

Multicomponent Cardiac Rehabilitation and Cardiovascular Outcomes in Patients With Stable Angina: A Systematic Review and Meta-analysis

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Abstract

Objective: To carry out a systematic review of the effect of cardiac rehabilitation (CR) and its components on cardiovascular outcomes in patients with stable angina.

Methods: We searched the databases including Ovid MEDLINE, Ovid Embase, Scopus, Web of Science, Google Scholar, and EBSCO CINAHL from their inception up to November 1, 2017. The search was not restricted to time or publication status but was limited to the English language. Two independent investigators screened the identified studies and extracted the data in duplicate. We reviewed the included studies and, where possible, pooled their results and conducted meta-analyses. Risk of bias was assessed using Cochrane Collaboration tools.

Results: The search identified 7508 studies. Ten randomized trials including 4005 participants with the mean (SD) age of 59.6 (5.7) years were considered eligible for inclusion in our analyses. The results of meta-analyses of exercise-based CR for patients with stable angina revealed that CR improved exercise capacity (the difference between baseline and follow-up was 0.76 watt [0.49 to 1.02] higher in the CR group vs the non-CR group) and decreased angina frequency (standard mean difference, -0.27 [CI, -0.43 to 0.11]). No significant differences were noted in other outcomes, including quality of life. Mortality could not be adequately assessed because it was analyzed in only 1 exercise-based CR study.

Conclusion: Our systematic review, involving a relatively small number of studies with low to moderate risk of bias and with considerable heterogeneity, found a significant decrease in angina frequency and increase in exercise capacity in patients with stable angina who participated in an exercise-based CR program. Studies involving the impact of components of CR are limited and generally report beneficial outcomes. Additional studies are needed to clarify the possible role of CR in the management of patients with stable angina.

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Coronary artery disease is a leading cause of death worldwide,¹ and stable angina is a common manifestation.² Stable angina is defined as chest discomfort due to reversible myocardial ischemia that is triggered by exercise, emotional stress, or other stressors and that is improved by rest or with medications. Management of stable angina is usually achieved with optimal medical and lifestyle therapy or revascularization therapy (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery).³⁻⁵ Current evidence suggests similar

longer term outcomes in these 2 approaches to stable angina, although symptom control may occur earlier with revascularization therapy than with optimal medical and lifestyle therapy.⁶

Cardiac rehabilitation (CR) is an evidence-based treatment for coronary artery disease management in patients who have stable angina.⁷ Cardiac rehabilitation is a comprehensive, multidisciplinary, systematic, and tailored approach to provide optimal medical, lifestyle, and psychosocial therapies for patients with a variety of cardiovascular diseases



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(CVDs). Studies of CR have reported that CR is associated with a reduction in morbidity and mortality rates after myocardial infarction (MI), PCI, and CABG.⁸ Studies reinforce the beneficial effects of exercise-based CR on major cardiovascular (CV) outcomes and modifiable CV risk factors.^{7,9,10} Whereas many CR outcome studies have included patients with MI, PCI, and CABG, less is known about CR and outcomes in patients with stable angina. However, given the benefits of CR in controlling CVD risk factors and systematically applying optimal medical and lifestyle therapies, clinical guidelines recommend CR in patients with stable angina.^{11,12} A Cochrane review reported the benefits of exercise-based CR on CV outcomes and health-related quality of life (HRQL) in patients with stable angina.¹³ Despite the results of this review, the exact effect of CR and its components (including exercise program, nutrition counseling, behavioral counseling, and smoking cessation programs as well as control of blood pressure, blood lipids, and diabetes mellitus) on outcomes is less clear. The aim of this study was to systematically review all of the studies that have assessed the effect of CR and its components on major CV outcomes, HRQL, and cardiopulmonary fitness in patients with stable angina.

METHODS

The protocol of the study was designed on the basis of the *Cochrane Handbook for Systematic Reviews of Intervention* and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. It was approved by the Institutional Review Board of Mayo Clinic.

The criteria that we used to screen eligible studies were as follows: randomized clinical trials or cohort studies that assessed the effect of CR on major CV outcomes, HRQL, and cardiopulmonary fitness in patients with stable angina. The studies that met the criteria were included in the study, and the studies with different design, intervention, or patient population were excluded. The lengths of follow-up and the language and publication status of the studies were not considered for screening of the studies.

We did a comprehensive and systematic search of databases, including Ovid MEDLINE, Ovid Embase, Scopus, Web of Science, Google Scholar, and EBSCO CINAHL, to find

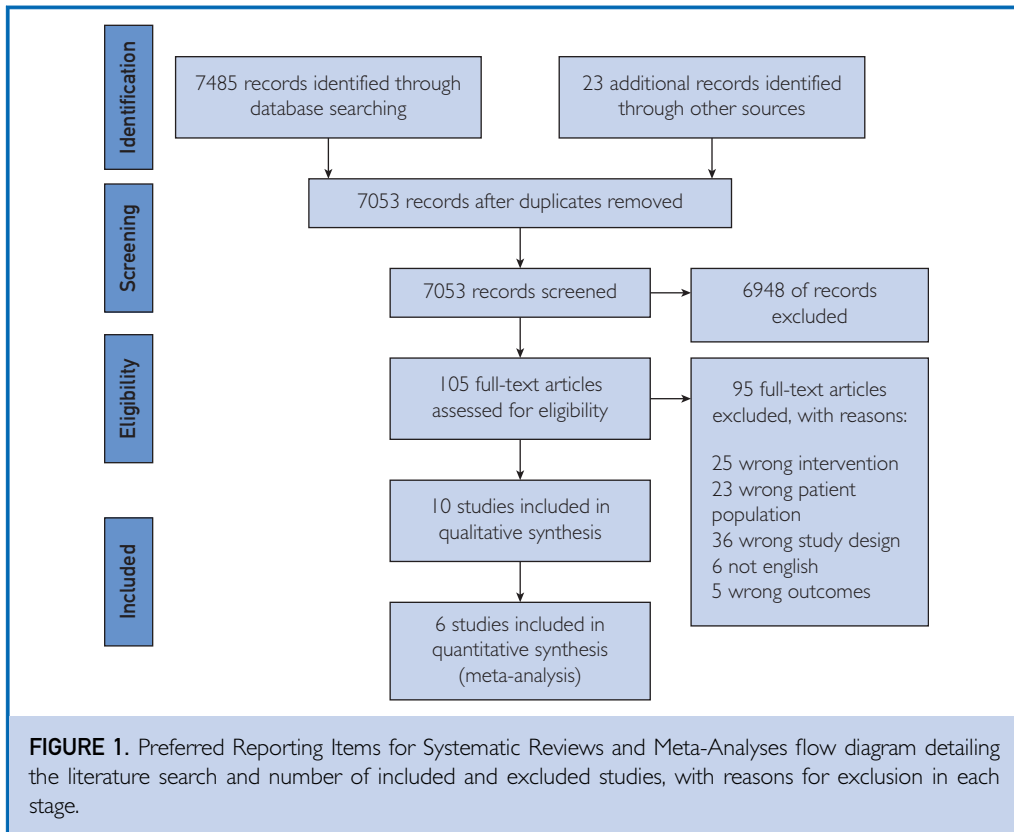
the eligible studies. An experienced librarian assisted with designing the search strategy and searched the databases from their inception up to November 1, 2017. The search was not restricted to any specific time and publication status but was limited to the English language. The details of the search strategy in Ovid MEDLINE and Embase Scopus are shown in [Appendix 1](#) (available online at <http://mcpiqjournal.org>).

Screening of the studies identified through our systematic search was done in 2 steps with use of systematic review software (Covidence). The first step included screening of published studies by the title and the abstracts of the studies, with 2 independent investigators (F.S. and Y.W.) screening the papers. The second step screened the selected studies further on the basis of their full texts. The entire screening process was done independently and in duplicate. [Figure 1](#) shows the details of the screening process, the number of studies excluded in each step, and the reasons for exclusions.

An investigator (F.S.) checked the references of the included studies as well as the databases for any missing studies and the gray literature including unsubmitted or unpublished manuscripts (because of multiple reasons, mainly their negative results). In addition, the authors of the included studies were contacted to identify any additional studies they previously carried out that were not published or that were missed in our search process.

Disagreement between the investigators in each stage of the work was resolved by discussion and consensus; if the agreement was not achievable, the senior author (R.J.T.) helped resolve the disagreement. Kappa statistic was used to measure the agreement between investigators in each step.

Studies that met the eligibility criteria were included for data extraction and further analysis. An Excel spreadsheet, developed by one of the investigators (F.S.), was used by the screening investigators (F.S. and Y.W.) for data extraction. The spreadsheet focused on the following information: general characteristics of the study (name of the first author, year of publication, and location of the study), study design (eg, randomized trial, observational studies), quality of the study,



characteristics of the CR intervention (number of sessions and the components of CR), characteristics of the control group, number of participants in each group, characteristics of the participants (age, sex, comorbidities), follow-up duration, list of outcomes (major CV outcomes, HRQL, and cardiopulmonary fitness), changes in outcomes in intervention, and control groups. In case data from a given study were not accessible, an investigator (F.S.) contacted the authors of the study for their assistance with the data extraction. The data extraction process was performed independently and in duplicate with a third investigator (F.S., J.M.-I.) to check for the accuracy of the data.

Cochrane Collaboration tools were used to assess the risk of bias in individual studies at both study and outcome levels. The tool for the assessment of the risk of bias in randomized clinical trials assessed the risk of bias in different levels of study, including sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias.¹⁴ The

tool that was used for observational studies (ROBINS-I) assessed different domains for any possible bias.¹⁵ The domains for evaluating the risk of bias were as follows: bias due to confounding, bias in selection of the participants into the study, bias in classification of exposures, bias due to departures from intended exposures, bias due to missing data, bias in measurement of outcomes, bias in selection of the reported result, and overall risk of bias. To evaluate publication bias, we used funnel plots for the outcomes being studied.

Because of the variety of the outcomes of interest in the study, the data were available in different forms of continuous variables and in a variety of counts and rates. We pooled the data across the studies and analyzed the data by different methods, including inverse variance effects model for continuous data and generic inverse variance model for counts and rates. The software used for the meta-analysis was RevMan v.5.3 (Cochrane Collaboration). The I^2 statistic was used to measure the heterogeneity objectively,

TABLE 1. Characteristics of the Studies Included in the Systematic Review and Meta-analysis of the Association Between Cardiac Rehabilitation and Different Cardiovascular Outcomes in Patients With Stable Angina

	First author	Year of publication	Study design	No. of participants	Mean follow-up	Setting (PICO)	Location of the study
1	Asbury ¹⁶	2012	Randomized clinical trial	40	2 months	Participants: refractory angina patients (65.1±7.3 years) Intervention: phase 3 cardiac rehabilitation program (exercise) Comparison: symptom diary control Outcomes: angina frequency, angina severity, weight, waist/hip ratio, heart rate, glucose, LDL, HDL, triglycerides, shuttle level and meter, blood pressure, quality of life, and psychological morbidity (Hospital Anxiety and Depression Scale, Health Anxiety Questionnaire, SF-36, health beliefs)	United Kingdom
2	Bundy ¹⁷	1994	Randomized clinical trial	29	2 months	Participants: chronic stable angina patients Intervention: stress management training Comparison: a group with no stress management training Outcomes: exercise tolerance, self-reported angina symptoms, medication use, anxiety levels	United Kingdom
3	Burr ¹⁸	2003	Randomized clinical trial	3114	3-9 years	Participants: men <70 years of age with angina Intervention: dietary advice (2 portions of oily fish each week or 3 fish oil capsules daily; eat more fruit, vegetables, and oats; or both of these interventions) Comparison: given no specific dietary advice Outcomes: mortality (all-cause, cardiovascular, sudden death)	United Kingdom
4	Devi ¹⁹	2014	Randomized clinical trial	94	1.5 months	Participants: patients diagnosed with stable angina Intervention: web-based cardiac rehabilitation program (including exercise, dietary advice, stress management, smoking reduction) Comparison: continue the usual treatment plan and not participating in a cardiac rehabilitation program Outcomes: daily average step count, energy expenditure, duration of sedentary activity and duration of moderate activity, angina frequency, weight, self-efficacy, emotional quality of life score	United Kingdom
5	Gallacher ²⁰	1997	Randomized clinical trial	378	6 months	Participants: men <70 years of age diagnosed with angina Intervention: stress management training Comparison: continue the usual treatment without intervention Outcomes: time pressure, driven behavior, attitude to achievement, inability to relax, role definition, domestic stress, health concerns, hostility, anxiety, depression	United Kingdom
6	Hambrecht ²¹	2004	Randomized clinical trial	101	12 months	Participants: male patients aged ≤70 years with stable angina Intervention: exercise Comparison: percutaneous coronary intervention Outcomes: ischemic events (death of cardiac causes, resuscitation after cardiac arrest, nonfatal myocardial infarction, cerebrovascular accident, CABG, PTCA, hospitalization, coronary angiography, major ischemic events, any ischemic event)	Germany

Continued on next page

TABLE 1. Continued

	First author	Year of publication	Study design	No. of participants	Mean follow-up	Setting (PICO)	Location of the study
7	Lewin ²²	1995	Randomized crossover trial	65	12 months	Participants: patients diagnosed with stable angina Intervention: exercise, stress management training, psychological status improvement, behavioral change, education Comparison: waiting list control group Outcomes: angina frequency, severity of angina, duration of angina, use of glyceryl trinitrate, disability	United Kingdom
8	Maxwell ²³	2002	Randomized crossover trial	36	2 weeks	Participants: stable outpatients with CAD and class II or III angina Intervention: dietary advice Comparison: continue the regular treatment Outcomes: endothelial function, treadmill exercise test, quality of life (SF-36), Seattle Angina Questionnaire	United States
9	Schuler ²⁴	1988	Randomized clinical trial	35	12 months	Participants: patients with coronary artery disease, stable angina pectoris, and mild hypercholesterolemia Intervention: exercise and dietary advice Comparison: continue usual medical care Outcomes: BMI, total cholesterol, LDL, HDL, VLDL, triglycerides, cholesterol/HDL, stress-induced myocardial ischemia, heart rate, blood pressure, physical work capacity	Germany
10	Schuler ²⁵	1992	Randomized clinical trial	113	12 months	Participants: patients with stable angina pectoris Intervention: exercise and dietary advice Comparison: continue usual medical care Outcomes: diameter reductions of coronary lesions, myocardial perfusion, weight, total cholesterol, triglycerides, HDL, physical work capacity, myocardial oxygen consumption, rate/pressure, stress-induced MI, coronary lesion, cardiovascular events	Germany

BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; SF-36, 36-Item Short Form Health Survey; VLDL, very-low-density lipoprotein.

TABLE 2. Risk of Bias in Different Domains^a and Overall Risk of Bias in Different Studies Included in the Systematic Review and Meta-analysis of the Association Between Cardiac Rehabilitation and Cardiovascular Outcomes in Patients With Stable Angina

	Sequence allocation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall risk ^b of bias
Asbury ¹⁶	●	●	●	●	●	●	●
Bundy ¹⁷	●	●	●	●	●	●	●
Burr ¹⁸	●	●	●	●	●	●	●
Devi ¹⁹	●	●	●	●	●	●	●
Gallacher ²⁰	●	●	●	●	●	●	●
Hambrecht ²¹	●	●	●	●	●	●	●
Lewin ²²	●	●	●	●	●	●	●
Maxwell ²³	●	●	●	●	●	●	●
Schuler ²⁴	●	●	●	●	●	●	●
Schuler ²⁵	●	●	●	●	●	●	●

^aDifferent colors show different amounts of risk of bias within different domains: green represents a low risk of bias, yellow represents an unclear risk of bias or not enough information is provided in the study to make a judgment, and red represents a serious to critical risk of bias within each domain.

^bShows the overall risk of bias in different studies in the range of low to critical (low, moderate, serious, and critical risk of bias). Green shows a low risk of bias, and yellow shows a moderate risk of bias.

and forest plots were inspected visually to subjectively measure the heterogeneity between studies in different analyses.

RESULTS

The primary search by the librarian identified 7485 published studies. We screened the identified studies by title and abstract, and we found 82 studies eligible for the full-text screening. In addition, 23 studies were found from hand-searching efforts (cross-referencing, searching by the name of the authors of the included studies, searching for gray literature). Among those eligible for full-text screening, 41 studies were found to be eligible for data extraction. During data extraction, 31 studies were excluded for a variety of reasons (Figure 1). In the end, 10 studies were found to be eligible for systematic review and possible meta-analysis.

Table 1 details the characteristics of the studies included in the systematic review. All of the included studies were randomized clinical trials; most of them were performed in the United Kingdom and Germany. The total number of the participants was 4005; mean \pm SD age was 59.6 \pm 5.7 years.

As Table 2 shows, the risk of bias was generally high in the domain of blinding of the participants and investigators to the study. In addition, another source of bias in the studies was incomplete outcome data;

however, the overall risk of bias was low in most of the studies and moderate in 2 studies. Results of CV and non-CV outcomes are presented in Table 3.

All-cause mortality was assessed in 2 studies^{18,25} involving a total of 3227 participants receiving CR interventions that were generally focused on diet or exercise therapies. In both of the studies, there was a nonsignificant trend toward higher all-cause mortality in the CR intervention group compared with the usual care group (Figure not shown). The result of pooled analysis did not find any significant association between CR and CV mortality (Figure 2), sudden death (Figure 3), a variety of CV events, and angina severity.

Furthermore, the association between CR and MI was assessed in 3 studies^{21,24,25} with a total of 249 participants. The major components of the CR intervention in these studies included exercise and dietary therapies, whereas the control group in the study by Hambrecht et al²¹ received PCI. There was no significant difference in incidence of MI in patients of the intervention and control groups (Figure 4).

Hambrecht et al²¹ and Schuler et al²⁵ evaluated the association between CR and stroke (Figure 5), coronary interventions (including PCI [Figure 6] and CABG surgery [Figure 7]), hospitalization (Figure 8), and maximum oxygen consumption (Figure 9) in

TABLE 3. Results of Different Outcomes Reported in the Studies Included in the Systematic Review of the Association Between Cardiac Rehabilitation and Cardiovascular and Non-cardiovascular Outcomes in Patients With Stable Angina

	All-cause mortality	Cardiovascular mortality	Sudden death	Myocardial infarction	Percutaneous coronary intervention	Coronary artery bypass graft	Stroke	Hospitalization	VO ₂ max	Functional exercise capacity	Anxiety score	Depression score	Angina frequency	Angina severity
Asbury ¹⁶	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	0.42 (-0.20 to 1.05)
Bundy ¹⁷	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	-0.51 (-1.25 to 0.23)	Not assessed
Burn ¹⁸	1.16 (1.04-1.29)	1.14 (0.98-1.33)	1.34 (0.96-1.87)	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed
Devi ¹⁹	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	-0.16 (-0.57 to 0.24)	-0.2 (-0.16 to 0.2)	Not assessed	Not assessed
Gallacher ²⁰	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	-0.07 (-0.27 to 0.4)	-0.03 (-0.24 to 0.17)	-0.27 (-0.48 to 0.07)	Not assessed
Hambrecht ²¹	Not assessed	Not assessed	Not assessed	0.32 (0.01-8.05)	0.28 (0.07-1.12)	0.32 (0.0-8.05)	0.64 (0.10-4)	0.12 (0.01-1.04)	2.88 (2.31- 3.44)	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed
Lewin ²²	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	-0.40 (-0.75 to 0.05)	-0.42 (-0.77 to 0.07)
Maxwell ²³	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	0.06 (-0.40 to 0.52)	Not assessed
Schuler ²⁴	Not assessed	Not assessed	Not assessed	0.17 (0.01-3.76)	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed
Schuler ²⁵	5.09 (0.25-103.64)	5.09 (0.25-103.64)	3.05 (0.13-71.55)	0.15 (0.01-2.75)	0.68 (0.12- 3.85)	0.34 (0.01-8.15)	3.05 (0.13-71.55)	1.02 (0.27- 3.85)	0.31 (-0.06 to 0.68)	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed

VO₂max, maximum oxygen consumption.

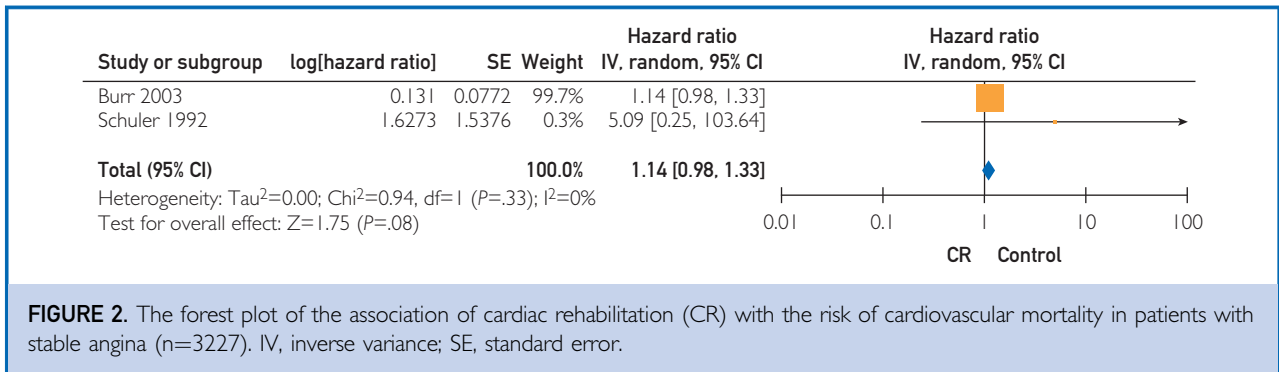


FIGURE 2. The forest plot of the association of cardiac rehabilitation (CR) with the risk of cardiovascular mortality in patients with stable angina (n=3227). IV, inverse variance; SE, standard error.

a total of 214 patients with stable angina. Neither study reported a significant association between CR and any of the outcomes.

Angina frequency was studied in 4 different studies^{17,20,22,23} involving 606 patients. Three studies reported a nonsignificant association between CR and angina frequency, and 1 study reported a significant decrease in angina frequency in patients who participated in a CR program. The meta-analysis found a significant association between participation in a CR program and lower angina frequency in patients with stable angina (standard mean difference [SMD], -0.27; CI, -0.43 to -0.11; Figure 10). However, no significant change was reported in angina severity, which was evaluated in 2 studies^{16,24} (Figure 11).

The association between CR and improvements in exercise capacity was evaluated in 4 different studies^{16,21,23,25} involving 290 participants. Asbury et al¹⁶ measured exercise capacity using the Progressive Shuttle Walk exercise tolerance test (reported progressive shuttle walk), and Hambrecht et al²¹ used the maximal symptom-limited ergo-

spirometry (reported physical work capacity as watts/minute); Maxwell et al²³ and Schuler et al²⁵ used an exercise treadmill test. Except for the study by Asbury et al,¹⁶ all other studies reported a significant association between CR and improved exercise capacity. The result of the meta-analysis did not find a significant association between CR and exercise capacity in patients with CR (SMD, 1.17; CI, -0.22 to 2.57); however, analysis using a fixed effect model found a significant increase in exercise capacity in the CR group (SMD, 0.77; CI, 0.53 to 1.02). This number is equal to a large effect size per Cohen benchmarks²⁶ (Figure 12).

Four studies^{16,19,20,23} analyzed the association between CR and HRQL in 548 participants with stable angina. Asbury et al¹⁶ measured HRQL using the Hospital Anxiety and Depression Scale, Health Anxiety Questionnaire, and the 36-Item Short Form Health Survey (SF-36) to evaluate different aspects of HRQL in participants. They reported that the HRQL measures were better in the control group than in the intervention group. Devi

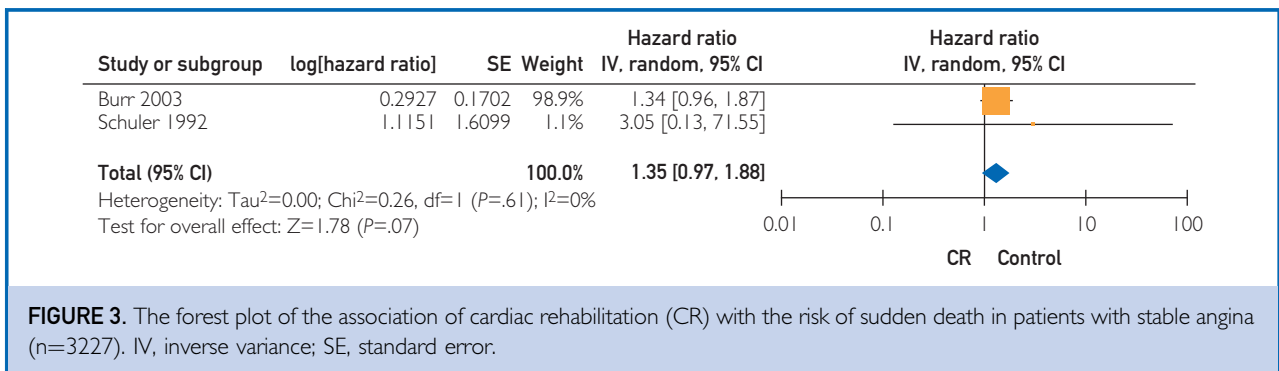
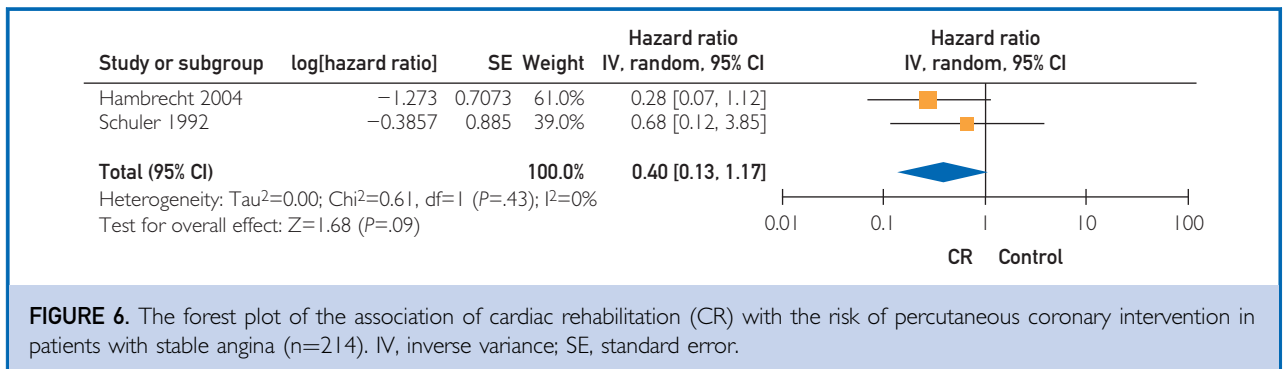
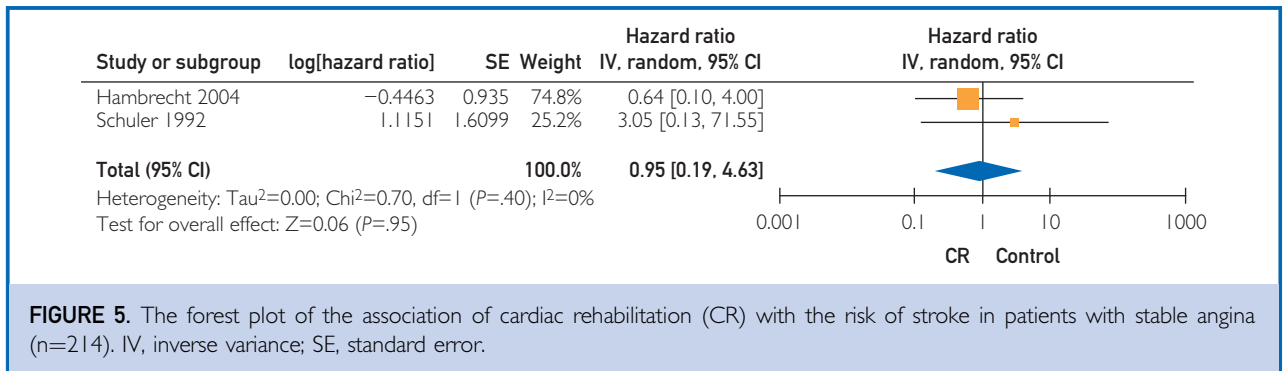
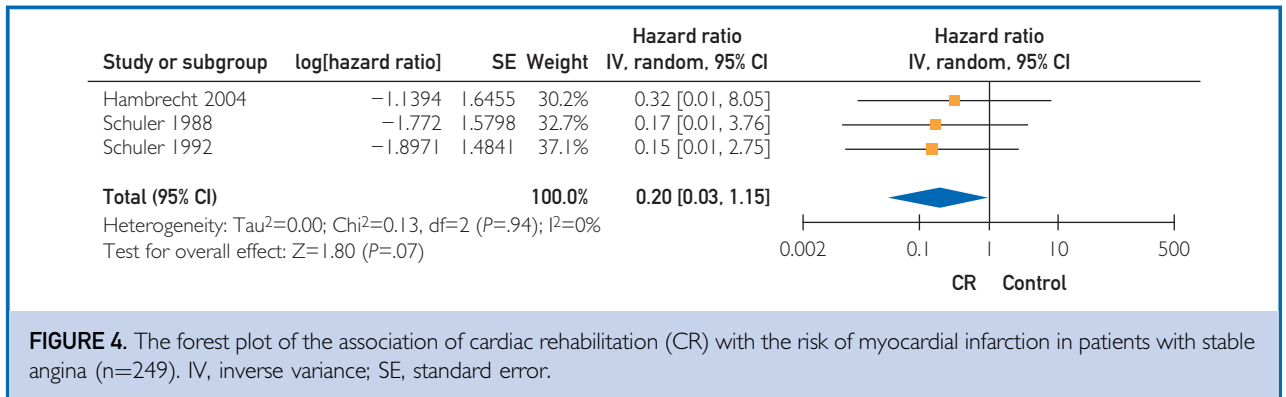


FIGURE 3. The forest plot of the association of cardiac rehabilitation (CR) with the risk of sudden death in patients with stable angina (n=3227). IV, inverse variance; SE, standard error.



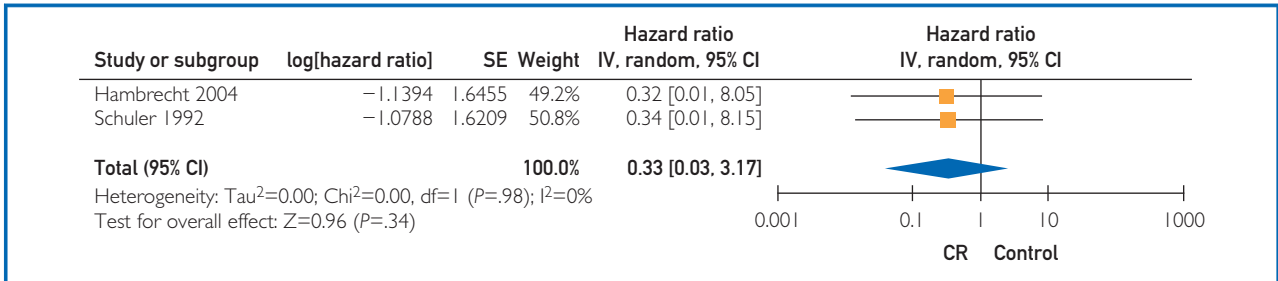


FIGURE 7. The forest plot of the association of cardiac rehabilitation (CR) with the risk of coronary artery bypass graft in patients with stable angina (n=214). IV, inverse variance; SE, standard error.

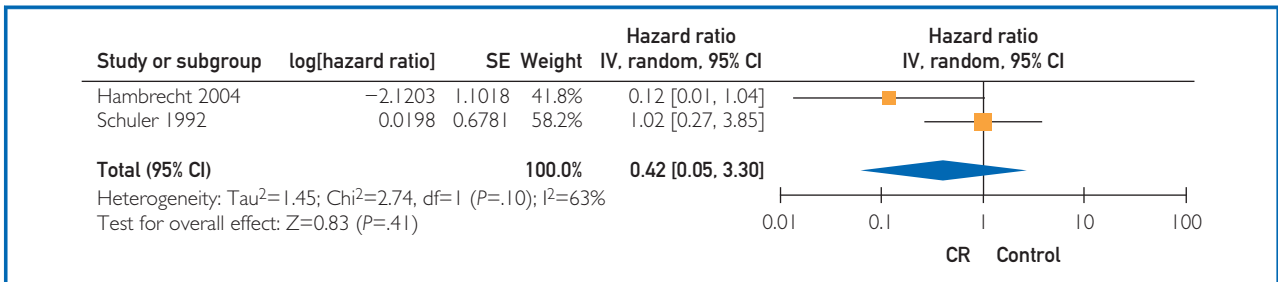


FIGURE 8. The forest plot of the association of cardiac rehabilitation (CR) with the risk of hospitalization in patients with stable angina (n=214). IV, inverse variance; SE, standard error.

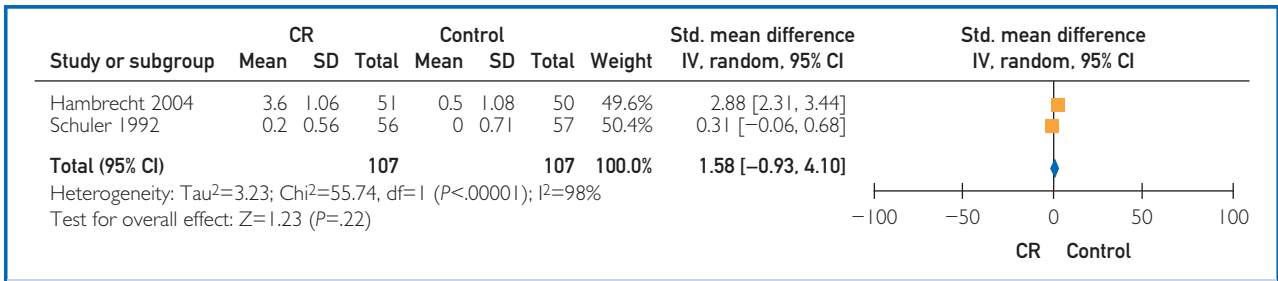


FIGURE 9. The forest plot of the association of cardiac rehabilitation (CR) with the change in maximum oxygen consumption in patients with stable angina (n=214). IV, inverse variance.

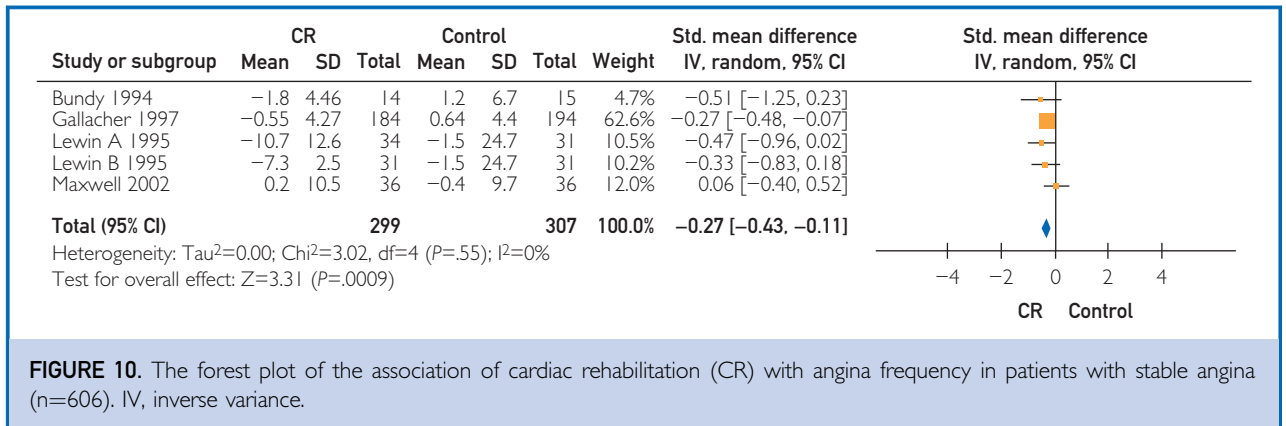


FIGURE 10. The forest plot of the association of cardiac rehabilitation (CR) with angina frequency in patients with stable angina (n=606). IV, inverse variance.

et al¹⁹ reported significant improvement in the emotional HRQL score in the CR intervention group, whereas Gallacher et al²⁰ evaluated participants' stress scores using the Derogatis Stress Profile questionnaire and reported that the total stress score decreased significantly in the intervention group. Maxwell et al²³ also reported that a CR intervention produced more favorable HRQL (using SF-36 and HRQL assessment tools).

Anxiety and depression scores in CR and non-CR participants were assessed by Devi et al¹⁹ and Gallacher et al.²⁰ Neither study reported a significant association between CR and lower anxiety or depression score in the 472 patients studied (Figures 13 and 14).

DISCUSSION

This systematic review investigated the association between comprehensive CR and CV outcomes in patients with stable angina. Our results found a statistically significant association between CR and lower angina frequency

as well as a clinically significant increase in exercise capacity in patients who had CR compared with the control group. There was no significant difference between the intervention and control groups with regard to peak oxygen consumption, suggesting a possible lack of effectiveness in the exercise intervention group. On the other hand, we failed to identify evidence of the association between CR and all-cause mortality, CV mortality, sudden death, MI, stroke, coronary intervention, hospitalization, maximum oxygen consumption, HRQL, anxiety score, depression score, and angina severity. Some of the null results we identified may have been due to the suggestion that exercise training may have been suboptimal in at least some of the studies we identified.

Cardiovascular diseases are the leading cause of death worldwide. Cardiac rehabilitation has been reported to be a crucial component of treatment and secondary prevention of various CVDs, including acute coronary

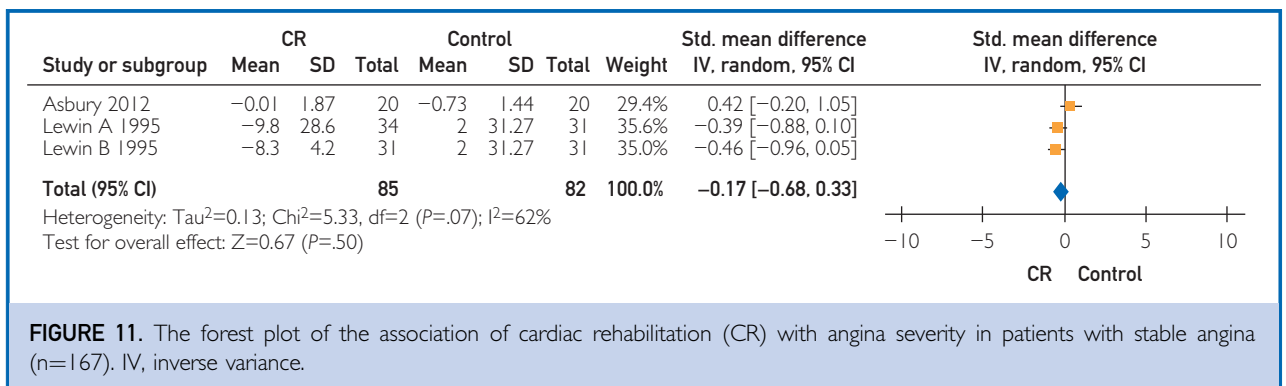


FIGURE 11. The forest plot of the association of cardiac rehabilitation (CR) with angina severity in patients with stable angina (n=167). IV, inverse variance.

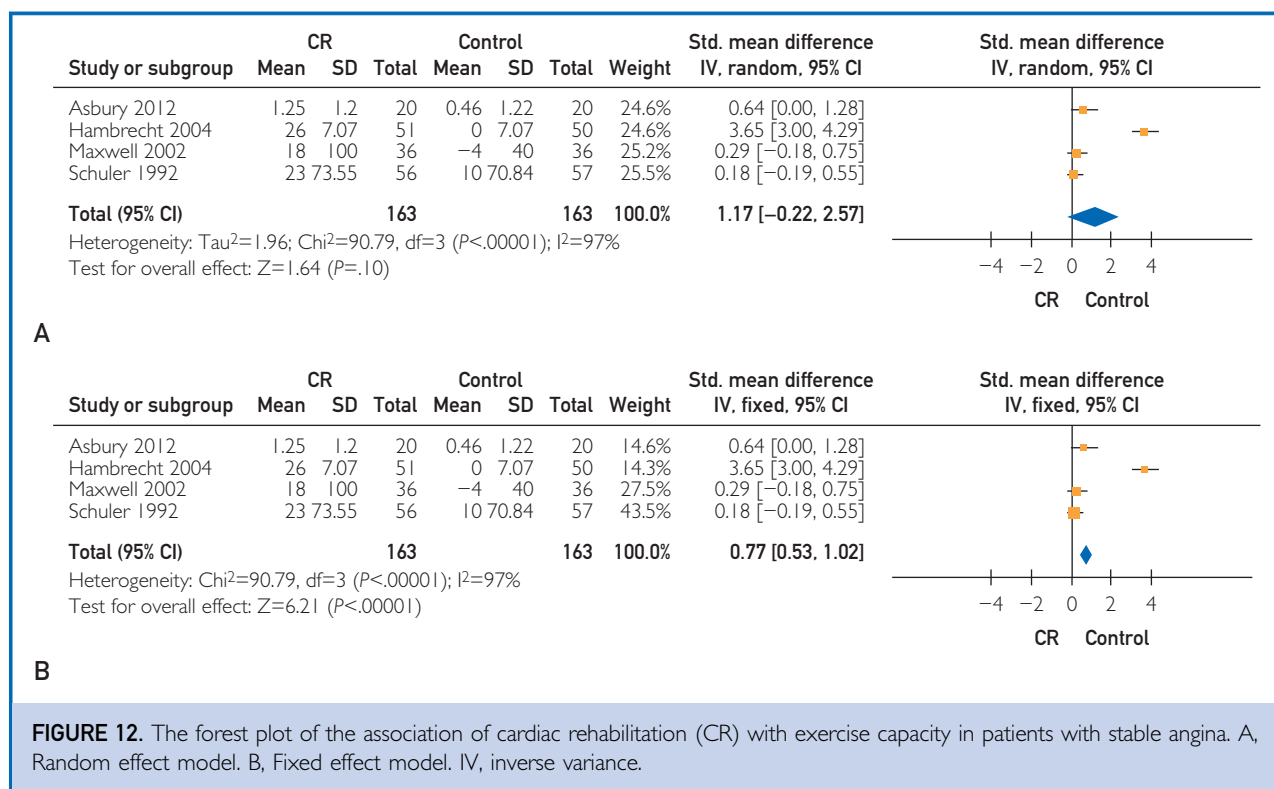
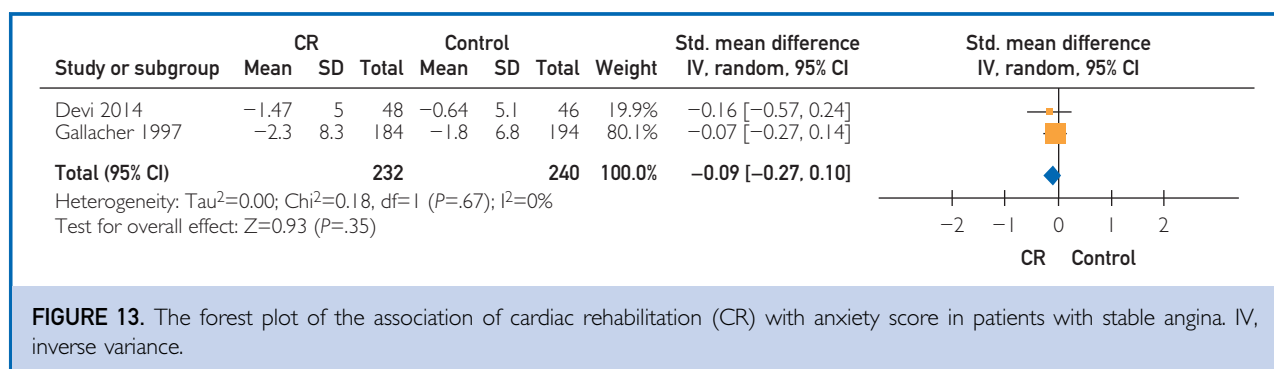
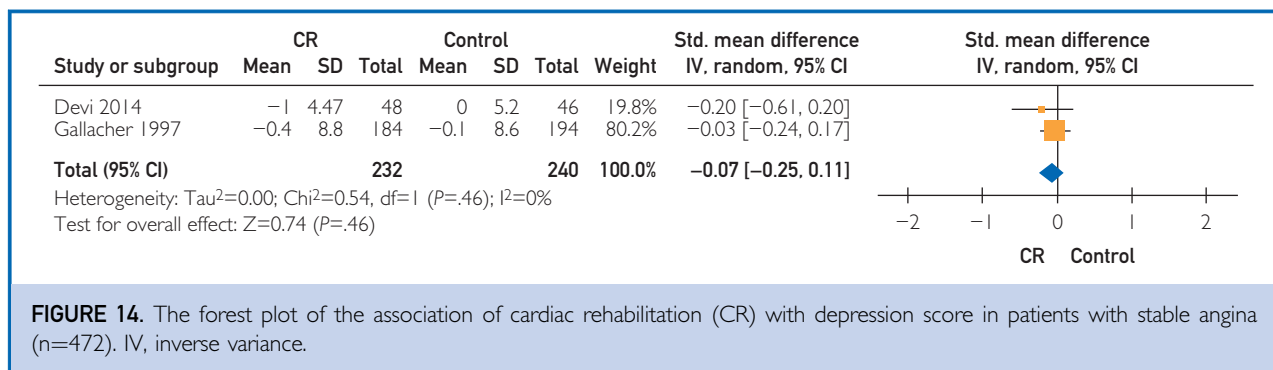


FIGURE 12. The forest plot of the association of cardiac rehabilitation (CR) with exercise capacity in patients with stable angina. A, Random effect model. B, Fixed effect model. IV, inverse variance.

syndrome, CABG surgery, PCI, heart valve surgery, and heart failure with reduced ejection fraction.²⁷ Each component of CR (ie, exercise training, nutrition counseling, behavioral counseling, and CVD risk factor treatment) has been reported to have beneficial effects on CVD risk factor control.^{7,9,10} However, data from our analysis and from other studies suggest limited benefit of CR for outcomes in patients with stable angina. An earlier systematic review and meta-analysis by Long et al²⁸ on the association

between “exercise-based CR” and CV outcomes in patients with stable angina failed to find a significant association between exercise-based CR and improved CV outcomes. The results from our study confirm the findings from the study by Long et al,²⁸ although there are a few key differences between the 2 studies. Our study included a wide scope of studies that assessed the impact on CV outcomes of interventions on any of the individual components of CR (ie, exercise training, nutrition counseling, psychological





counseling, patient education, and risk factor treatment). Also, unlike the Long study, we have limited our study to participants with angina only (and have excluded studies with patients having other CVD conditions). In addition, our study includes published papers that were not reported in the Long study, including both randomized controlled trials and observational studies (the Long paper contained only data from randomized controlled trials). The results of our study are also in line with the results from nearly all of the studies included in our analysis, with one exception—the study by Maxwell reported higher angina frequency in CR participants undergoing a dietary intervention only.

Our systematic review found 2 studies that tested the association between CR and all-cause mortality in their patients. In both studies, there was a nonsignificant association toward higher all-cause mortality in the CR intervention group compared with control. However, several limitations of this finding are notable, mainly in the study by Burr et al,¹⁸ which was also the main study with a significantly larger population of patients. In that study, the intervention for the CR group was dietary only (counseling to increase intake of fruits and vegetables, plus the recommendation to take a fish oil capsule). In addition, the definition of angina was indirect and based on the report from the patient's primary care provider of a patient's history of previous nitrate use. Furthermore, adherence to the dietary counseling was reported to be very poor among participants.

We also found that CR participation reduced angina frequency and increased exercise capacity. This is in line with the results of

previous studies that have found that various components of CR, including exercise training, weight loss, and smoking cessation, can reduce the frequency of angina.²⁹⁻³¹ These effects are likely to be related to the beneficial effects of these lifestyle changes on a variety of vascular and rheologic factors.^{29,32} Exercise itself, one of the most fundamental and effective components of CR, has been found not only to affect several of the other components of CR³³⁻³⁷ but also to improve endothelial function, to decrease oxidative stress and arterial stiffness, and to increase myocardial perfusion.³⁸⁻⁴⁰ These effects alone suggest that exercise training during CR should lead to beneficial improvements in angina and CVD outcomes.

There are limitations to our study. First, relatively few studies met entry criteria for our study. Second, significant heterogeneity was noted between studies included in our analysis. This heterogeneity was, in large part, due to differences in how clearly stable angina was defined and described in the studies. Additional heterogeneity in our study was due to the variation in the CR intervention modalities used, their frequency, and the patient's adherence. In addition, most of the studies in our analysis had a relatively short follow-up period, from weeks to months, which is typically not long enough to detect most major CV outcomes.

CONCLUSION

We found that CR is associated with a reduced frequency of stable angina and improved exercise capacity. However, limitations to our data reduce our ability to fully evaluate the impact of CR on outcomes in patients with angina. Additional research is needed to clarify the

potential role of CR for patients with stable angina.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <https://mcpiqjournal.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: CABG = coronary artery bypass graft; CR = cardiac rehabilitation; CV = cardiovascular; CVD = cardiovascular disease; HRQL = health-related quality of life; MI = myocardial infarction; PCI = percutaneous coronary intervention; SMD = standard mean difference



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Grant Support: The work was supported by the Division of Preventive Cardiology, Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN.

Potential Competing Interests: The authors report no competing interests.

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