[35]. Furthermore, their protocol did not specify the method used to assess chest pain severity, leaving their approach unclear. This omission and lack of methodological detail further contribute to the incomplete data available for synthesis and analysis in this SR.

Using vote-counting, a trend was observed favoring CR in reducing the severity of angina among patients living with MVA. Methodological differences between the two studies included variations in pain assessment scales (5-point vs. 4-point scales), CR duration (eight vs. four weeks), and CR type (comprehensive vs. exercise-only).[26,32]

For this outcome, both studies had 'some concerns' for the risk of bias. The limited data available from these studies prevented the assessment of the risk of bias due to missing evidence. As per GRADE, we determined the quality of evidence to be of very low quality due to concerns about the risk of bias, inconsistency, indirectness, and imprecision.

HRQoL

The assessment of HRQoL was carried out and reported in four studies.[31-34] Three studies reported HRQoL using validated patient-reported outcome measures (PROMs) that measure

general health status: specifically the Sickness Impact Profile (SIP)[31] and the Short Form-36 (SF-36).[32,33] The other study reported HRQoL using a disease-specific validated PROM: the Seattle Angina Questionnaire (SAQ).[34] Calculating a summary score across these varied questionnaires is cautioned against in the literature[36], therefore, our meta-analysis for this outcome focused on the SF-36 domains using random-effects meta-analysis (two studies, n=76). A potential typographical error in the SF-36 social functioning domain reported by Asbury *et al*[32] led us to adopt a narrative synthesis approach for this domain. We assessed heterogeneity across the individual SF-36 domains. Due to heterogeneity observed in the forest plots of some domains, meta-analyses were only feasible for the physical role limitation, emotional role limitation, vitality, and general health domains. The pooled effect estimates across these four domains revealed a trend favoring the CR intervention (Figure 3). Effect sizes for physical role limitation (MD 22.34, 95% CI 0.58 to 44.10, two studies, n=76, I^2=75%) and emotional role limitation (MD 17.70, 95% CI 7.18 to 28.22, two studies, n=76, I^2=0%) exceeded the MCID reported in the literature of 18.75 and 16.7 respectively.[37] However, the CIs included values both below and above the MCID, suggesting variability and uncertainty in clinical significance. The vitality (MD 14.13, 95% CI -4.96 to 33.22, two studies, n=76, I^2=86%) and general health domains (MD 14.45, 95% CI -1.92 to 30.81, two studies, n=76, I^2=80%) did not achieve the MCID thresholds of 18.75 and 15, respectively.[37] In addition, the CIs also included values both below and above the MCID, suggesting high variability and uncertainty in clinical significance.

Narrative synthesis of physical functioning, mental health, and pain domains showed minimal changes in Asbury *et al*[32] results, with effect sizes of 2.70 (95% CI -8.90 to 14.30, n=58), -0.60 (95% CI -8.54 to 7.34, n=58), and -2.00 (95% CI -13.11 to 9.11, n=58), respectively. Feizi *at al*[33] results indicated substantial improvements with effect sizes of 28.12 (95% CI 16.44 to 39.80, n=18) for the physical functioning domain, 21.49 (95% CI 9.54 to 33.44, n=18) for the mental health domain, and 40.26 (95% CI 31.52 to 49.00, n=18) for the pain domain. Vote-counting revealed a trend favoring CR only for the physical functioning domain.

The SIP results showed a trend favoring CR. The SAQ results also favored CR, with improvements in angina stability (MD 18.70, 95% CI 3.73 to 33.67, n=56), disease perception (MD 12.90, 95% CI 1.86 to 23.94, n=56), and angina frequency domains (MD 11.80, 95% CI 2.49 to

21.11, n=56). More modest improvements were seen in treatment satisfaction (MD 8.10, 95% CI -2.58 to 18.78, n=56) and physical limitation (MD 6.40, 95% CI -3.65 to 16.45, n=56).

For HRQoL, the risk of bias was assessed as high in three studies[32-34] and 'some concerns'[31] in the other, with overall low ROB-ME judgment. As per GRADE, we determined the quality of evidence to be very low due to risk of bias, inconsistency, indirectness, and imprecision.

Exercise capacity

Exercise capacity was assessed in three studies using the cardiopulmonary exercise test (CPET), conducted either on a bicycle ergometer[30,34] or on a treadmill[26] with breath-by-breath gas exchange measurements. Two studies reported both peak aerobic capacity (peak VO_2) and peak work rate[30,34], while the third study only reported peak VO_2[26]. The reporting units for peak VO_2 varied across the studies, incorporating both relative and absolute measures. Due to the unavailability of participants' weight data, it was not feasible to convert the data to a common unit, therefore we conducted a meta-analysis by calculating the SMD. The pooled effect estimates favor CR (SMD 1.06, 95% CI -0.07 to 2.19, three studies, n=101, I^2=82%), see Figure 4. A SMD of 1.06 is estimated to be equivalent to a 4.16mL/kg/min change in peak VO_2. This is thought to be clinically meaningful based on established standards for other cardiovascular conditions, where a 1mL/kg/min increase is regarded as clinically significant.[38-41]

For exercise capacity, the risk of bias was assessed as 'some concerns' for two studies and 'high risk' for one, with overall low ROB-ME judgment. As per GRADE, we determined the quality of evidence to be very low due to concerns regarding risk of bias, inconsistency, and imprecision.

Effect of CR on secondary outcomes

Adverse events

Two studies reported adverse events related to exercise.[30,31,34] Erickson *et al*[30] and Tyni-Lenne *et al*[31] (two articles reporting on the same study) indicated that some participants experienced post-exercise fatigue. Bove *et al*[34] noted minor side effects from the dietary intervention in the CR group, with no adverse events directly attributable to exercise.

Patient adherence

Three studies reported patient adherence.[31,32,34] Tyni-Lenne *et al*[31] and Asbury *et al*[32] defined adherence as the mean percentage of total training sessions attended by the group, both reporting a 90% adherence rate. Bove *et al* defined adherence as attending more than half of the CR training sessions, with 77% of participants meeting this criterion.[34]

Sub-group analyses and sensitivity analysis

We were unable to perform the sub-analyses and sensitivity as planned due to insufficient numbers of studies included in this systematic review.

Discussion

This systematic review identified five RCTs comprising 222 participants with a diagnosis of MVA, comparing the effects of CR with a non-exercise control group. Meta-analysis showed that there may be an improvement in exercise capacity following CR compared with control, however, our confidence in the effect estimates is very limited. The impact of CR on the severity of angina and HRQoL remains highly uncertain.

The age distribution of the participants in the included studies are consistent with the typical demographic profile for the patients living with MVA, with the majority of the participants being women.[42] Of the participants across the included studies, 97.3% were women, with only one study[26] enrolling male participants. This skewed data mirrors the higher prevalence of MVA among peri-menopausal women, who account for approximately 70% of the patients with this condition.[42] The safety profile of CR in this population is well-supported by the absence of cardiovascular events reported by the included studies.[30,31,34] This highlights that CR, when conducted under appropriate clinical guidance and supervision, is a safe intervention across diverse patient groups, including those with MVA. Importantly, the predominance of women included in these studies, not only reflects the epidemiology of MVA, but also reinforces the safety of CR in women, including those of childbearing potential. While MVA remains a condition requiring tailored management, it does not seem to pose additional risks during CR compared to other cardiac conditions.[43] This suggests that patients living with MVA may safely participate in CR programs while reaping the benefits of improved cardiovascular health, reduced symptoms, and enhanced HRQoL. Furthermore, women often display distinct characteristics in the

presentation and pathophysiology of coronary artery disease, requiring tailored approaches.[44] The predominance of women in our systematic review demonstrates that inclusive enrolment in cardiovascular research is possible. Such inclusivity is essential to enhancing the generalizability and applicability of emerging evidence, especially given the variations in disease prevalence, response to treatment, and health outcomes between sexes and among diverse populations.[45] Together, these findings highlight the importance of sex-specific and condition-specific approaches in cardiovascular care, ensuring that interventions such as CR are both safe and effective for diverse patient populations.

The 2024 ESC guidelines for chronic coronary syndromes note that INOCA patients represent only 25% of those with angina and nonobstructive coronary arteries (ANOCA), highlighting diagnostic challenges.[5] ANOCA is often missed by conventional non-invasive imaging, which is more effective at detecting segmental than diffuse ischemia.[5] Our meta-analysis included studies adhering to the COVADIS criteria[21], requiring ischemia demonstration through conventional tests. While ensuring methodological rigor, this possibly excluded patients with diffuse ischemia, contributing to the included studies' small sample sizes. Further research should also focus on more inclusive diagnostic approaches, such as invasive coronary function testing, to better capture the full spectrum of ANOCA.

Adherence to cardiac CR programs is critical for their effectiveness in improving cardiovascular outcomes. The British Heart Foundation reports a 77% adherence rate for CR in the UK[46], and the EUROASPIRE IV survey found that 81% of the patients attended at least half of the program sessions[47]. Bove *et al*[34] study, which had a 24-week intervention, reported a similar adherence rate of 77%. However, the two other studies[31,32], both with eight-week interventions, documented a 90% adherence rate. Although the reported adherence rates are promising, uncertainty remains regarding engagement with exercise and other lifestyle changes implemented during the CR program after the program completion. The literature reports a gradual decline in engagement over time, highlighting the challenge of maintaining long-term participation, which is essential for achieving the full benefits of CR. Initial motivation may drive higher attendance early on, yet physical barriers like lack of transport, financial costs, or availability of phase IV CR in the community, may limit adherence in the longer term.[48] Personal barriers such as embarrassment to participating in group exercise, misunderstanding the purpose of CR, or lack of perceived

improvement in symptoms or risk factors may also contribute to the observed decline in adherence over time.[48] Moreover, the setting in which CR sessions are delivered may influence adherence rates. Implementing a mixed-setting approach may improve flexibility and accessibility, potentially leading to greater adherence.[49]

Three studies reported on exercise capacity, all using CPET to assess this outcome. CPET is widely regarded as the gold standard for measuring peak VO_2 and overall exercise capacity, as it provides a comprehensive evaluation of the integrated functions of the cardiovascular, pulmonary, and muscular systems during physical activity.[50] Its non-invasive nature, along with the ability to objectively measure key physiological parameters, makes CPET a reliable and reproducible tool in clinical research. This is particularly evident when the outcome assessors are blinded to minimize bias, as was the case in two of the included studies[26,34]. Whilst the certainty of the evidence was categorized as 'very low', the effect size estimate of 4.16 mL/kg/min in peak VO_2, in favor of CR, aligns with previous reviews[16,51] demonstrating the effectiveness of CR in improving the exercise capacity of cardiac patients.

Most of the studies included in this systematic review delivered comprehensive CR[30-34], with two studies including additional groups that received relaxation training alone or in combination with comprehensive CR. Although the studies describe the components of exercise and relaxation training, they lack descriptions of other key elements of comprehensive CR, such as lifestyle modifications and risk factor management. Given the absence of specific disease-modifying therapies for MVA, comprehensive CR that emphasizes lifestyle modifications and risk factor management may be particularly beneficial for patients living with MVA.[5] Educating patients about adopting healthy behaviors — such as engaging in regular physical activity, smoking cessation, following a Mediterranean or whole-food, plant-based diet, maintaining good sleep hygiene, and managing stress — may empower them to develop personalized strategies for symptoms and trigger management, while improving overall cardiovascular health and general well-being. These lifestyle interventions are pivotal in managing risk factors such as hypertension, diabetes, and hyperlipidemia, which can lead to improved outcomes and symptom control in patients living with MVA.[5] Furthermore, recent qualitative research highlights the value of coordinated care among healthcare professionals in creating comprehensive strategies that address not only the physical aspects of living with MVA but also the psychological and emotional dimensions.[52] This

multifaceted approach may help patients understand their unique symptoms, triggers, and comorbidities, fostering a sense of agency in their care. By considering the full spectrum of patients' experiences and needs, healthcare providers can significantly enhance the effectiveness of comprehensive CR and improve overall health outcomes for individuals living with this condition.

Limitations of the review process and evidence

The generalizability of this review is significantly constrained by the limited number of eligible studies and their small sample sizes. This restriction hinders the ability to draw conclusions applicable to diverse populations and clinical settings. Additionally, smaller sample sizes often lead to reduced statistical power, which affects the reliability of findings and their applicability beyond the studied cohorts. The quality of evidence was graded as very low certainty for all the primary outcomes according to the GRADE framework. These judgments indicate that we have very limited confidence in the effect estimates calculated, suggesting that further research might significantly alter the effect estimates presented by our meta-analysis.

Our review process, although thorough and methodical, had its limitations. We followed our pre-published protocol to minimize bias during the systematic review.[17] We conducted a comprehensive literature search, including published and unpublished studies, and contacted authors for additional information. However, by excluding before-and-after studies to enhance precision, we may have overlooked important evidence, narrowing the scope of our analysis. Furthermore, while we did not restrict our search to English-language articles, the absence of translations for all foreign-language studies may have led to an incomplete representation of this body of literature. This limitation could have narrowed the scope of evidence included in our systematic review, thereby affecting the comprehensiveness and generalizability of our conclusions.

Data pooling in systematic reviews is a valuable method for synthesizing available evidence; however, it has notable limitations, particularly when the available studies are small-scale, and employ diverse PROMs. Although HRQoL was the most commonly reported outcome in the included studies, the variability in PROMs used and the recommendation to not calculate a summary score across these PROMs, resulted in the inclusion of only half of the studies reporting

this outcome in the meta-analysis. This highlights the challenge of reconciling diverse PROMs, which limits the synthesis and interpretation of findings, and emphasizes the urgent need for a core outcome set in future cardiovascular research.[53]

Implications for clinical practice and future research

We remain very uncertain as to the effect of CR compared to usual care on patients living with MVA. The current evidence base is limited, highlighting the urgent need for further research to establish the potential benefits and risks of CR specifically for this population through adequately powered RCTs. These trials should aim to include robust endpoints and a representative sample that reflects the differences in disease prevalence and treatment response between sexes, thereby enhancing the generalization of the findings. Moreover, future research should prioritize the evaluation of CR programs with sufficient duration to address the well-documented challenges of maintaining long-term adherence, which is critical for achieving the full benefits of CR. Furthermore, the incorporation of standardized PROMs in cardiovascular research would improve the comparability and robustness of evidence across studies, facilitating a more comprehensive understanding of CR's impact on patients living with MVA.

Conclusion

CR may improve exercise capacity in patients living with MVA in comparison to control; however, the evidence is very uncertain. Limited evidence exists for CR's effects on the severity of angina and HRQoL. High-quality RCTs are needed to rigorously determine the impact of CR on the severity of angina, HRQoL and exercise capacity in patients living with MVA.

Acknowledgments

R&D Department from the Royal Papworth Hospital NHS Foundation Trust allowed JO to undertake the fellowships part-time.

Funding

This systematic review was funded by NHS England and the National Institute for Health and Care Research (ICA Pre-doctoral Clinical and Practitioner Academic Fellowship, grant award NIHR301932: JO) and Cambridge Clinical Research Fellowship (research fellowship, grant award 90042: JO) funded by the Addenbrooke's Charitable Trust and Cambridge Biomedical Centre.

The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health and Care Research, the Department of Health and Social Care, the Addenbrooke's Charitable Trust, or the Cambridge Biomedical Centre.

Conflict of interest

None declared

Authors contributions

JO contributed to the conception and design, acquisition of data, analysis and interpretation of data, drafted the article, revised the draft critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

SPH contributed to the conception and design, analysis and interpretation of data, revised the draft critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

PH contributed to the analysis and interpretation of data, revised the draft critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

MF contributed to the conception and design, revised the draft critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

CD contributed to the conception and design, revised the draft critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

FF contributed to the analysis and interpretation of data, revised the draft critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

AW contributed to the conception and design, acquisition of data, analysis and interpretation of data, revised the draft critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Figures

Figure 1. PRISMA flowchart for the selection of eligible studies

Figure 2. Risk of bias summary: reviewers' judgments about each risk of bias item for each included study and outcome

Figure 3. Comparison 1 Exercise-based cardiac rehabilitation versus control for MVA, Primary outcome 2 HRQoL

Figure 4. Comparison 1 Exercise-based cardiac rehabilitation versus control for MVA, Primary outcome 3 Exercise Capacity

Figure legends

Not applicable – no further explanation is needed beyond the figure title.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request. Appendices (supplementary material)

Tables

Table 1. Characteristics of included articles

References

1. Collaborators GBDCoD. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;**392**:1736-1788. doi: 10.1016/S0140-6736(18)32203-7
2. British Heart Foundation. Global Heart & Circulatory Diseases Factsheet. https://www.bhf.org.uk/what-we-do/our-research/heart-statistics (Accessed 27/06/2024)
3. Kunadian V, Chieffo A, Camici PG*, et al.* An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. *Eur Heart J* 2020;**41**:3504-3520. doi: 10.1093/eurheartj/ehaa503
4. Aribas E, Roeters van Lennep JE, Elias-Smale SE*, et al.* Prevalence of microvascular angina among patients with stable symptoms in the absence of obstructive coronary artery disease: a systematic review. *Cardiovasc Res* 2022;**118**:763-771. doi: 10.1093/cvr/cvab061
5. Vrints C, Andreotti F, Koskinas KC*, et al.* 2024 ESC Guidelines for the management of chronic coronary syndromes. *Eur Heart J* 2024. doi: 10.1093/eurheartj/ehae177
6. Samuels BA, Shah SM, Widmer RJ*, et al.* Comprehensive Management of ANOCA, Part 1-Definition, Patient Population, and Diagnosis: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2023;**82**:1245-1263. doi: 10.1016/j.jacc.2023.06.043
7. Jespersen L, Hvelplund A, Abildstrom SZ*, et al.* Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. *Eur Heart J* 2012;**33**:734-744. doi: 10.1093/eurheartj/ehr331
8. Jespersen L, Abildstrom SZ, Hvelplund A, Prescott E. Persistent angina: highly prevalent and associated with long-term anxiety, depression, low physical functioning, and quality of life in stable angina pectoris. *Clin Res Cardiol* 2013;**102**:571-581. doi: 10.1007/s00392-013-0568-z

9. Johnson BD, Shaw LJ, Buchthal SD*, et al.* Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease: results from the National Institutes of Health-National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation* 2004;**109**:2993-2999. doi: 10.1161/01.CIR.0000130642.79868.B2
10. Olson M, Kelsey S, Matthews K*, et al.* Symptoms, myocardial ischaemia and quality of life in women: Results from the NHLBI-sponsored WISE Study. *European Heart Journal* 2003;**24**:1506-1514. doi: 10.1016/s0195-668x(03)00279-3
11. Smilowitz NR, Prasad M, Widmer RJ*, et al.* Comprehensive Management of ANOCA, Part 2—Program Development, Treatment, and Research Initiatives: JACC State-of-the-Art Review. *Journal of the American College of Cardiology* 2023;**82**:1264-1279. doi: https://doi.org/10.1016/j.jacc.2023.06.044
12. British Association for Cardiovascular Prevention and Rehabilitation. The BACPR Standards and Core Components for Cardiovascular Disease Prevention and Rehabilitation

https://www.bacpr.org/__data/assets/pdf_file/0021/64236/BACPR-Standards-and-Core-Components-2023.pdf] (Accessed 27/06/2024)
13. Anderson L, Dewhirst AM, He J*, et al.* Exercise-based cardiac rehabilitation for patients with stable angina. *Cochrane Database of Systematic Reviews* 2017. doi: 10.1002/14651858.Cd012786
14. de Koning IA, Heutinck JM, Vromen T*, et al.* Cardiac rehabilitation vs. percutaneous coronary intervention for stable angina pectoris: a retrospective study of effects on major adverse cardiovascular events and associated healthcare costs. *European Journal of Preventive Cardiology* 2024;**31**:1987-1990. doi: 10.1093/eurjpc/zwae164
15. Dibben G, Faulkner J, Oldridge N*, et al.* Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2021;**11**:CD001800. doi: 10.1002/14651858.CD001800.pub4
16. Kissel CK, Nikoletou D. Cardiac Rehabilitation and Exercise Prescription in Symptomatic Patients with Non-Obstructive Coronary Artery Disease—a Systematic Review. *Current Treatment Options in Cardiovascular Medicine* 2018;**20**. doi: 10.1007/s11936-018-0667-2
17. Oliveira J, Welsh A. Exercise-based cardiac rehabilitation effects on severity of angina, health-related quality of life and exercise capacity in adults with a probable or definitive diagnosis of microvascular angina: protocol for a systematic review and planned meta-analysis. *PROSPERO CRD42023397119* 2023. doi:
18. Higgins J, Thomas J, Chandler J*, et al.* Cochrane Handbook for Systematic Reviews of Interventions. In: Cochrane; 2023.
19. Page MJ, Moher D, Bossuyt PM*, et al.* PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ* 2021:n160. doi: 10.1136/bmj.n160
20. Campbell M, McKenzie JE, Sowden A*, et al.* Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ* 2020;**368**:l6890. doi: 10.1136/bmj.l6890

21. Ong P, Camici PG, Beltrame JF*, et al.* International standardization of diagnostic criteria for microvascular angina. *International Journal of Cardiology* 2018;**250**:16-20. doi: 10.1016/j.ijcard.2017.08.068
22. The EndNote Team. EndNote Reference Manager. In. Philadelphia, PA: Clarivate; 2013.
23. Sterne JAC, Savovic J, Page MJ*, et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898. doi: 10.1136/bmj.l4898
24. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. https://mcguinlu.shinyapps.io/robvis/ (Accessed 15/03/2024)
25. Page MJ, Sterne JAC, Boutron I*, et al.* Risk Of Bias due to Missing Evidence (ROB-ME): a new tool for assessing risk of non-reporting biases in evidence syntheses. https://www.riskofbias.info/welcome/rob-me-tool
26. Rahmani R, Niyazi S, Sobh-Rakhshankhah A*, et al.* Effects of a Cardiac Rehabilitation Program Versus Usual Care on Cardiopulmonary Function in Patients With Cardiac Syndrome X. *Journal of Cardiopulmonary Rehabilitation and Prevention* 2020;**40**:41-47. doi: 10.1097/hcr.0000000000000439
27. Nordic Cochrane Centre. Review Manager (RevMan5). In: Nordic Cochrane Centre, The Cochrane Collaboration; 2020.
28. Supervia M, Turk-Adawi K, Lopez-Jimenez F*, et al.* Nature of Cardiac Rehabilitation Around the Globe. *EClinicalMedicine* 2019;**13**:46-56. doi: 10.1016/j.eclinm.2019.06.006
29. GRADEpro GDT. GRADEpro Guideline Development Tool. In: McMaster University and Evidence Prime; 2021.
30. Eriksson BE, Tyni-Lenne R, Svedenhag J*, et al.* Physical training in Syndrome X: physical training counteracts deconditioning and pain in Syndrome X. *Journal of the American College of Cardiology* 2000;**36**:1619-1625. doi:
31. Tyni-Lenne R, Stryjan S, Eriksson B, Berglund M, Sylven C. Beneficial therapeutic effects of physical training and relaxation therapy in women with coronary syndrome X. *Physiother Res Int* 2002;**7**:35-43. doi: 10.1002/pri.239
32. Asbury EA, Slattery C, Grant A*, et al.* Cardiac rehabilitation for the treatment of women with chest pain and normal coronary arteries. *Menopause* 2008;**15**:454-460. doi: 10.1097/gme.0b013e31815982eb
33. Feizi A, Ghaderi C, Dehghani MR, Khalkhali HR, Sheikhi S. Effect of phase III cardiac rehabilitation and relaxation on the quality of life in patients with cardiac syndrome X. *Iranian Journal of Nursing and Midwifery Research* 2012;**17**:547-552. doi:
34. Bove KB, Nilsson M, Pedersen LR*, et al.* Comprehensive treatment of microvascular angina in overweight women - a randomized controlled pilot trial. *PloS one* 2020;**15**:e0240722. doi: https://dx.doi.org/10.1371/journal.pone.0240722
35. Feizi A. Effect of cardiac rehabilitation and relaxation on the quality of life in patients with cardiac syndrome x in hospitals affiliated to Urmia University of Medical Sciences. https://irct.behdasht.gov.ir/trial/9934
36. Carr A. Adult Measures of Quality of Life: The Arthritis Impact Measurement Scales (AIMS/AIMS2), Disease Repercussion Profile (DRP), EuroQoL, Nottingham Health Profile (NHP), Patient Generated Index (PGI), Quality of Well-Being Scale (QWB), RAQoL, Short Form-36 (SF-36), Sickness Impact Profile (SIP), SIP-RA, and World Health

Organization's Quality of Life Instruments (WHOQoL, WHOQoL-100, WHOQoL-Bref). *Arthritis & Rheumatism* 2003;**49**:S113-S133. doi: 10.1002/art.11414
37. Wyrwich KW, Spertus JA, Kroenke K*, et al.* Clinically important differences in health status for patients with heart disease: an expert consensus panel report. *Am Heart J* 2004;**147**:615-622. doi: 10.1016/j.ahj.2003.10.039
38. Mikkelsen N, Cadarso-Suárez C, Lado-Baleato O*, et al.* Improvement in VO2peak predicts readmissions for cardiovascular disease and mortality in patients undergoing cardiac rehabilitation. *European Journal of Preventive Cardiology* 2020;**27**:811-819. doi: 10.1177/2047487319887835
39. Kavanagh T, Mertens DJ, Hamm LF*, et al.* Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. *Circulation* 2002;**106**:666-671. doi: 10.1161/01.cir.0000024413.15949.ed
40. Swank AM, Horton J, Fleg JL*, et al.* Modest increase in peak VO2 is related to better clinical outcomes in chronic heart failure patients: results from heart failure and a controlled trial to investigate outcomes of exercise training. *Circ Heart Fail* 2012;**5**:579-585. doi: 10.1161/CIRCHEARTFAILURE.111.965186
41. Keteyian SJ, Brawner CA, Savage PD*, et al.* Peak aerobic capacity predicts prognosis in patients with coronary heart disease. *Am Heart J* 2008;**156**:292-300. doi: 10.1016/j.ahj.2008.03.017
42. Ford TJ, Yii E, Sidik N*, et al.* Ischemia and No Obstructive Coronary Artery Disease: Prevalence and Correlates of Coronary Vasomotion Disorders. *Circ Cardiovasc Interv* 2019;**12**:e008126. doi: 10.1161/CIRCINTERVENTIONS.119.008126
43. Thompson PD, Franklin BA, Balady GJ*, et al.* Exercise and Acute Cardiovascular Events. *Circulation* 2007;**115**:2358-2368. doi: doi:10.1161/CIRCULATIONAHA.107.181485
44. Taqueti VR. Sex Differences in the Coronary System. In: Kerkhof PLM, Miller VM, eds. Sex-Specific Analysis of Cardiovascular Function. Cham: Springer International Publishing; 2018, p257-278.
45. Cho L, Vest AR, O'Donoghue ML*, et al.* Increasing Participation of Women in Cardiovascular Trials: JACC Council Perspectives. *J Am Coll Cardiol* 2021;**78**:737-751. doi: 10.1016/j.jacc.2021.06.022
46. British Heart Foundation. The National Audit of Cardiac Rehabilitation. Annual Statistical Report https://www.bhf.org.uk/-/media/files/information-and-support/publications/hcps/bhf_nacr_report_2017---digital.pdf?rev=5d595ba8c4334f37922877311609276b#:~:text=We%20also%20welcome%20how%20NACR,in%20well%2Dresourced%20clinical%20trials. (Accessed 27/06/2024)
47. Kotseva K, Wood D, De Bacquer D. Determinants of participation and risk factor control according to attendance in cardiac rehabilitation programmes in coronary patients in Europe: EUROASPIRE IV survey. *European Journal of Preventive Cardiology* 2018;**25**:1242-1251. doi: 10.1177/2047487318781359
48. Neubeck L, Freedman SB, Clark AM*, et al.* Participating in cardiac rehabilitation: a systematic review and meta-synthesis of qualitative data. *Eur J Prev Cardiol* 2012;**19**:494-503. doi: 10.1177/1741826711409326

49. Santiago de Araujo Pio C, Chaves GS, Davies P, Taylor RS, Grace SL. Interventions to promote patient utilisation of cardiac rehabilitation. *Cochrane Database Syst Rev* 2019;**2**:CD007131. doi: 10.1002/14651858.CD007131.pub4
50. American College of Sports Medicine. Clinical Exercise Testing. In: Pescatello LS, Arena R, Riebe D, Thompson A, eds. ACSM's Guidelines for exercise testing and Prescription 9th ed: Wolters Kluwer Health; 2013, p114-141.
51. Long L, Anderson L, He J*, et al.* Exercise-based cardiac rehabilitation for stable angina: systematic review and meta-analysis. *Open Heart* 2019;**6**:e000989. doi: 10.1136/openhrt-2018-000989
52. Humphreys H, Paddock D, Brown S*, et al.* Living with myocardial ischaemia and no obstructive coronary arteries: a qualitative study. *Open Heart* 2024;**11**. doi: 10.1136/openhrt-2023-002569
53. Williamson PR, Altman DG, Bagley H*, et al.* The COMET Handbook: version 1.0. *Trials* 2017;**18**:280. doi: 10.1186/s13063-017-1978-4

Table 1. Characteristics of included studies

Study	Population		Intervention(s)/Control	Outcomes				
				Severity of angina	HRQoL	Exercise capacity	Adverse events	Patient adherence
Eriksson *et al* 2000[30] Sweden Single centre Funding: NR Conflicts: NR	*N randomized* *Age, yr (mean±SD)* *MVA (%)* *Female (%)*	26 56±8 100% 100%	A (8): Body awareness 2x/wk for 8wks; then cCR (cycle ergometer) 3x/wk for 8wks (50% of peak work rate), 30 min; dose of exercise < 1000 units B (8): cCR (cycle ergometer) 3x/wk for 8wks (50% of peak WR), 30 min; dose of exercise < 1000 units C (10): Control; normal activities for 8wks	NA	NA	CPET, cycle ergometer: • Peak Work (W) • Peak VO_2 (L/min)	Reported	Adherence to intervention Dropouts
Tyni-Lenne *et al* 2002[31] Sweden Single center Funding: NR Conflicts: NR	*N randomized* *Age, yr (mean±SD)* *MVA (%)* *Female (%)*	24* 55±8* 100% 100%	A (8): cCR (cycle ergometer) 3x/wk for 8wks (50% of peak work rate), 30 min; dose of exercise < 1000 units B (8): Relaxation training (modified Jacobson's approach & autogenous training) 2x/wk for 8wks, 60min C (8): Control; normal activities for 8wks	NA	SIP	(The same outcome measures were reported in both publications[30,31], results presented in the first publication were used for this SR)*	Reported	Adherence to intervention Dropouts
Asbury *et al* 2008[32]	*N randomized*	64	A (32) Phase III cCR, (aerobic conditioning; functional capacity;	Standard 5-point pain scale	SF-36	NA	NR	Adherence to intervention

UK Single centre Funding: *"No external funding was obtained for completion of this project"* Conflicts: None declared	*Age, yr (mean±SD)* *MVA (%)* *Female (%)*	57.3±8.6 100% 100%	muscular strength; endurance) 2x/wk; 1 80-min hospital-based CR class 60–75% of age-predicted HRR and at least 1 exercise session at home) for 8wks; dose of exercise unknown B (32) symptom monitoring (diary completion); normal activities for 8wks. Follow up: 8wks	(at 8wks and 16wks)				Dropouts Withdrawals
Feizi *et al* 2012[33] Iran Single centre Funding: Vice-Chancellery of Research and Technology, Urmia University of Medical Sciences Conflicts: None declared	*N randomized* *Age, yr (mean±SD)* *MVA (%)* *Female (%)*	40 50.8±6.8† 100% 100%	A (7) Control; normal activities B (11) Phase III cCR (stretching exercises and walking) 3×/wk; 60–65% of MHR, at first 25min with increase to 40min per session; sessions done mainly at home, monitoring by phone for 8wks; dose of exercise < 1000 units C (11) Jacobson's PMR; 15min daily at home for 8wks D (11) Phase III cCR and Jacobson's PMR as described for groups B and C for 8wks; dose of exercise < 1000 units	NR	SF-36	NA	NR	NR

Bove *et al* 2020[34] Denmark Single centre Funding: Capital Region of Denmark Research Foundation, Bispebjerg-Frederiksberg Hospital Internal Foundation, Eva og Henry Frænkels Memorial Foundation, Christensson-Cesons Family Foundation and Department of Cardiology Bispebjerg-Frederiksberg Hospital. Conflicts: None declared	*N randomized* *Age, yr (mean±SD)* *MVA (%)* *Female (%)*	62 63.7±6.0† 100% 100%	A (30) cCR (Aerobic interval training and resistance exercise; cycle ergometer) with weight loss; 2x/week; 45-60min per session; outpatient and home-based; for 24wks; dose of exercise ≥ 1000 units B (32) Control; normal activities for 24wks	NA	SAQ	CPET, cycle ergometer: • Peak VO_2 (mL/min) • Peak VO_2 Body Weight (mL/kg/min) • Peak VO_2 FFM (mL/min/kg $FFM^{0.67}$) • Max workload (W)	Reported	Adherence to intervention Dropouts
Rahmani *et al* 2020[26] Iran Single center Funding: Tehran University of Medical Sciences & Health Services	*N randomized* *Age, yr (mean±SD)* *MVA (%)* *Female (%)*	30 53.3±7.9† 100% 73.3%	A (15) CR, (treadmill, cycle, and arm ergometer exercises) 3x/wk; 60min hospital-based CR class 40–60% of age-predicted HRR or BORG scale of 11-15 out of 20) for 4wks; dose of exercise ≥ 1000 units B (15) Control; normal activities for 4wks	4 point scale (ACSM 's Guideline for Exercise Testing and prescription)	NA	CPET, treadmill: • Peak VO_2 (mL/kg/min)	NR	Adherence to intervention Dropouts

Conflicts: None declared

Abbreviations: *NR* Not reported; *NA* Not applicable for this study; *N* number; SD standard deviation; *yr* years; *MVA* microvascular angina; *wk* week; *wks* weeks; c*CR* comprehensive cardiac rehabilitation; *min* minutes; *CPET* cardiopulmonary exercise test; *W* watts; VO_2 volume of oxygen; *L/min* liters of oxygen per minute; *6MWT* six-minute walk test; *m* meters; *beats/min* beats per minute; *RPE* rating of perceived exertion; *UK* United Kingdom; *HRR* heart rate reserve; *ITT* intention-to-treat; # fracture; *MHR* maximum heart rate; *PMR* progressive muscle relaxation; *mL/kg/min* milliliters of oxygen per kilogram of the body mass per minute; *FFM* fat-free mass; *CR* cardiac rehabilitation; *ACSM* American College of Sports Medicine.

Symbols

** Confirmation by the corresponding author for the reports Eriksson et al 2000[30] and Tyni-Lenne et al 2002[31] that these reports refer to the same study. Tyni-Lenne et al 2002[31] reports a smaller sample size than that reported by Eriksson et al 2000[30]. Tyni -Lenne et al 2002[31] reports less two participants in their control group and reports one withdrawal from the control group. Reported results for Peak VO_2 are the same after intervention in the control and CR groups in both trials.*

‡ When descriptive statistics were reported by group only, these were combined using the formulae for combining summary statistics across two groups as recommended by Cochrane, Chapter 6, section 6.5.2.10.[18]

1

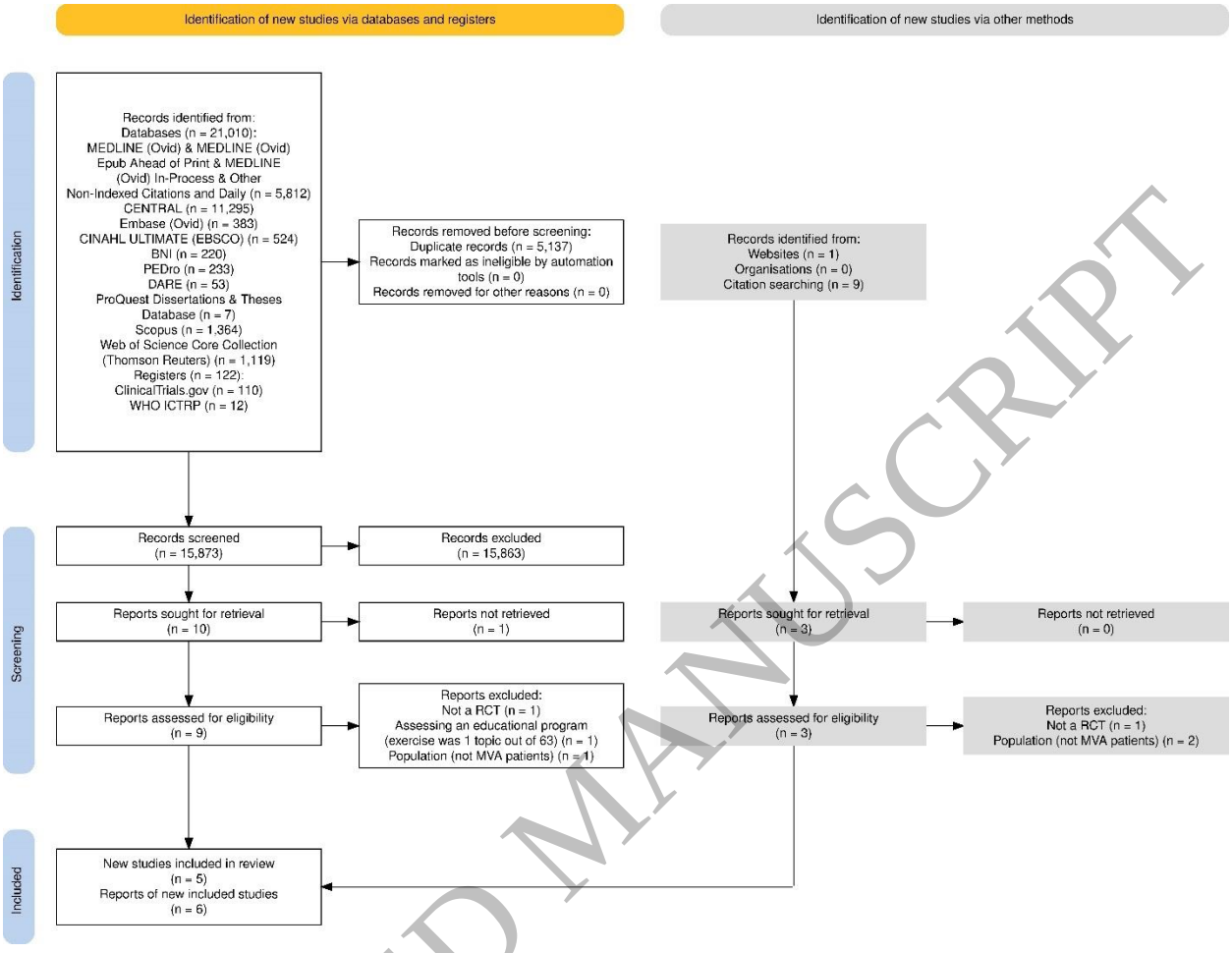
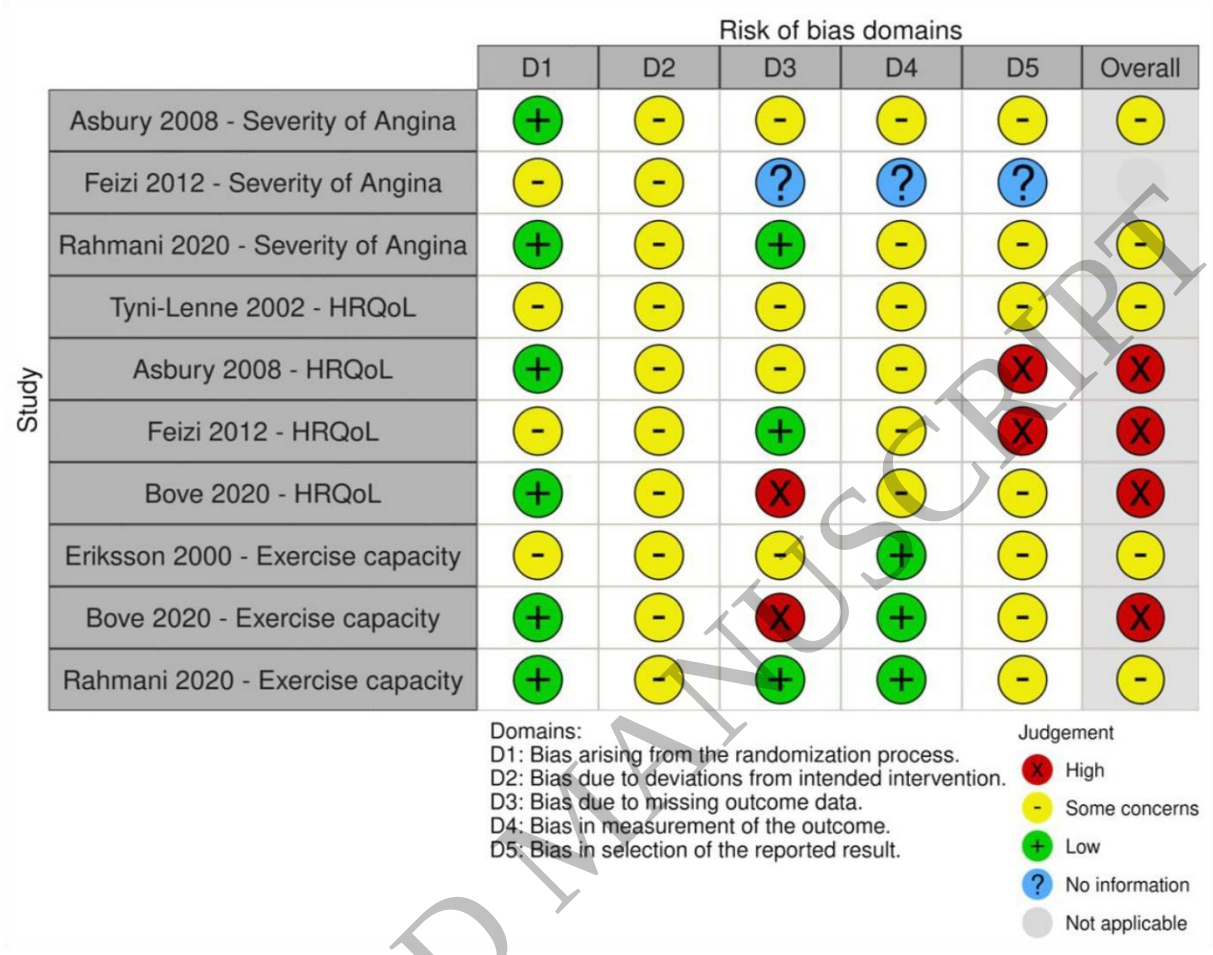


Figure 1
411x315 mm (DPI)



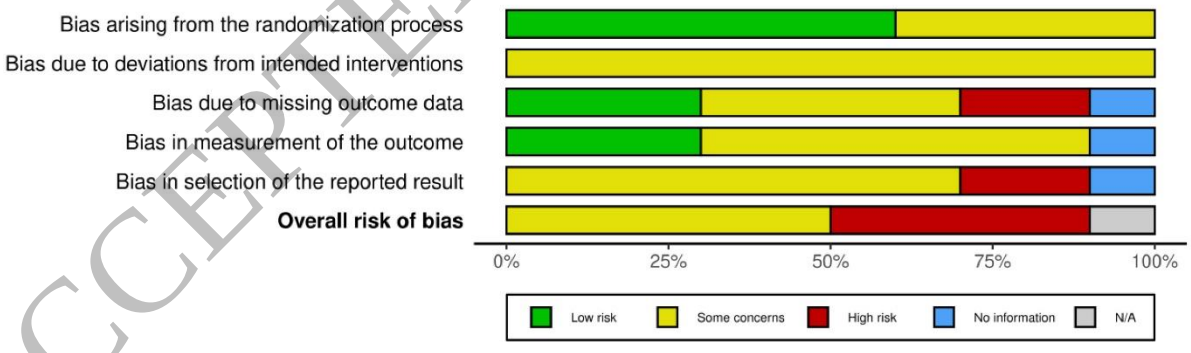
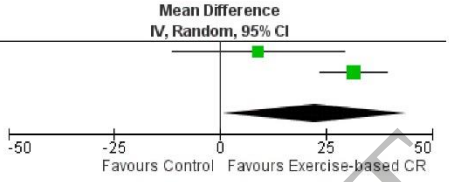


Figure 2
160x178 mm (DPI)

SF-36 Physical role limitation domain

Study or Subgroup	Exercise-based CR Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Asbury 2008	53.8	40.4	29	44.8	39.1	29	40.9%	9.00 [-11.46, 29.46]	2008
Feizi 2012	61.93	7.1	11	30.35	9.14	7	59.1%	31.58 [23.61, 39.55]	2012
Total (95% CI)			**40**			**36**	**100.0%**	**22.34 [0.58, 44.10]**	

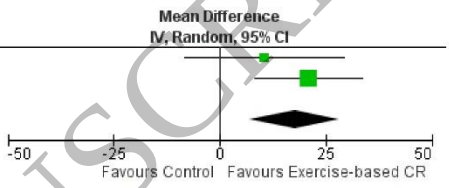
Heterogeneity: Tau² = 192.17; Chi² = 4.06, df = 1 (P = 0.04); I² = 75%
Test for overall effect: Z = 2.01 (P = 0.04)



SF-36 Emotional role limitation domain

Study or Subgroup	Exercise-based CR Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Asbury 2008	79.4	34.1	29	68.9	38.7	29	31.4%	10.50 [-8.27, 29.27]	2008
Feizi 2012	50.75	10.17	11	29.76	15.1	7	68.6%	20.99 [8.29, 33.69]	2012
Total (95% CI)			**40**			**36**	**100.0%**	**17.70 [7.18, 28.22]**	

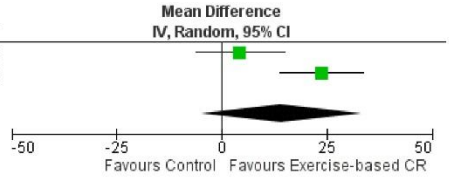
Heterogeneity: Tau² = 0.00; Chi² = 0.82, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 3.30 (P = 0.0010)



SF-36 Vitality domain

Study or Subgroup	Exercise-based CR Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Asbury 2008	49.8	19.2	29	45.5	21.7	29	49.5%	4.30 [-6.25, 14.85]	2008
Feizi 2012	50.56	9.03	11	26.78	11.24	7	50.5%	23.78 [13.89, 33.67]	2012
Total (95% CI)			**40**			**36**	**100.0%**	**14.13 [-4.96, 33.22]**	

Heterogeneity: Tau² = 162.53; Chi² = 6.97, df = 1 (P = 0.008); I² = 86%
Test for overall effect: Z = 1.45 (P = 0.15)



SF-36 General health domain

Study or Subgroup	Exercise-based CR Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Asbury 2008	57.6	17	29	51	17	29	53.1%	6.60 [-2.15, 15.35]	2008
Feizi 2012	56.06	9.38	11	32.73	14.31	7	46.9%	23.33 [11.37, 35.29]	2012
Total (95% CI)			**40**			**36**	**100.0%**	**14.45 [-1.92, 30.81]**	

Heterogeneity: Tau² = 111.35; Chi² = 4.89, df = 1 (P = 0.03); I² = 80%
Test for overall effect: Z = 1.73 (P = 0.08)

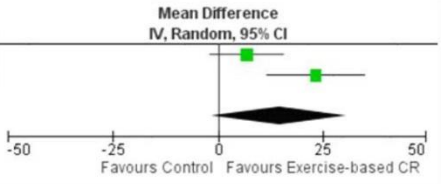


Figure 3
161x166 mm (DPI)

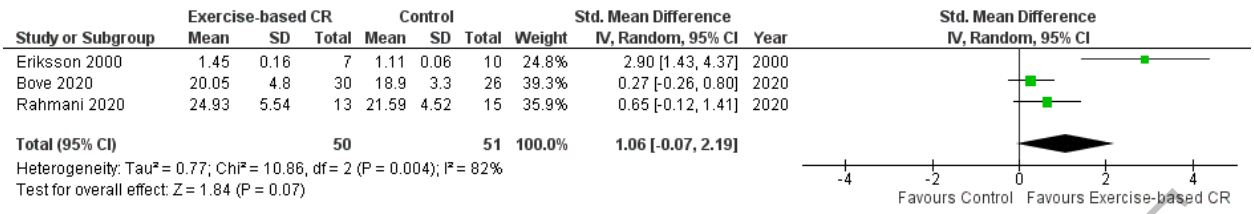
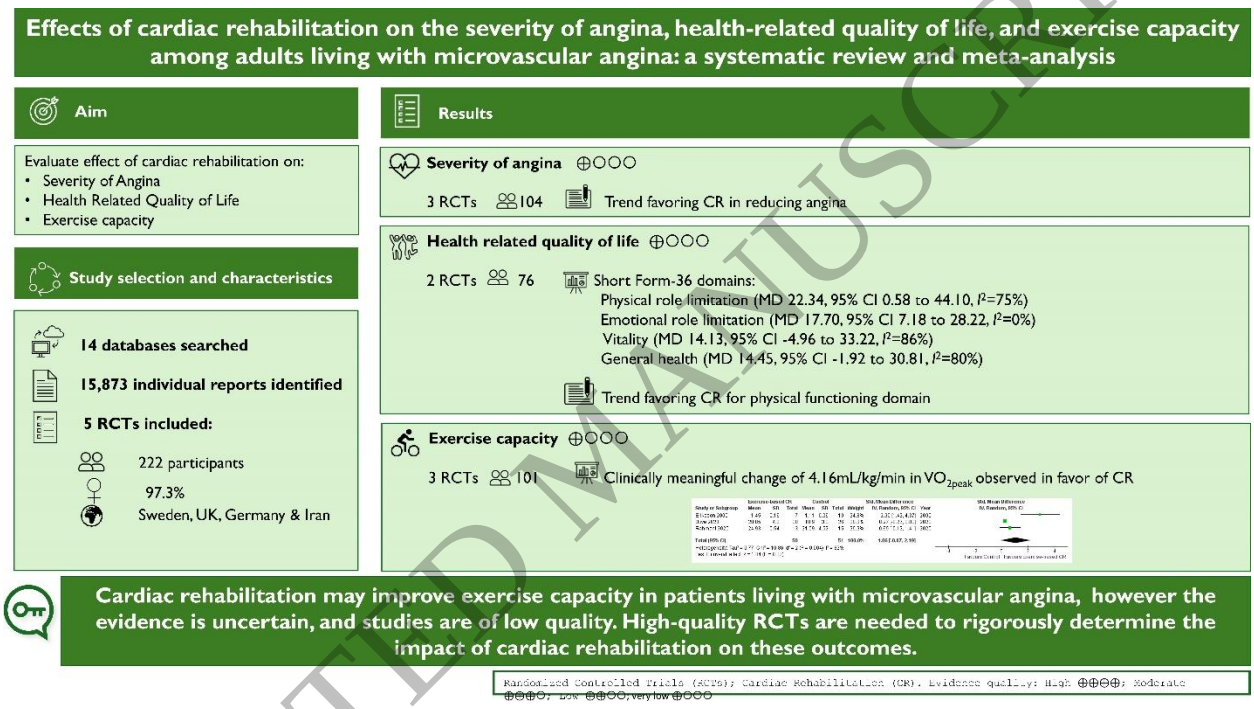


Figure 4
249x42 mm (DPI)



Graphical Abstract
324x180 mm (DPI)