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Effect of Cardiac Rehabilitation Dose on Mortality and Morbidity: A Systematic Review and Meta-regression Analysis

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Abstract

Objective: To ascertain the effect of cardiac rehabilitation (CR) dose (ie, duration × frequency/wk; categorized as low [<12 sessions], medium [12-35 sessions], or high [≥36 sessions]) on mortality and morbidity.

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 of 4 or higher 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 (ie, no dose). In meta-regression, greater dose was significantly related to lower all-cause mortality (high: −0.77; SE, 0.22; $P<.001$; medium: −0.80; SE, 0.21; $P<.001$) when compared with low dose. With regard to morbidity, meta-analysis revealed that dose was significantly associated with fewer percutaneous coronary interventions (high: relative risk, 0.65; 95% CI, 0.50-0.84; medium/low: relative risk, 1.04; 95% CI, 0.74-1.48; between subgroup difference $P=.03$). This reduction was also significant in meta-regression (high vs medium/low: −0.73; SE, 0.20; $P<.001$). 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 percutaneous coronary interventions. Future studies should examine the effect of actual dose of CR, and trials are needed comparing different doses.

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Cardiovascular (CV) disease (CVD) is one of the most prevalent health conditions globally.[1] With advances in early treatment, many patients are surviving an initial cardiac event, and hence, many people are 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.[3-5] It is well-established that CCR is a cost-effective model of care[6,7] that reduces CV mortality by approximately 25% and hospital readmissions by 18%.[8]

Comprehensive cardiac rehabilitation programs around the world are of varying durations, and sessions are offered at varying frequencies.[9] For example, in a recent review of cardiac rehabilitation (CR) guidelines,[10] the recommended duration ranged from a minimum of 3 weeks in Germany (although this often presents as an inpatient CR program) 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 Association of Cardiovascular and Pulmonary Rehabilitation and the European Association for Cardiovascular Prevention and Rehabilitation, was a minimum of 3 sessions per week, whereas

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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 studies have found that the more CCR patients receive, the better their outcomes.[11-16]

To our knowledge, 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. The effect of CR dose on mortality and morbidity has been scantly examined in the literature previously, with variable and inconsistent definitions (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. Cardiac rehabilitation dose was operationalized by multiplying the number of weeks of exercise (ie, program duration) by the number of training sessions per week (ie, frequency) and by the average duration of exercise sessions in minutes (Rod Taylor, PhD, written communication, May 2016). Dose was then stratified as 1000 or less vs more than 1000 "units." No associations between dose and outcomes were observed in the first 2 meta-analyses, but in the most recent one, patients who had 1000 or more than 1000 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 or more months' duration, had significantly lower CV mortality and MI but not all-cause mortality. There have also been some primary studies that 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, a quantitative review with the primary objective of assessing how CCR affects mortality and morbidity and what CCR dose is most effective is warranted. Arguably, these are the most important CCR outcomes for patients and the health care system. Therefore, the purpose of this study was to examine the effect of CCR dose on all-cause and CV-related mortality, all-cause and CV-related hospitalization, nonfatal 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 No. 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 (M.P.) for each of the databases presented in Figure 1. The strategies utilized the PICO (population, intervention, comparison, outcome) model and were limited to humans, with no date restrictions through 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 presented in Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org).

Reference lists from relevant reviews (eg, those reported in Table 1) were individually 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, for studies that reported some but not all needed aspects of dose, the investigators were contacted to request additional information. These studies were included if the information was received.

Inclusion and Exclusion Criteria

We searched for articles that reported CCR dose in more than one condition with mortality or morbidity outcomes reported for each condition. Comprehensive cardiac rehabilitation was defined as an outpatient (ie, phase II)[23] program offering structured exercise training and at least patient education. Programs had to consist of 4 or more sessions (ie, minimum dose). The program could be delivered in supervised (ie, hospital- or