THE EFFECT OF CARDIAC REHABILITATION DOSE IN REDUCING MORTALITY & MORBIDITY: HOW LOW CAN WE GO? – A SYSTEMATIC REVIEW AND META-REGRESSION

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FINANCIAL SUPPORT AND CONFLICT OF INTEREST DISCLOSURE: All authors declare that there is no funding or conflicts of interest.

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ABSTRACT

OBJECTIVE: To ascertain the effect of CR dose (i.e., duration x frequency/week; categorized as low [<12 sessions], medium [12-35], or high [≥36]) on mortality and morbidity.

PATIENTS AND METHODS: The Cochrane, CINAHL, EMBASE, PsycINFO and MEDLINE databases were systematically searched from inception through November 30, 2015. Inclusion criteria included randomized or non-randomized studies, with a minimum CR dose ≥4, and presence of a control/comparison group. Citations were considered for inclusion, and data were extracted in included studies independently by 2 investigators. Studies were pooled using random-effects meta-analysis, and meta-regression where warranted (covariates included study quality, country, publication year, and diagnosis).

RESULTS: Of 4630 unique citations, 33 trials were included comparing CR to usual care (i.e., no dose). In meta-regression, greater dose was significantly related to lower all-cause mortality (high= -.77, Standard Error [SE]=.22, *P*<.001; medium=-0.80, SE=0.21, *P*<.001), when compared to low dose.

With regard to morbidity, meta-analysis showed dose was significantly associated with less percutaneous coronary intervention (PCI; high: RR=.65, 95% CI .50 -.84, and medium/low: RR=1.04, 95% CI .74-1.48; *P*=.03). This was also significant in meta-regression (high vs. medium/low=-.73, SE=.20, *P*<.001). Publication bias was not evident. No dose-response association was found for cardiovascular mortality, all-cause hospitalization, coronary artery bypass graft surgery, or myocardial infarction.

CONCLUSION: A minimum of 36 CR sessions may be needed to reduce PCI. Future studies should examine the effect of actual dose of CR, and trials are needed comparing different doses.

PROSPERO REGISTRATION: CRD42016036029

LIST OF ABBREVIATIONS

CABG = coronary artery bypass graft

CCR = comprehensive cardiac rehabilitation

CVD = cardiovascular disease

HF = heart failure

MI = myocardial infarction

PCI = percutaneous coronary intervention

BACKGROUND

Cardiovascular disease (CVD) is one of the most prevalent health conditions globally [1]. With advances in acute treatment, many patients are surviving an initial cardiac event, and hence there are many people living with chronic CVD. These patients are at increased risk of a subsequent event [2]. Comprehensive cardiac rehabilitation (CCR) is an outpatient chronic disease management program designed to optimize secondary prevention [3,4,5]. It is well-established that CCR is a cost-effective model of care[6,7], which reduces CV mortality by approximately 25% and hospital re-admissions by 18% [8].

CCR programs around the world are of varying durations, and sessions are offered at varying frequencies [9]. For example, in a recent review of CR guidelines [10], the recommended duration ranged from a minimum of 3 weeks in Germany (although this is often residential) to a maximum of 12 months in Austria. The frequency recommended by the American Association of Cardiovascular and Pulmonary Rehabilitation, as well as the Canadian and European Associations of Cardiovascular Prevention and Rehabilitation was a minimum of 3 sessions per week, whereas guidelines for Austria, Australia, Japan and the United Kingdom recommend 3 or fewer per week. Therefore, the "dose" is not standard, and is generally based on funding policies and past practice. This variation significantly affects costs to deliver CCR, capacity to serve patients, and also outcomes achieved. Indeed, previous work has shown that the more CCR patients receive, the better their outcomes [11,12,13,14,15,16].

There are no evidence-based recommendations on which CCR programs can base decisions on what dose should be offered to patients to achieve optimal clinical outcomes to our knowledge. The effect of CR dose on mortality and morbidity has been scantly examined in the literature previously, with variable and inconsistent definitions (see Table 1).

In the Cochrane reviews on CR, sensitivity analyses on dose were performed, first in 2004 [17], and again in 2011 [18] and 2016 [8] updates. CR dose was operationalized by multiplying the number of weeks of exercise (i.e., program duration) by the number of training sessions per week (i.e., frequency) and by the average duration of exercise sessions in minutes (personal communication). Dose was then stratified as ≤ vs > 1,000 "units". No associations between dose and outcomes were observed in the first 2 meta-analyses, but in the most recent one, patients who had ≥1,000 units had 25% lower CV mortality and 26% lower myocardial infarction (MI). Similarly, in the meta-analysis by Lawler et al [19], patients exposed to a higher dose of CR, in this case a program of ≥3 months duration, had significantly lower CV mortality and MI, but not all-cause mortality. There have also been some primary studies which examined dose (Table 1), all which operationalized it based on number of sessions, using various thresholds. These studies report a dose-response association between CR participation and mortality / morbidity.

Given these mixed and indeterminate findings, it is warranted to undertake a quantitative review with the primary objective of assessing how and what CCR dose affects mortality and morbidity. Arguably these are the most important CCR outcomes for patients and the healthcare system. The purpose of this paper was therefore to examine the effect of CCR dose on all-cause and CV-related mortality, all-cause and CV-related hospitalization, non-fatal MI, and revascularization – namely coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI). The aim was to determine a minimum effective dose of CCR, to inform policy and practice.

METHODS

A protocol was developed and registered in the International Prospective Register of Systematic Reviews (ID=CRD42016036029)[21]. The methodology was based on the Cochrane Collaboration handbook [22].

SEARCH STRATEGY AND DATA SOURCES

The systematic search strategies were developed with an information specialist (MP) for each of the databases shown in Figure 1. The strategies utilized the PICO model and were limited to humans, with no date restrictions, through to November 2015. Subject heading terms relating to CCR and free text terms such as “dose”, “duration”, “mortality”, and “morbidity” were used. As an example, the search strategy for MEDLINE is shown in Supplemental Table 1.

Reference lists from relevant reviews (e.g., those reported in Table 1) were hand-searched for potentially-relevant articles. The main authors of conference abstracts and dissertations were contacted for any peer-reviewed publications stemming from their work that could be considered for inclusion. In addition, studies that reported some but not all needed aspects of dose were contacted to request additional information. These studies were included if the information was received.

INCLUSION AND EXCLUSION CRITERIA

Articles were sought which reported CCR dose in more than one condition with mortality or morbidity outcomes reported for each condition. CCR was defined as an outpatient (i.e., phase II) [23] program offering structured exercise training and at least patient education. Programs had to consist of ≥4 sessions (i.e., minimum dose). The program could be delivered in supervised (i.e., hospital or medical center-based) or unsupervised (i.e., home or community-based) settings. Programs offering both were considered “hybrid”.

Dose of CCR had to be explicitly reported for each condition, namely the duration of program in weeks and the frequency of sessions per week. For example, the dose of a typical CR program in the United States prescribing 3 sessions per week for 12 weeks would be 36.

Outcomes were mortality (all-cause or CV) or morbidity (i.e., hospitalization [all-cause or CV cause], non-fatal MI, CABG surgery, PCI,), with no time limit. Studies had to report on adult patients with CCR-qualifying cardiac conditions (i.e., acute coronary syndrome, chronic stable angina, stable heart failure[24] [HF], or post-revascularization procedure [CABG and PCI]) referred to CCR. Randomized controlled trials, non-randomized studies, and primary observational studies were included.

Finally, only peer-reviewed studies in English, Spanish and Portuguese languages were included. Studies that were not original quantitative research (i.e., meta-analyses, systematic reviews, published letters, abstract only, comments, editorials, case-series and case reports), and non-peer reviewed publications (e.g., dissertations) were excluded. Additionally, studies that included *solely* patients who underwent heart transplantation, had ventricular assist devices, arrhythmias and valve procedures were excluded. Moreover, residential and multi-site studies where patients participated in CCR programs of differing doses, and outcomes were not reported by dose, were excluded.

STUDY SELECTION

The title and abstract of identified citations from all databases. Following calibration meetings with the senior author, citations were independently evaluated by two reviewers (CP & SA). Citations were rejected if the reviewer determined that the paper did not relate to CCR dose and outcomes. Discrepancies were resolved by a third independent reviewer (SLG).

The full-text of relevant citations were obtained. Two reviewers (CP & SA) independently assessed the papers for inclusion based on the criteria outlined above. Discrepancies were resolved between reviewers, and if agreement was not possible a third independent reviewer was consulted (SM).

DATA EXTRACTION PROCESS & QUALITY ASSESSMENT

Two investigators (CS and SA) independently extracted data from articles, after calibration and pilot testing. Discrepancies were resolved by a third reviewer (SM).

Given studies of various research designs were included, a quality assessment tool applicable to randomized and non-randomized studies was selected. The tool by Downs and Black [25] consisting of 27 items was used. The last item regarding power calculation was modified to be dichotomous; therefore the maximum score was 27, with higher scores indicative of higher quality. Two reviewers (CS and BL) independently assessed each study regarding its quality. Discrepancies were resolved between the reviewers. The median quality rating was used to differentiate between high versus low quality for sensitivity analyses.

DATA SYNTHESIS AND ANALYSIS

Studies were considered based on whether they compared 2 or more CCR doses, or 1 dose versus usual care for the purposes of pooling. Many included studies with 2 doses delivered sessions in a different setting in each arm (i.e., one arm supervised and the other home-based; e.g., [26,27]), and it was considered inappropriate to test effect of dose when setting may also impact outcome. In some other studies with 2 doses, the same number of sessions were offered in both arms, but they were delivered less frequently over a longer duration for example (i.e., distributed) [28,29] or the difference in dose was based on duration of sessions; therefore for the purposes of this study dose would have been equivalent in both arms and therefore quantitative comparison was deemed inappropriate. Ultimately

there was only 1 study with 2 doses considered appropriate for testing [30], and thus there were insufficient 2-dose studies to undertake pooled analysis. Therefore, meta-analysis was performed only on studies with 1 dose versus no dose (i.e., usual care, or slightly enhanced usual care in some instances).

Exploring dose as a continuous variable was not fruitful in our preliminary analyses; This could be because dose is not normally distributed (e.g., all studies in the United States offer 36 sessions). Therefore, our approach to categorize dose was considered from an empirical and practical standpoint. First a forest plot was created, sorted in descending order of dose (i.e., sessions). Further visual inspection and evidence from previous literature [13,31] was used to develop 3 categories of dose: low was 4-11 sessions, medium was 12-35 session, and high was ≥36 sessions. Where there were <2 studies in a given dose categorization for a specific outcome, the studies were included in the next larger dose category.

Data were analyzed using the Comprehensive Meta-Analysis Software version 3 (Biostat, Englewood, NJ). First, a mixed-effects meta-analysis was conducted for each outcome, where dose category was considered in subgroup analysis if significant. Pooled risk ratios between CCR and usual care were estimated by random-effect models with the DerSimonian-Laird method[32].

Where significant, heterogeneity for each meta-analysis was assessed by the I^2 statistic [33]. I^2 >40% were considered indicative of a moderate level of heterogeneity, warranting further investigation through meta-regression. Indeed, considering dose as a covariate through meta-regression is considered a stronger approach than subgroup analysis in meta-analysis [34].

A meta-regression was conducted to examine the association between dose categorization and outcomes, using a random-effect model, while accounting for other covariates that may be sources of

heterogeneity. Session frequency and program duration were also considered as a "set" to test whether either of these aspects of dose were particularly influential alone or as a group. Pre-specified covariates included follow-up duration (months), country where the study was conducted (Europe, North America vs other), study design (e.g., randomized trial), study quality, publication year (given that standard background preventive medical therapy has improved over time, and that there have been changes in approaches regarding some of the outcomes; e.g., the definition of MI, indications for and use of drug-eluting vs bare metal stents, and recommendations regarding choice of revascularization modality), mean age of the participants, and diagnosis (i.e., MI, HF, various). To avoid "over-fitting" the models and reduce the possibility of false-positive results, only the covariates that were significant or trended toward significance (i.e., $p<.07$) were included in the final meta-regression models [35]. Collinearity among the covariates was considered by examining the correlation matrix of the regression coefficient estimates. Finally, scatter "bubble" plots were constructed to graphically display the adjusted association between CCR dose and outcome.

ASSESSMENT OF REPORTING BIASES

For all outcomes, publication bias was considered by reviewing the funnel plot, and the Egger test of the intercept in the funnel plot [36]. If significant, the Duval and Tweedie trim and fill procedure was performed, to estimate the number of studies required to make the funnel plot more symmetric and to estimate the impact of these additional studies on the outcome.

RESULTS

SEARCH RESULTS

Figure 1 displays the results of the search, and application of inclusion/exclusion criteria. Authors of all primary studies shown in Table 1 were contacted, if these studies were not eligible for inclusion

due to lack of information (i.e., hazard ratios reported but not outcome event data; none responded). Ultimately 33 studies were included (Table 2).

CHARACTERISTICS OF INCLUDED STUDIES

Study Characteristics

Characteristics of each included study are shown in Table 2. Publication year ranged from 1972-2013 (median=2005). With regard to design, 22 (66.6%) were RCTs, 7 (21.2%) non-randomized trials, and 4 (12.1%) were observational cohort (retrospective or prospective) studies. The majority of studies were conducted in Europe (n=21, 63.6%), while 6 (18.1%) were conducted in Australasia, 5 (15.1%) in North America, and 1 (3.0%) in Africa[69]. Seven (21.2%) were multi-site studies.

With regard to quality assessment, the median quality rating was 20/27, and ranged from 16-25. Overall, 21 (63.6%) studies were rated as "high" quality (i.e., ≥20; Table 2). The number of studies reporting each outcome and the median follow-up time for each are shown in Table 3.

CCR Characteristics and Dose

CCR characteristics are shown in Table 2. Across all included studies, the median program duration was 12 weeks (mean±SD [standard deviation]=16.8±14.6; range=4-52). With regard to frequency, the overall median number of prescribed sessions/week was 2.5 (mean±SD=2.6±1.1; range=1-5). The mean dose across all included studies was 51.3±62.4 sessions, with a median of 30, and a range of 9-260.

Patient Characteristics

The included studies comprised 15,133 participants, with the largest study accounting for 26.9% (n=4084) of total participants[37]. Women accounted for approximately one-fifth of all study

participants (19.7%, n=2983). The mean age of participants was 60.1±6.5, ranging from 51.0 [49] -75.4 [41] years. With regard to cardiac diagnoses, thirteen (39.3%) studies enrolled patients post-MI only, 5 (15.1%) studies included HF patients only, and 14 (42.4%) studies enrolled patients with various cardiac diagnoses or procedures.

EFFECT OF DOSE ON CLINICAL OUTCOMES

A summary of findings is shown in Table 3.

Mortality

All-Cause Mortality

Of the studies reporting all-cause mortality, two reported no events/deaths in both groups,[54,44] and thus were excluded from the meta-analysis. The forest plot with dose subgroups is shown in Figure 2a. The effect of dose subgroup was not significant. Significant heterogeneity was observed.

In the meta-regression model (Figure 2b and Supplemental Table 2), the test of significance for dose as a set (low, medium, high dose) on all-cause mortality was significant with the most influential covariates held constant. CCR programs that prescribe a high dose are more effective in providing a mortality advantage than CCR programs that prescribe a low dose. Similarly, medium-dose CCR programs were more effective than low-dose programs. There was no significant association between all-cause mortality and session duration or frequency individually (data not shown). The parsimonious model accounted for the heterogeneity.

Cardiovascular Mortality

Supplemental Figure 1 displays the forest plot for subgroup analysis of the effect of CCR dose categorization on CV-related mortality. As shown, no significant association was observed.

Morbidity

All-Cause Hospitalization

Due to the small number of low dose studies for this outcome, low and medium dose studies were combined. Meta-analysis revealed no significant association of CCR dose with all-cause hospitalization (Supplemental Figure 2).

Cardiovascular-Related Hospitalization

Supplemental Figure 3 displays the forest plot for the meta-analysis testing the subgroup effect of CCR dose categorization on CV-related hospitalization. The effect of dose subgroup was not significant. Significant heterogeneity was observed.

The meta-regression adjusted for country where the study was conducted. The overall model was not significant.

Non-Fatal Myocardial Infarction

Supplemental Figure 4 displays the forest plot for the meta-analysis testing the subgroup effect of CCR dose categorization on MI. As shown, there was no significant reduction in the risk of MI by CCR dose. Heterogeneity was limited.

Coronary Artery Bypass Graft Surgery

Supplemental Figure 5 displays the forest plot for the non-significant meta-analysis testing the subgroup effect of CCR dose categorization on CABG (trend observed). Heterogeneity was limited.

Percutaneous Coronary Intervention

As there was only one low-dose study, low and medium dose studies were combined. Figure 3a displays the forest plot for the meta-analysis testing the subgroup effect of CCR dose on PCI. There was a significant reduction in the risk of having a PCI procedure with high dose CCR, but not with low/medium dose CCR, when compared to usual care. Heterogeneity exceeded threshold.

In meta-regression analysis, the association of CCR dose with PCI sustained adjustment for length of follow-up and country where the study was conducted (Supplemental Table 3, Figure 3b). There was a greater effect size for reduction in PCI with high compared to low/medium dose CCR. There was no significant association between all-cause mortality and session duration or frequency individually (data not shown). This parsimonious model accounted for the heterogeneity.

PUBLICATION BIAS

Funnel plots were generated for all outcomes with ≥10 studies. There was no evidence of funnel plot asymmetry nor significant Egger tests for any outcome suggesting no publication bias (Supplemental Figure 6 for PCI), except in the case of all-cause mortality (Figure 4). The Egger's tests was also significant for this outcome. The trim and fill method results are also shown below the Figure, and suggest 4 studies would be required to mitigate publication bias. The corresponding adjusted point estimate and confidence intervals suggest the effect would nevertheless remain significant, and therefore it was considered warranted to undertake meta-regression.

DISCUSSION

This first ever meta-regression with a primary objective of examining CR dose suggests that dose of CCR may impact mortality and morbidity. While a dose-response association was not observed for many outcomes, results suggested cardiac patients should be prescribed at least 36 sessions to reduce

PCI. Results also suggested that patients should be prescribed at least 12 sessions to reduce all-cause mortality, however this warrants replication given dose overall as a subgroup was not significant in the meta-analysis (however meta-regression is the more sound way to test dose effects) and publication bias may have been at play. Results did not suggest that program duration or frequency alone had an impact on these outcomes, but that overall dose (i.e., total number of sessions, regardless of the time frame over which patients engage in CR) was what mattered. Unfortunately there were insufficient low-dose studies examining PCI outcomes and dose was not analyzed as a continuous variable, therefore a minimal CCR dose threshold cannot yet be quantified. Overall however, these findings, consistent with the primary studies on dose reported in Table 1, hold important ramifications for delivery of CCR globally.

Indeed country was a significant covariate in both the all-cause mortality and PCI meta-regressions. It is established that recommended CCR dose varies broadly by country,[10,70] based on reimbursement policies for example.[71] This raises questions about the sufficiency of dose of CCR delivered in practice around the globe, and hence CCR care quality. These results suggest that CCR as delivered in the United States [72] (i.e., 36 sessions) and Ontario, Canada [73] (i.e., 40 sessions) is sufficient to achieve the mortality and morbidity reductions, if patients adhere to their prescribed program [8]. However, CCR as delivered in parts of Europe and the United Kingdom may not be sufficiently intense. It is well-established that the minimum standard of CCR in the United Kingdom is 8 weeks (frequency is not specified but RAMIT stated 1-2 times/week) [74] [31]. In the Rehab After Myocardial Infarction Trial (RAMIT) [31], patients on average received only 10.5 sessions (1.5 sessions/week x 7 weeks); The results reported in the present review may explain their null findings. Disconcertingly, a recent report shows only 2/3rds of CR programs in the United Kingdom even meet this minimum 8–week standard [75]. Augmenting CCR dose across countries where standard prescriptions are below the

minimum thresholds herein should be advocated, which would require significant policy, capacity and funding changes.

It was surprising that CCR dose was not associated with CV mortality, as it was associated with this outcome in previous meta-analyses (Table 1) [8,19]. This may be explained by the fewer studies included in this review due to the specific inclusion criteria regarding dose reporting. Indeed, only 10 studies were included for this outcome. Still, the findings reported here should not be interpreted to suggest that CCR participation is not associated with the outcomes under investigation for this reason. The effect of dose on all-cause mortality was trending toward significance in the 3 other meta-analyses where it was tested, and was significant in all the primary studies where it was tested (Table 1), consistent with the findings herein. The impact on all-cause mortality could be due to the fact that the elements of CR impact common risk factors for other chronic non-communicable diseases such as cancer, chronic obstructive pulmonary disease and diabetes.

Consistent with the present findings of a significant impact of dose on PCI, again the association was very close to significant in the only other meta-analysis where it was tested (Table 1) [8]. All-cause hospitalization was not tested in any other meta-analysis, and hence comparison with the null findings herein is not possible at this time. MI was tested in 3 previous meta-analyses, with 2 of the 3 showing null findings, consistent with the findings of the current analyses. Finally, the 2 previous meta-analyses that tested the impact of dose on CABG also found no association (Table 1).

Caution is warranted in interpreting the findings herein. First, where few studies were available for a given outcome, the number of covariates which could be considered was limited. However, for the significant outcomes of all-cause mortality and PCI, all significant covariates were included. Second, while analyses were adjusted by many factors which may have influenced the outcomes, there may

have been others that were not considered. For instance, few studies reported comprehensively the components of CR delivered to take this into consideration. Third, the findings for all-cause mortality should not be over-interpreted considering publication bias may be at play. The findings for PCI however were not impacted by publication bias. Finally, all meta-analyses are observational and hence causal conclusions should not be drawn. As this study sought details regarding dose, non-randomized trials were included which may in particular warrant caution (however the majority of studies were randomized).

Replication and further research is warranted prior to confirming the minimum dose of CCR to impact mortality and morbidity. Indeed, there are some inconsistencies in findings in the literature, which are likely related to different approaches to the question, and in particular different approaches to dose operationalization. First, the test of association between dose and outcome would be much stronger if not prescribed, but actual dose received, was tested. CCR researchers are urged to collect and report received, not only prescribed, dose of CCR in all publications to support an individual participant data meta-analysis in future. Indeed, our recent meta-analysis found patients adhered to only 2/3rds of prescribed sessions[76]; reasons for dropout include distance, perceiving exercise as tiring or painful, work and family responsibilities, as well as clinical factors.[77,78] Therefore, a second important consideration in the subsequent iteration of this work would be to consider disease severity and comorbidities. There could be bias such that sicker patients cannot continue CR for clinical reasons; hence they would receive a lower dose and also have more events (i.e., selection bias). Alternatively, patients who are more ill and hence deconditioned, such as older patients, or those with HF (considered herein) or comorbid diabetes, may need less dose to achieve improved mortality and morbidity. This information would enable tailoring of CCR prescriptions based on patient risk/case-mix, and potentially cost-containment.

Third, more primary randomized trials are required comparing different doses of CR so more specific recommendations regarding dose can be forwarded. It would be informative to test this within the same country, to rule out any differences in standard CCR practice, given that programs are generally higher dose in North America when compared to Europe (although the analyses adjusted for country). Given the impending changes to reimbursement in the United States in particular, this may represent an important opportunity to examine the impact of lower dose versus the standard 36 sessions offered in this country. Fourth, the impact of CCR dose on quality of life, another important outcome, should be investigated. Fifth, ultimately the question of dose was tested primarily in supervised CCR programs. Investigating the minimum effective CCR dose in unsupervised settings should also be pursued. Sixth, why dose was related to percutaneous but not surgical revascularization rates is curious (although a trend was observed); this could be due to the higher number of percutaneous than surgical procedures, differences in the profiles of patients undergoing these procedures, differential impact of CR on outcomes,[51] and different rates of mortality even in the absence of CCR in these populations.[79] Further study is warranted prior to drawing inferences. Seventh, unfortunately there were very few studies that reported exercise intensity and session duration to consider these important components of CR dose. However, these likely vary by patient and over the course of CCR and hence it may be difficult to adjust for them. A more sophisticated approach should be considered to capture all elements of CR dose in future examinations (see for example Kuo et al., 2016 in Table 1).[20] On a related note, how dose is defined should be further considered. Herein, a floor of 4 sessions was used; it may have been difficult to detect a difference in outcomes from studies where the "no CCR dose" comparison arm received enhanced usual care (e.g., in 6/33 studies, patients may have had 1 or 2 visits with a healthcare provider to receive education or counselling). If this could be considered more carefully, perhaps a better test of the effect of low-dose CR on outcomes could be achieved.

CONCLUSION

A significant association exists between CCR sessions and all-cause mortality as well as PCI. There was 35% less PCI where CCR participants were prescribed at least 36 sessions. Overall results suggest a minimum of 12 CCR sessions may be needed to improve clinical outcomes, although greater benefits may be achieved with at least 36. CR guidelines globally should promote prescription of at least this many sessions by all programs. Future studies should examine the effect of actual dose of CR, and trials are needed comparing different doses.

ACKNOWLEDGMENTS

We gratefully acknowledge Ms. Saba Ali and Beatrice Luu for efforts in quality assessment and data extraction.

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FIGURES TITLES AND LEGENDS

FIGURE 1 – Study Selection PRISMA Flow Diagram

CABG, coronary artery bypass graft; CCTR, Central Register of Controlled Trials; CDSR, Cochrane Database of Systematic Reviews, CINAHL; Cumulative Index to Nursing and Allied Health Literature; CCR, Comprehensive Cardiac Rehabilitation; CV, Cardiovascular; MI, myocardial infarction; PCI, percutaneous coronary intervention.

FIGURE 2 – Effect of Cardiac Rehabilitation Dose on All-cause Mortality

a. Forest plot

Heterogeneity: I^2= 58.58%, *P*<.001;

Test for dose subgroups (mixed-effect analysis), *P*=.61.

Values for dose categories are Low=<12; Medium=12-35; High≥36 sessions.

CCR, comprehensive cardiac rehabilitation; CI, confidence interval.

Note: The box sizes are proportional to the weight of each study in the analysis. The red diamonds represent the pooled relative risk for the given dose category, and its width represents its 95% confidence interval.

b. Bubble Plot

Adjusted for study quality, country, publication year, and diagnosis.

Dose categories are Low=<12; Medium=12-35; High≥36 sessions.

Note: Bubbles represent studies with size relative to the precision of each estimate; horizontal lines represent 95% confidence intervals.

FIGURE 3 - Effect of Cardiac Rehabilitation Dose on Percutaneous Coronary Intervention

a. Forest plot

Heterogeneity: I^2= 45.70%, *P*=.42;

Test for dose subgroups (mixed-effect analysis), *P*=.03.

Dose categories are Low-Medium dose<35; High dose≥36 sessions.

CI, confidence interval; Med, medium.

b. Bubble Plot

Adjusted for length of follow-up, and country.

Dose categories are Low-Medium dose<35; High dose≥36 sessions.

FIGURE 4 – Tests for Publication Bias for All-Cause Mortality

Egger's test for small-study effects: *P*=.006

TABLE 1 - Summary of Previous Seminal Studies on Cardiac Rehabilitation Dose

			Outcomes						
	CR Dose				Morbidity				
Design Author, year, country	**Definition**	**Categorization**	**Mortality**		**Hospitalization**		**MI**	**CABG**	**PCI**
			All-cause	**CV-related**	**All-cause**	**CV-related**[a]			
Meta-analyses									
Taylor et al, 2004[17]	Number of weeks of exercise X average number of sessions /week X average duration of session in minutes	< 1000 units	OR = 0.81; (0.50 -1.32)	-	-	-	-	-	-
		≥ 1000 units	OR = 0.75; (0.55 - 1.02)	-	-	-	-	-	-
Heran et al., 2011[18]	Number of weeks of exercise X average number of sessions/week	< 1000 vs ≥ 1000 units	RR = 1.00; (1.00 to 1.00)	RR = 1.00 (1.00 - 1.00)	-	-	RR = 1.00 (1.00 - 1.00)	RR = 1.00 (1.00 - 1.00)	RR=1.00 (1.00 - 1.00)

	X average duration of session in minutes								
Lawler et al., 2011[19]	Duration of CR	0.5 to 3 months	OR = 0.71 (0.51-1.01)	OR = 0.83 (0.31-2.22)	-	-	OR = 0.69 (0.43-1.11)	-	-
		> 3 months	OR = 0.77 (0.54 - 1.09)	OR = 0.57 (0.37 - 0.88)	-	-	OR = 0.40 (0.24 - 0.66)	-	-
Anderson et al. 2016[8]	Number of weeks of exercise training X average number of sessions/week X average duration of session in minutes	< 1,000 units ≥ 1000 units	RR = 0.89 (0.26–3.15) RR = 1.01 (0.89–1.15)	RR = 0.47 (0.19–1.15) RR = 0.75 (0.65–0.86)	- -	RR = 0.70 (0.48–1.00) RR = 0.85 (0.71–1.01)	RR = 0.72 (0.30–1.70) RR = 0.74 (0.59–0.93)	RR = 0.96 (0.35–2.66) RR = 0.99 (0.78–1.27)	RR = 1.22 (0.34–4.34) RR = 0.80 (0.62–1.03)
Primary studies									
Whellan et al. 2001, USA[12]	Number of sessions	≤ 6 sessions	HR = 0.39 (0.15 – 0.62)	-	-	-	-	-	-
		> 6 sessions	HR = 0.10 (0.03 – 0.39)	-	-	-	-	-	-

Suaya et al. 2009, USA[13]	Number of sessions	High Users (25 or more sessions)	16.3% cumulative mortality at 5 years	-	-	-	-	-	-
		Low-users (1 – 24 sessions)	24.6% cumulative mortality at 5 years	-	-	-	-	-	-
Hammill, 2010, USA[14]	Number of CR sessions patients attended	36 sessions vs 24 sessions	HR = 0.86 (0.77 – 0.97)	-	-	-	HR = 0.88 (0.83 – 0.93)	-	-
		36 sessions vs 12 sessions	HR = 0.71 (0.64 – 0.78)	-	-	-	HR = 0.77 (0.69 – 0.86	-	-
		36 sessions	HR = 0.42 (0.38 – 0.47)	-	-	-	HR = 0.68 (0.58 –	-	-

		vs 1 session					0.81)		
Doll, 2015[15]	HR for every additional 5 CR sessions	-	HR = 0.87 (0.83 – 0.92)	-	HR = 0.69 (0.65 – 0.73)	-	-	-	-
Kuo, 2016[20]	Number of Sessions	< 6 sessions	Event-free survival rate 61.4%	-	-	-	-	-	-
		≥ 6 sessions	Event-free survival rate 57.8%[b]	-	-	-	-	-	-
	Exercise intensity difference ratio between first and last training session[c]	<12%	60.5% (HR: 0.482, 95% CI: 0.358–1.008)[b]	-	-	-	-	-	-
		≥12%	66.7% (HR: 0.601; 95% CI: 0.243–0.956)	-	-	-	-	-	-

Values are odds ratio, relative risk, hazard ratio, values in parentheses report 95% confidence intervals.

CR; cardiac rehabilitation, CV; cardiovascular, MI; myocardial infarction, PCI; percutaneous coronary intervention, CABG; coronary artery bypass graft; -, not available

[a]major adverse cardiac events: death, readmission for MI, stroke, or revascularization.

[b] difference not significant.

[c] the proportion of the difference between the peak intensities achieved in the first and last sessions divided by the peak intensity achieved in the first session.

TABLE 2. Study and Patient Characteristics of Included Papers, N=33

Study first author, year, country	Study design, quality score (/27)	Participants: analyzed sample size, cardiac diagnoses, mean age, male n. (%)	CR setting, Duration in weeks x Frequency / week = Dose[a]	Study outcomes, follow-up time (months)
Alter et al, [37] 2009, Canada	Observational, Retrospective, 21	4084, ACS, HF, PCI, CABG, 59.40, 3471 (87)	Hybrid, 52 x 5 = 260	ACM (62)
Austin et al, [38] 2008, United Kingdom	RCT, 20	200, HF, 73.50, 132 (66)	Supervised, 16 x 1 = 16	ACM, ACH (60)
Beauchamp et al, [39] 2013, Australia	Observational, Retrospective, 20	544, ACS, PCI, CABG, 62.55, 397 (73)	Supervised, 9 x 1 = 9	ACM (170)
Bengtsson et al, [40] 1983, Sweden	RCT, 21	116, ACS, 56.20, 99 (85)	Supervised, 12 x 2 = 24	ACM, MI (14)
Bondestam et al, [41] 1995, Sweden	Non-randomized trial, 17	190, ACS, 75.45, 110 (58)	Supervised, 6 x 1 = 6	ACM, ACH, CH, MI (12)
Briffa et al, [42] 2005, Australia	RCT, 21	113, ACS, PCI, CABG, 61.35, 82 (73)	Supervised, 6 x 3 = 18	ACM, CM, ACH, MI, CABG, PCI (12)
Carlsson et al, [43] 1998, Sweden	RCT, 20	289, ACS, PCI, CABG, 62.10, 217 (75)	Supervised, 10 x 2.5 = 25	ACM (12)
Chung et al, [44] 2010, Taiwan	RCT, 22	87, ACS, 57.70, 78 (90)	Supervised, 8 x 3 = 24	ACM, CH, PCI (12)

Davidson et al, [45] 2010, Australia	RCT, 25	105, ACS, HF, PCI, CABG, COPD, 72.75, 65 (62)	Hybrid, 12 x 5 = 60	ACM, ACH, CH (12)
Dendale et al, [46] 2005, Belgium	Non-randomized trial, 16	223, ACS, PCI, 65.00, 160 (72)	Supervised, 12 x 3 = 36	ACM, MI (15)
Dendale et al, [47] 2008, Belgium	Non-randomized trial, 17	213, ACS, PCI, 61.70, 155 (73)	Supervised, 12 x 3 = 36	ACM, CM, ACH, CH, MI, CABG, PCI (54)
Denollet et al, [48] 2001, Belgium	Non-randomized trial, 18	150, ACS, CABG, 57.55, 150 (100)	Supervised, 12 x 3 = 36	ACM (108)
Erdman et al, [49] 1986, Netherlands	RCT, 16	80, ACS, 51.00, 80 (100)	Supervised, 24 x 1 = 24	ACM, MI (60)
Fridlund et al, [50] 1991, Sweden	RCT, 21	114, ACS, 56.30, 99 (87)	Supervised, 24 x 1 = 24	ACM, MI (12)
Hansen et al, [51] 2009, Belgium	Non-randomized trial, 18	677, ACS, CABG, 65.60, 467 (69)	Hybrid, 12 x 3 = 36	ACM, MI, CABG, PCI (24)
Hedback et al, [52] 2001, Sweden	Non-randomized trial, 19	147, ACS, CABG, 57.15, 118 (80)	Supervised, 12 x 2 = 24	ACM, CM, ACH, MI, CABG, PCI (120)
Kentala et al, [53] 1972, Finland	Non-randomized	158, ACS, 52.90, 158 (100)	Supervised, 52 x 2.5 = 130	ACM, CM (20)

	trial, 19			
Kovoor et al, [54] 2006, Australia	RCT, 22	142, ACS, HF, 56.00, 123 (87)	Supervised, 5 x 3 = 15	ACM, MI, CABG, PCI (6)
La Rovere et al, [55] 2002, Italy	RCT, 22	95, ACS, 51.50, 95 (100)	Supervised, 4 x 5 = 20	CM, MI, CABG (120)
Leizorovicz et al, [56] 1991, France	RCT, 20	121, ACS, NR, NR, NR	Supervised, 6 x 3 = 18	ACM, MI, CABG (24)
Lidell et al, [57] 1996, Sweden	RCT, 22	116, ACS, 56.30, 101 (87)	Supervised, 24 x 1 = 24	ACM, ACH, MI, CABG, PCI (60)
Maroto Montero et al, [58], 2005, Spain	RCT, 19	180, ACS, 51.45, NR, NR	Hybrid, 12 x 3 = 36	ACM, CM, MI, CABG, PCI (120)
Mehani et al, [59] 2013, Egypt	RCT, 21	40, HF, 56.40, 40 (100)	Supervised, 28 x 3 = 84	ACM, CM (7)
Nielsen et al, [60] 2008, Denmark	Observational, Prospective, 20	200, ACS, 59.80, 150 (75)	Supervised, 6 x 2 = 12	ACM, MI, CABG, PCI (24)
O'Connor et al, [61] 2009, USA	RCT, 23	2331, ACS, HF, PCI, 59.25, 1678 (72)	Hybrid, 12 x 3 = 36	ACM, CM, MI (30)
Oldridge et al, [62] 1991, Canada	RCT, 17	201, ACS, 52.80, 177 (88)	Supervised, 8 x 2 = 16	ACM (12)
Schuler et al, [63] 1992, Germany	RCT, 21	113, ACS, 53.50, 113 (100)	Hybrid, 52 x 5 = 260	ACM, CM, MI, CABG, PCI (12)
Sivarajan et al, [64] 1982, USA	RCT, 19	170, ACS, 56.70, 136 (80)	Hybrid, 12 x 1 = 12	ACM, CM, CABG (6)
The Vestfold Heartcare	RCT, 23	197, ACS, PCI, CABG,	Supervised, 15 x 2 =	ACM, CH (24)

Study Group et al, [65] 2003, Norway		54.50, 161 (82)	30	
West et al, [31] 2012, United Kingdom	RCT, 22	1813, ACS, 64.45, 1323 (73)	Supervised, 7 x 1.5 = 10.5	ACM, CH, MI, CABG, PCI (96)
Yu et al, [66] 2004, Hong Kong	RCT, 20	204, ACS, PCI, 64.00, 155 (76)	Supervised, 8 x 2 = 16	ACM, ACH (24)
Zeng et al, [67] 2013, USA	Observation al, Prospective, 18	950, ACS, PCI, CABG 72.50, 617 (65)	Supervised, 52 x 3 = 156	ACM, ACH, CH (36)
Zwisler et al, [68] 2008, Denmark	RCT, 24	770, ACS, HF, PCI, CABG, 66.00, 493(64)	Supervised, 6 x 2 = 12	ACM, ACH, CH, MI, CABG, PCI (12)

Values are number of participants (%) or average (mean). [a]duration of program in weeks X average number of sessions/week.

ACM, all-cause mortality; ACH, all-cause hospitalization; ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CH, cardiovascular hospitalization; CM, cardiovascular mortality; CR, cardiac rehabilitation; COPD, chronic obstructive pulmonary disease; HF, heart failure; HRmax, heart rate maximum; HRres, heart rate reserve; HRrest, Heart Rate Resting; MI, myocardial infarction; N, no; NR, not reported; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; USA, United States of America; VR, valve repair or replacement; VO_2max, VO_2 maximum; Y, yes.

TABLE 3 - Summary of Meta-Analysis Findings by Dose for Each Outcome

Outcome	**Number of studies**	**Follow-up (years)[a]**	**Events/number of patients (CCR)**	**Events/number of patients (usual care)**	**RR for dose categories[b] (95% CI)**
All-cause Mortality	32	2.00±3.44	711/7344	965/7465	Low 0.74 (0.47 to 1.15) Medium 0.58 (0.37 to 0.91) High 0.56 (0.41 to 0.78)
CV mortality	10	2.25±4.16	164/1780	199/1780	Medium 0.55 (0.29 to 1.04) High 0.87 (0.65 to 1.16)
All-cause Hospitalization	10	2.50±2.88	1023/1421	1526/1647	Low/Medium 0.84 (0.68 to 1.03) High 0.82 (0.48 to 1.40)
CV Hospitalization	8	1.50±2.49	556/2078	728/2317	Low 0.76 (0.49 to 1.18) Medium 0.64 (0.39 to 1.06) High 0.61 (0.40 to 0.95)
Non-fatal MI	20	2.00±3.33	194/3964	231/3831	Low 0.80 (0.57 to 1.12) Medium 0.75 (0.50 to 1.11) High 0.80 (0.46 to 1.40)
Coronary Artery Bypass Graft	14	2.00±3.67	135/2515	143/2396	Medium 0.99 (0.76 to 1.29)

Surgery					High 0.60 (0.36 to 0.98)
Percutaneous Coronary Intervention	12	2.00±3.64	232/2362	203/2250	Low/Medium 1.04 (0.73 to 1.48) High 0.65 (0.50 to 0.84)

Values are relative risk by dose category. [a]Values for follow-up are expressed by median and standard deviation. [b]Duration of program in weeks x average number of sessions/week.

CCR; comprehensive cardiovascular rehabilitation; CI: Confidence Interval; CV: cardiovascular; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; NA: not applicable

FIGURE 1

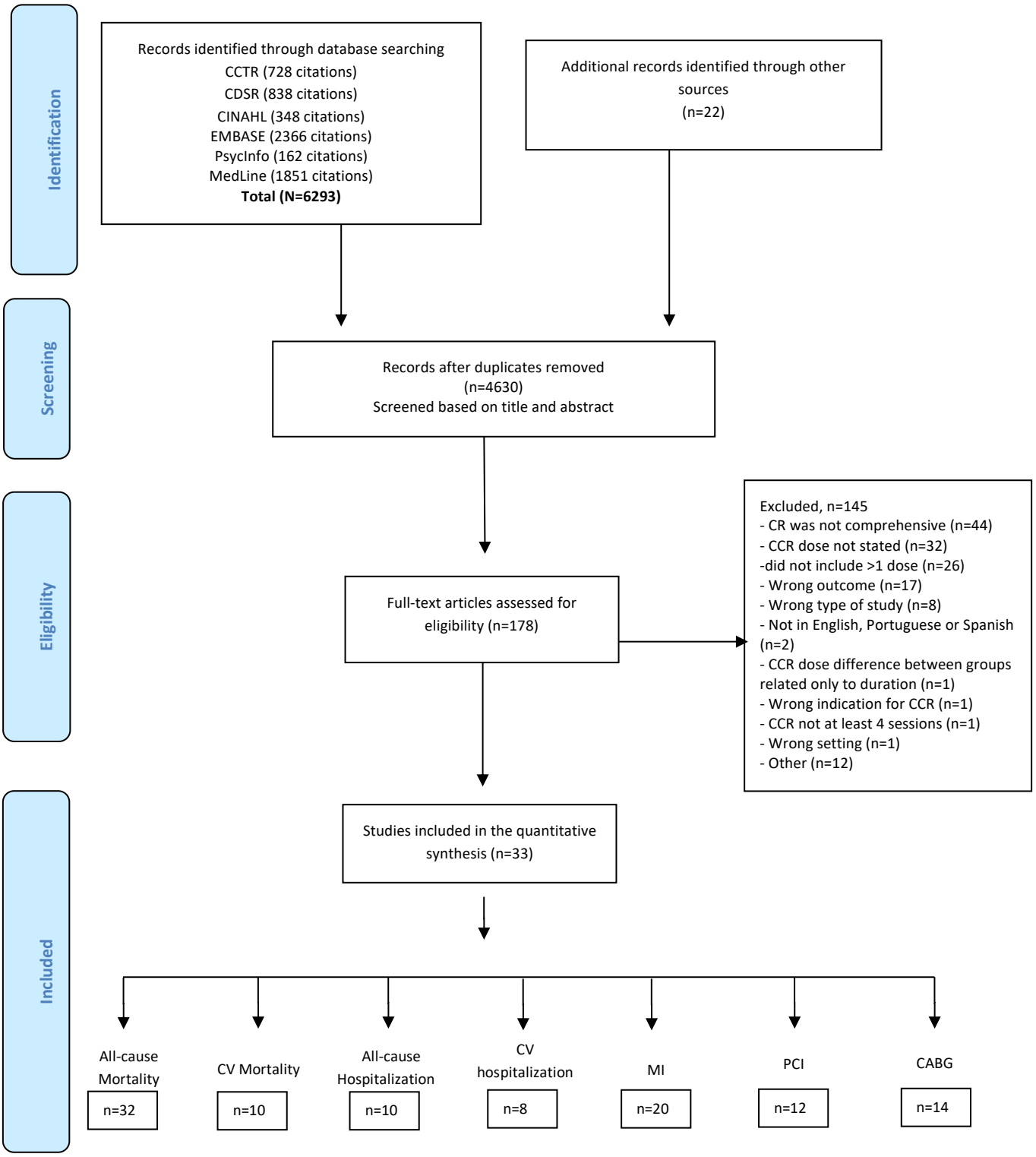
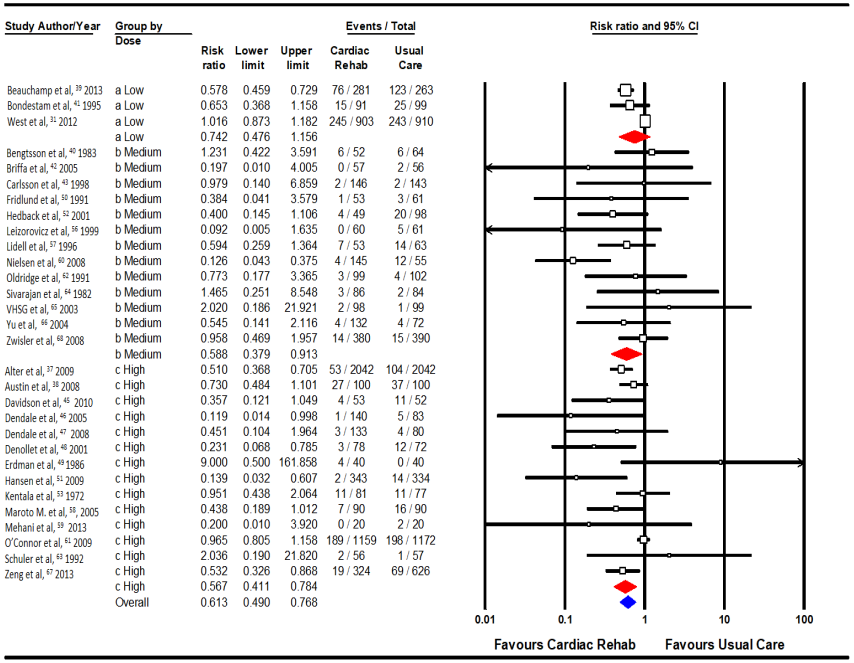

Identification
Records identified through database searching
CCTR (728 citations)
CDSR (838 citations)
CINAHL (348 citations)
EMBASE (2366 citations)
PsycInfo (162 citations)
MedLine (1851 citations)
Total (N=6293)
Additional records identified through other sources
(n=22)
Screening
Records after duplicates removed
(n=4630)
Screened based on title and abstract
Eligibility
Full-text articles assessed for eligibility (n=178)
Excluded, n=145
- CR was not comprehensive (n=44)
- CCR dose not stated (n=32)
-did not include >1 dose (n=26)
- Wrong outcome (n=17)
- Wrong type of study (n=8)
- Not in English, Portuguese or Spanish (n=2)
- CCR dose difference between groups related only to duration (n=1)
- Wrong indication for CCR (n=1)
- CCR not at least 4 sessions (n=1)
- Wrong setting (n=1)
- Other (n=12)
Included
Studies included in the quantitative synthesis (n=33)
All-cause Mortality
n=32
CV Mortality
n=10
All-cause Hospitalization
n=10
CV hospitalization
n=8
MI
n=20
PCI
n=12
CABG
n=14

FIGURE 2



Study Author/Year	Group by Dose	Risk ratio	Lower limit	Upper limit	Events / Total: Cardiac Rehab	Events / Total: Usual Care
Beauchamp et al, [39] 2013	a Low	0.578	0.459	0.729	76 / 281	123 / 263
Bondestam et al, [41] 1995	a Low	0.653	0.368	1.158	15 / 91	25 / 99
West et al, [31] 2012	a Low	1.016	0.873	1.182	245 / 903	243 / 910
	a Low	0.742	0.476	1.156		
Bengtsson et al, [40] 1983	b Medium	1.231	0.422	3.591	6 / 52	6 / 64
Briffa et al, [42] 2005	b Medium	0.197	0.010	4.005	0 / 57	2 / 56
Carlsson et al, [43] 1998	b Medium	0.979	0.140	6.859	2 / 146	2 / 143
Fridlund et al, [50] 1991	b Medium	0.384	0.041	3.579	1 / 53	3 / 61
Hedback et al, [52] 2001	b Medium	0.400	0.145	1.106	4 / 49	20 / 98
Leizorovicz et al, [56] 1999	b Medium	0.092	0.005	1.635	0 / 60	5 / 61
Lidell et al, [57] 1996	b Medium	0.594	0.259	1.364	7 / 53	14 / 63
Nielsen et al, [60] 2008	b Medium	0.126	0.043	0.375	4 / 145	12 / 55
Oldridge et al, [62] 1991	b Medium	0.773	0.177	3.365	3 / 99	4 / 102
Sivarajan et al, [64] 1982	b Medium	1.465	0.251	8.548	3 / 86	2 / 84
VHSG et al, [65] 2003	b Medium	2.020	0.186	21.921	2 / 98	1 / 99
Yu et al, [66] 2004	b Medium	0.545	0.141	2.116	4 / 132	4 / 72
Zwisler et al, [68] 2008	b Medium	0.958	0.469	1.957	14 / 380	15 / 390
	b Medium	0.588	0.379	0.913		
Alter et al, [37] 2009	c High	0.510	0.368	0.705	53 / 2042	104 / 2042
Austin et al, [38] 2008	c High	0.730	0.484	1.101	27 / 100	37 / 100
Davidson et al, [45] 2010	c High	0.357	0.121	1.049	4 / 53	11 / 52
Dendale et al, [46] 2005	c High	0.119	0.014	0.998	1 / 140	5 / 83
Dendale et al, [47] 2008	c High	0.451	0.104	1.964	3 / 133	4 / 80
Denollet et al, [48] 2001	c High	0.231	0.068	0.785	3 / 78	12 / 72
Erdman et al, [49] 1986	c High	9.000	0.500	161.858	4 / 40	0 / 40
Hansen et al, [51] 2009	c High	0.139	0.032	0.607	2 / 343	14 / 334
Kentala et al, [53] 1972	c High	0.951	0.438	2.064	11 / 81	11 / 77
Maroto M. et al, [55], 2005	c High	0.438	0.189	1.012	7 / 90	16 / 90
Mehani et al, [59] 2013	c High	0.200	0.010	3.920	0 / 20	2 / 20
O'Connor et al, [61] 2009	c High	0.965	0.805	1.158	189 / 1159	198 / 1172
Schuler et al, [63] 1992	c High	2.036	0.190	21.820	2 / 56	1 / 57
Zeng et al, [67] 2013	c High	0.532	0.326	0.868	19 / 324	69 / 626
	c High	0.567	0.411	0.784		
	Overall	0.613	0.490	0.768		

Risk ratio and 95% CI

0.01 0.1 1 10 100

Favours Cardiac Rehab Favours Usual Care

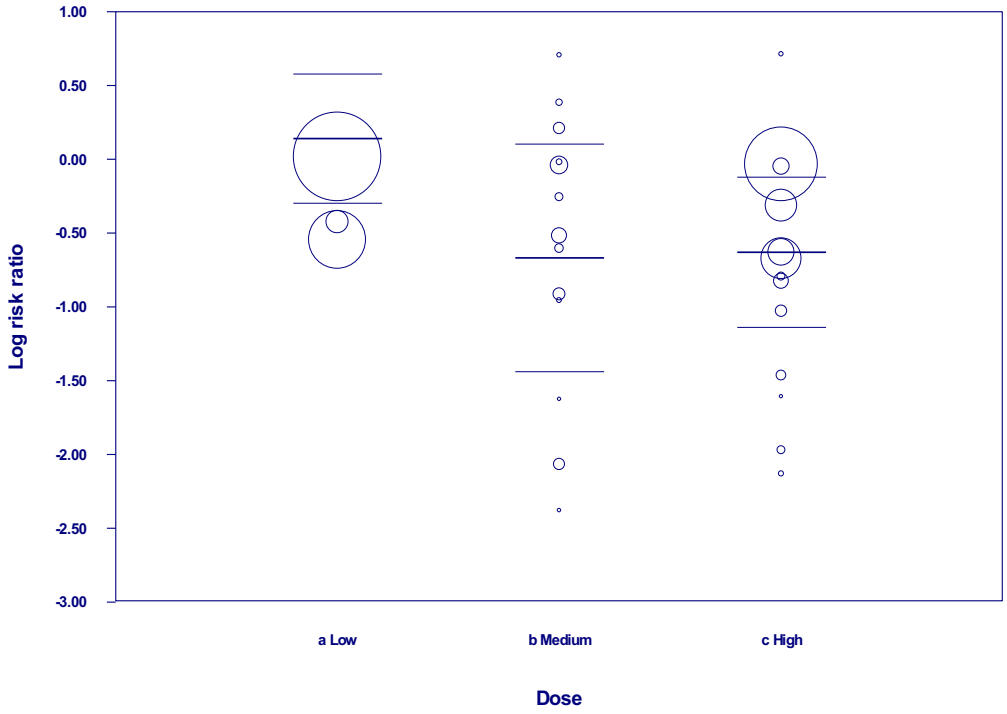
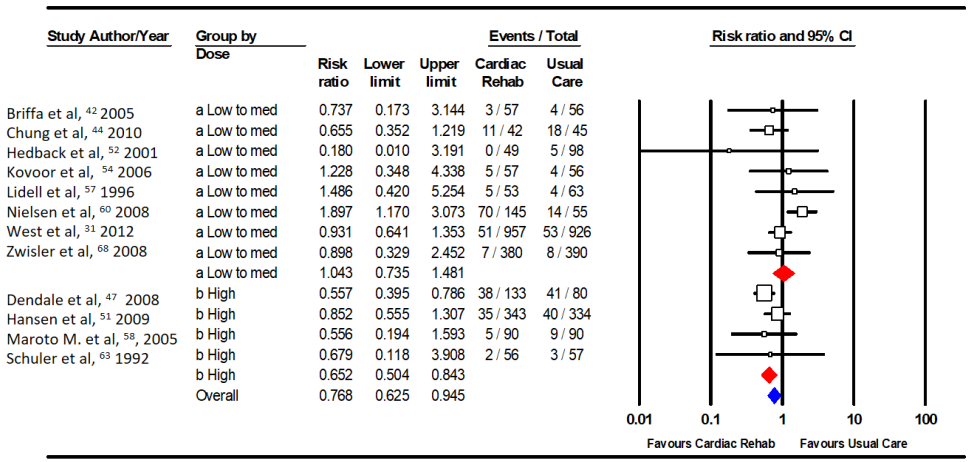


FIGURE 3


Study Author/Year
Group by Dose
Events / Total
Risk ratio and 95% CI
Risk ratio
Lower limit
Upper limit
Cardiac Rehab
Usual Care
Briffa et al, [42] 2005 a Low to med 0.737 0.173 3.144 3 / 57 4 / 56
Chung et al, [44] 2010 a Low to med 0.655 0.352 1.219 11 / 42 18 / 45
Hedback et al, [52] 2001 a Low to med 0.180 0.010 3.191 0 / 49 5 / 98
Kovoor et al, [54] 2006 a Low to med 1.228 0.348 4.338 5 / 57 4 / 56
Lidell et al, [57] 1996 a Low to med 1.486 0.420 5.254 5 / 53 4 / 63
Nielsen et al, [60] 2008 a Low to med 1.897 1.170 3.073 70 / 145 14 / 55
West et al, [31] 2012 a Low to med 0.931 0.641 1.353 51 / 957 53 / 926
Zwisler et al, [68] 2008 a Low to med 0.898 0.329 2.452 7 / 380 8 / 390
a Low to med 1.043 0.735 1.481
Dendale et al, [47] 2008 b High 0.557 0.395 0.786 38 / 133 41 / 80
Hansen et al, [51] 2009 b High 0.852 0.555 1.307 35 / 343 40 / 334
Maroto M. et al, [58], 2005 b High 0.556 0.194 1.593 5 / 90 9 / 90
Schuler et al, [63] 1992 b High 0.679 0.118 3.908 2 / 56 3 / 57
b High 0.652 0.504 0.843
Overall 0.768 0.625 0.945
0.01
0.1
1
10
100
Favours Cardiac Rehab
Favours Usual Care

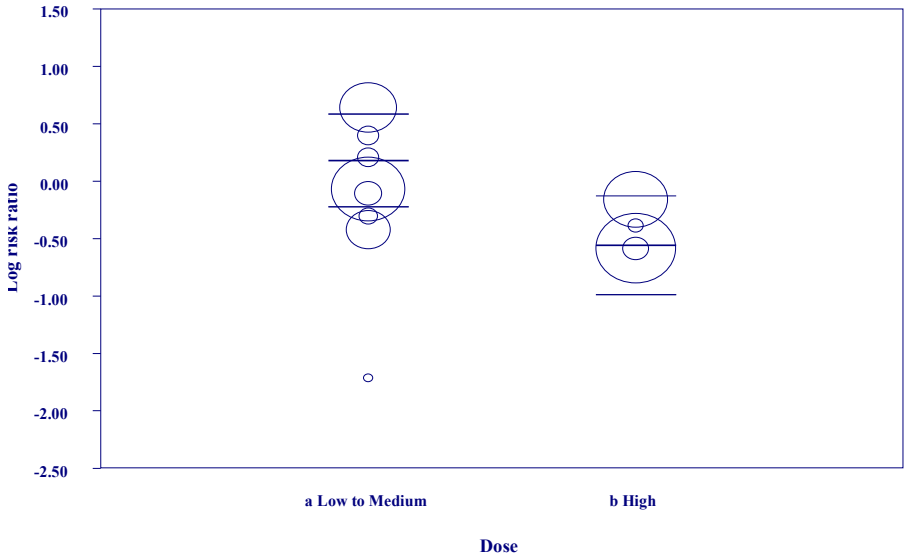
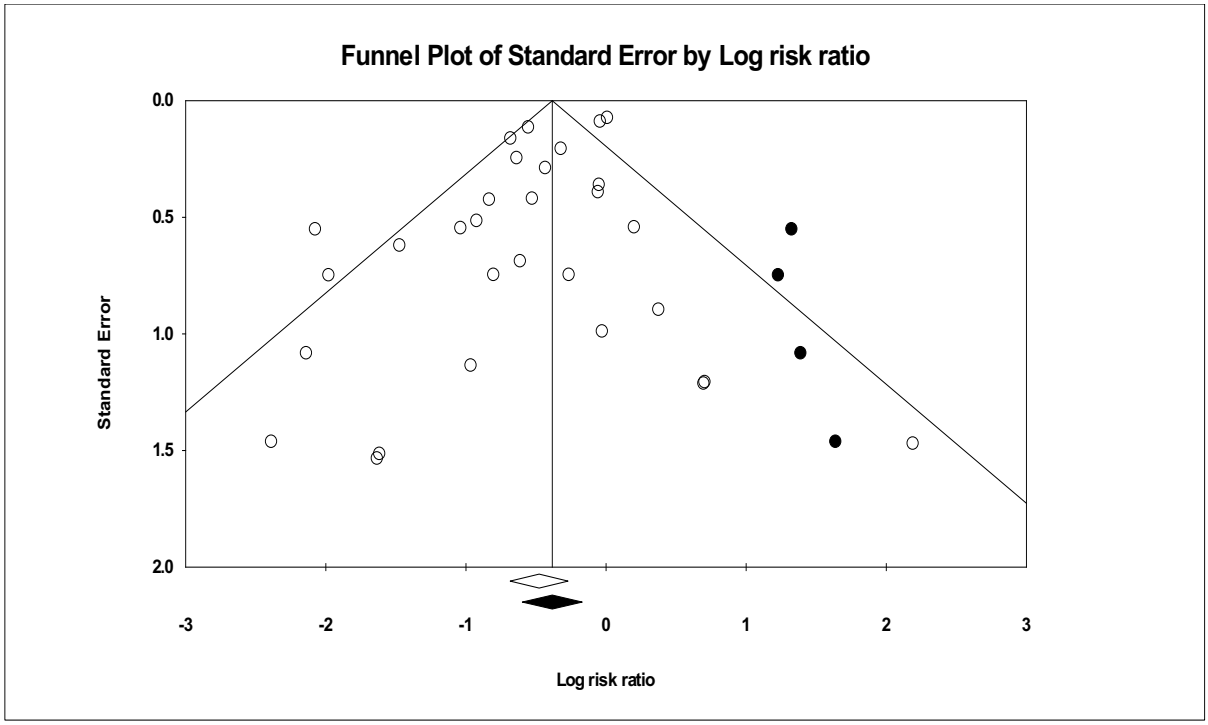

1.50
1.00
0.50
0.00
-0.50
-1.00
-1.50
-2.00
-2.50
Log risk ratio
a Low to Medium
b High
Dose

FIGURE 4



Duval and Tweedie's trim and fill

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		0.78327	0.71734	0.85525	0.62020	0.50431	0.76272	72.18444
Adjusted values	4	0.79899	0.73214	0.87193	0.68125	0.55003	0.84378	87.85775

SUPPLEMENTAL RESULTS AND DISPLAY ITEMS

RESULTS:

Additional characteristics of cardiac rehabilitation programs in included studies

Only 6 (18.1%) studies reported actual CCR attendance; this was often expressed as a proportion and was reported inconsistently and hence could not be used in analysis. Twenty-nine (87.8%) studies reported CCR session duration. The median number of minutes per CCR session was 60 (mean±SD=66.8±26.6; range=27.5-120.0). Twelve (36.3%) studies reported the prescribed exercise intensity. This was most often (n=5, 15.1% of studies) expressed as a target range, expressed as percentage of the peak heart rate achieved on an exercise stress test or a percentage of a predicted maximal heart rate. This inconsistency again precluded incorporation in statistical analyses.

The CCR programs were most often delivered in a supervised setting (n=25 [75.7%] studies), and 8 (24.2%) studies offered a hybrid program (Table 2). Seven (21.2%) studies included resistance training as a component of the exercise program.

SUPPLEMENTAL TABLE 1 - MEDLINE Search Strategy

1	[Population: Specified Cardiac Conditions)
2	Heart Diseases/
3	exp Heart Arrest/
4	exp Heart Failure/
5	exp Myocardial Ischemia/
6	exp Percutaneous Coronary Intervention/
7	((cardiac or heart) adj3(arrest* or event*)).tw.kw
8	((myocardial or heart) adj3 (ischemia* or infarct* or stun*)).tw.kw
9	(coronary adj3 (disease* or occlusion* or stenosis or syndrome*)).tw.kw
10	(angina adj3 (stable or unstable or pectoris)).tw.kw
11	or/3-11
12	[intervention:Exercise/Cardiac Rehab]
13	rh.fs.
14	exp Exercise/
15	exp Exercise Movement Techniques/
16	exp Exercise Therapy/
17	Patient Education as Topic/ and exercise*.tw,kw.
18	Health Education/ and exercise*. tw,kw.
19	(education adj3 (health or patient* or cardiac)).tw,kw.

20 ((cardiac or heart) adj3 rehab*.af.

21 (exercise* adj3 (train* therap* or program* or prescription* or prescribe* or controlled or rehab* or schedule* or regimen)).tw,kw.

22 (Intervention* adj3 (exercise* or education*)).tw,kw.

23 or/14-23

24 [Comparator: Session Duration]

25 Time Factors/

26 Time/

27 Time-toTreatment/

28 "episode of care"/

29 (dose or dosage).tw,kw

30 ((session* or therap* or exercise* or train* or program* or optimal or cardiac rehab*) adj4 (length* or duration* or frequenc* or per week or volume* or minute* or "min" or intensity or "days/week" or intens* or more or fewer or average* or characteristic* or earlier or longer or delayed or shorter or month*)).tw,kw.

31 or/26-31

32 [Outcomes: As noted]

33 exp Mortality/

34 exp Morbidity/

35 "Quality of Life"/

36 exp treatment outcome/

37	(morbidit* or mortalit* or “quality of life”).tw,kw.
38	(outcome* adj3 (patient* or clinical* or rehab*)).tw,kw.
39	(treatment* adj3 (outcome* or effective* or efficacy)).tw,kw.
40	or/34-40
41	12 and 24 and 32 and 41
42	[Exclude minor publication types]
43	editorial.pt.
44	letter.pt.
45	comment.pt.
46	news.pt.
47	patient education handout.pt.
48	or/44-48
49	42 not 49
50	[Limit to Humans]
51	(animals not (humans and animals)).sh.
52	50 not 52
53	remove duplicates from 53

This table has not been edited, and the authors take responsibility for the accuracy of all data.

SUPPLEMENTAL TABLE 2 - Meta-regression Model for All-Cause Mortality

Covariate	Sets	Coefficient ± SE	95% CI	p	p (set)
Intercept		61.11 ± 21.41	9.13, 103.08	<.001	
Dose	Medium	-0.80 ± 0.21	-1.23, -0.37	<.001	<.001
	High	-0.77 ± 0.22	-1.20, -0.33	<.001	
Study Quality		0.07 ± 0.04	-0.004, 0.15	.06	
Country					
	North America	0.35 ± 0.18	-0.007, 0.72	.05	<.001
	Others	-0.48 ± 0.14	-0.76, -0.20	<.001	
Year		-0.03 ± 0.01	-0.05, -0.01	<.001	
Diagnosis		-0.53 ± 0.18	-0.90, -0.17	<.001	

Tau^2 = <.001, I^2 = .00%, Q = 21.46, df = 22, *P*=.49
CI; confidence interval; SE: standard error

This table has not been edited, and the authors take responsibility for the accuracy of all data.

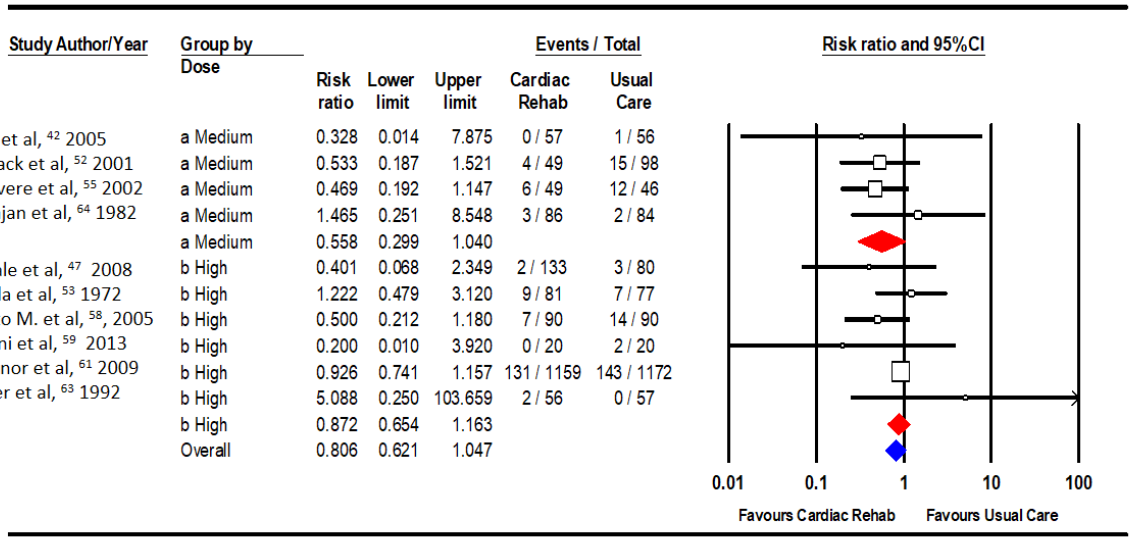
SUPPLEMENTAL TABLE 3 - Meta-regression Model for Percutaneous Coronary Intervention

Covariate	Sets	Coefficient ± SE	95% CI	p
Intercept		0.64 ± 0.24	0.16, 1.12	<.001
Dose	High	- 0.73 ± 0.20	-1.13, -0.34	<.001
Follow-up (months)		-0.006 ± 0.002	-0.01, -0.001	.01
Country	Non-Europe/North American	-0.87 ± 0.34	-1.54, -0.19	.01

Tau^2 = <.001, I^2 = .00%, Q = 4.81, df = 8, *P*=.77
CI; confidence interval; SE: standard error

This table has not been edited, and the authors take responsibility for the accuracy of all data.

SUPPLEMENTAL FIGURE 1 - Forest Plot of Effect of Cardiac Rehabilitation Dose on Cardiovascular Mortality



Heterogeneity: I^2= .00%, *P*=.46

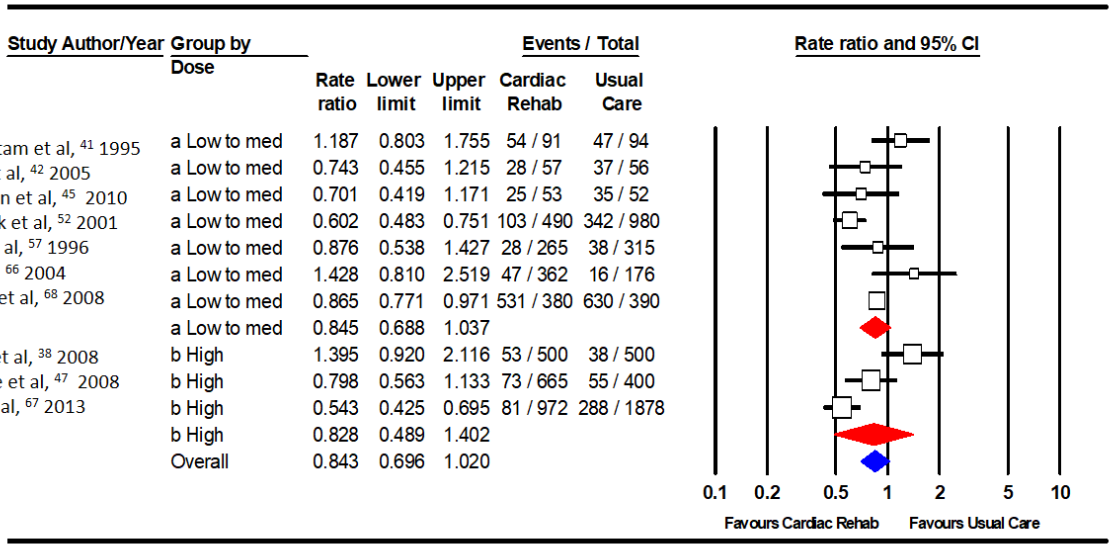
Test for dose subgroups (mixed-effect analysis), *P*=.20.

Values for dose categories are Medium dose=12-35 sessions; High dose=≥36.

CI, confidence interval.

This figure has not been edited, and the authors take responsibility for the accuracy of all data.

SUPPLEMENTAL FIGURE 2 - Forest Plot of Effect of Cardiac Rehabilitation Dose on All-Cause Hospitalization



Heterogeneity: I^2= 72.56%, *P*<.001

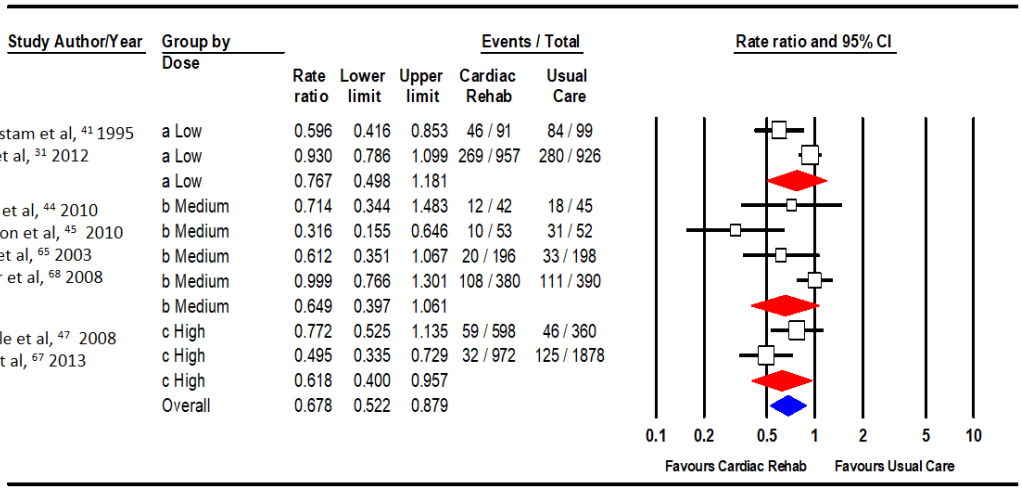
Test for dose subgroups (mixed-effect analysis), *P*=.94.

Values for dose categories are Low-Medium dose=<35; High dose=≥36.

CI, confidence interval; Med, medium.

This figure has not been edited, and the authors take responsibility for the accuracy of all data.

SUPPLEMENTAL FIGURE 3– Forest plot of effect of Cardiac Rehabilitation Dose on Cardiovascular-related Hospitalization



Heterogeneity: I^2= 67.85%, *P*=.003;

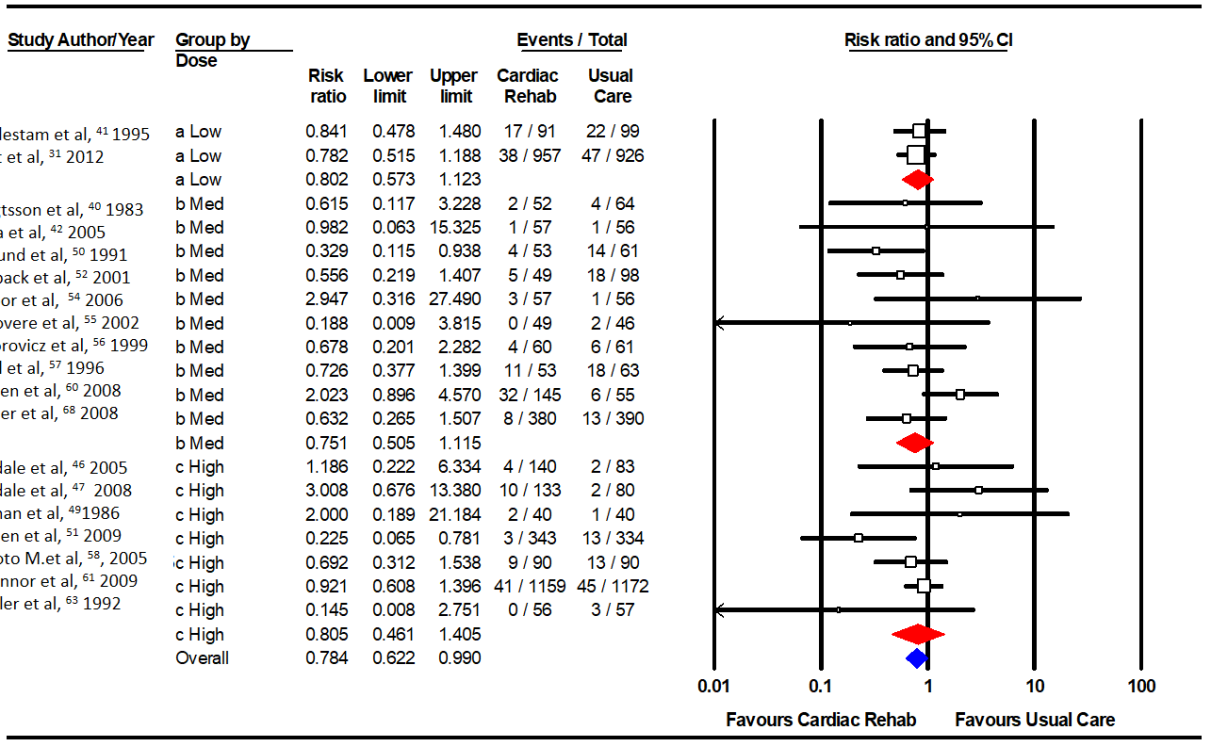
Test for dose subgroups (mixed-effect analysis), *P*=.77.

Values for dose categories are Low=<12; Medium=12-35 High=≥36 sessions.

CI, confidence interval.

This figure has not been edited, and the authors take responsibility for the accuracy of all data.

SUPPLEMENTAL FIGURE 4 - Forest Plot of Effect of Cardiac Rehabilitation Dose on Non-Fatal Myocardial Infarction



Heterogeneity: I^2= 15.89%, *P*=.26

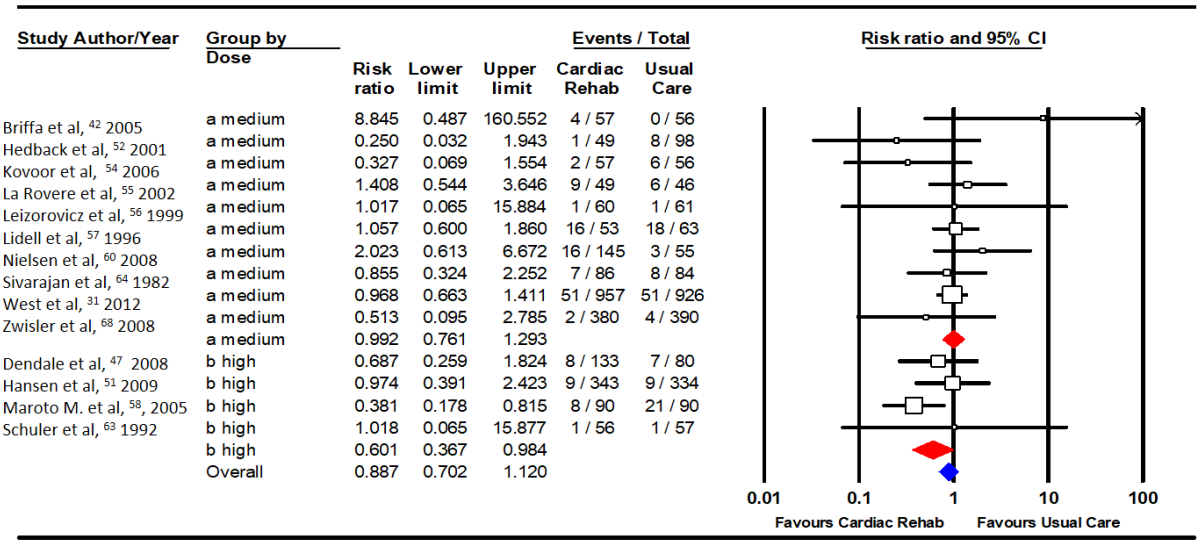
Test for dose subgroups (mixed-effect analysis), *P*=.96.

Values for dose categories are Low dose=<12; Medium dose=12-35; High dose=≥36 sessions.

CI, confidence interval; Med, medium.

This figure has not been edited, and the authors take responsibility for the accuracy of all data.

SUPPLEMENTAL FIGURE 5 - Forest Plot of Effect of Cardiac Rehabilitation Dose on Coronary Artery Bypass Graft



Heterogeneity: I^2= 7.73%, *P*=.36

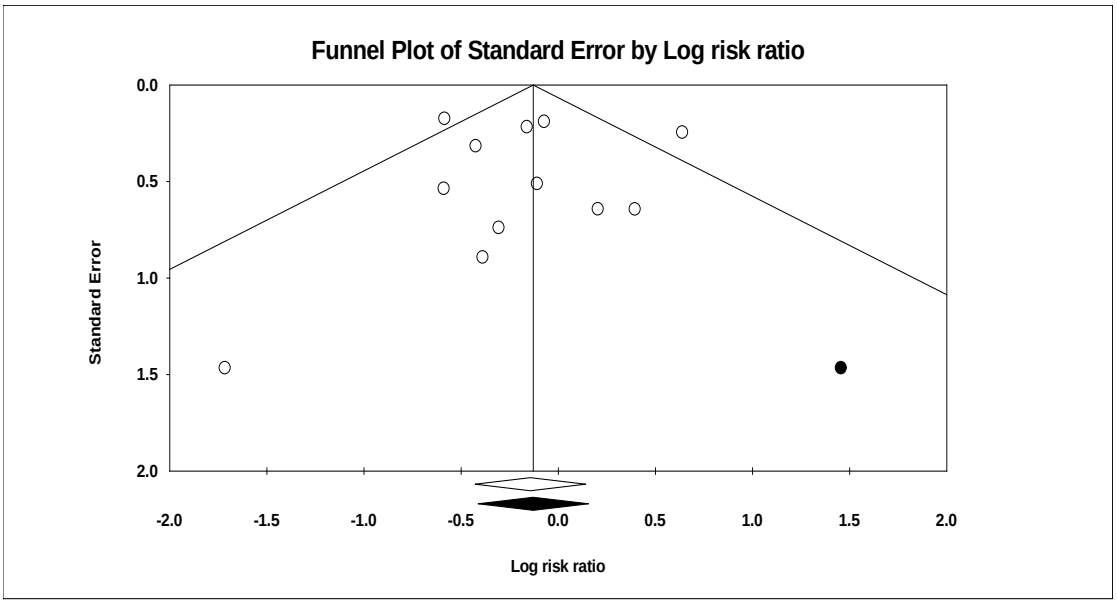
Test for dose subgroups (mixed-effect analysis), *P*=.08.

Values for dose categories are Medium dose<35; High dose=≥36 sessions.

CI, confidence interval.

This figure has not been edited, and the authors take responsibility for the accuracy of all data.

SUPPLEMENTAL FIGURE 6 – Test for Publication Bias for Percutaneous Coronary Intervention



Duval and Tweedie's trim and fill

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		0.84419	0.70752	1.00726	0.86610	0.65188	1.15071	20.25654
Adjusted values	1	0.84936	0.71209	1.01310	0.87918	0.66167	1.16818	21.48107

Egger's test for small-study effects: *P*=.49

This figure has not been edited, and the authors take responsibility for the accuracy of all data.