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A Clinical and Economic Review of Exercise-Based Cardiac Rehabilitation Programs for Coronary Artery Disease

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A Clinical and Economic Review of Exercise-Based Cardiac Rehabilitation Programs for Coronary Artery Disease

August 2003

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This Overview is based on the Technology Report commissioned by CCOHTA: Brown A, Taylor R, Noorani H, Stone J, Skidmore B. **Exercise-based cardiac rehabilitation programs for coronary artery disease: a systematic clinical and economic review**. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2003. Technology report no 34.

REPORT *IN BRIEF*

August 2003

CCOHTA

A Clinical and Economic Review of Exercise-Based Cardiac Rehabilitation Programs for Coronary Artery Disease

Technology Name

Exercise-based cardiac rehabilitation programs for patients with coronary artery disease

Disease/Condition

Cardiovascular disease is the leading cause of death in Canada; over 50% of all cardiovascular deaths are due to coronary artery disease. Cardiovascular disease also accounts for billions of dollars spent in Canada's health care system annually and billions of dollars in lost productivity.

Technology Description

Cardiac rehabilitation (CR) programs are used to enhance recovery and to prevent future cardiac events in patients with coronary artery disease. CR programs are either based on "exercise-only" interventions, or can consist of a "comprehensive care" approach that includes psychological interventions and education in managing risk factors, in addition to training in physical exercise.

The Issue

CR programs vary widely; however, virtually all CR programs in Canada offer a component dedicated to physical exercise. Only about 10% of eligible patients actually enrol in CR programs. A previous systematic review of clinical evidence (by the Cochrane Collaboration) reporting on these programs covered the period up to 1998. Several new trials have occurred since then. In addition, previous systematic reviews did not include economic evidence.

This report assesses the clinical- and cost-effectiveness of CR programs and the potential policy and research implications for the health sector.

Methodology

Randomized controlled trials of CR programs with an exercise component were systematically reviewed in two groups: comprehensive care or exercise-only. The study population was men and women of all ages, with documented coronary artery disease, in hospital and community-based settings. The main outcome measures were total mortality and cardiac mortality. Forty-six clinical trials were analyzed in the clinical meta-analysis. Economic studies using the same population and interventions were also systematically reviewed; three full economic evaluations and three cost studies. Comprehensive searches of the literature and consultations with clinical experts were used to review the potential impact of CR programs on health policy.

Conclusions

CR programs that include exercise, both exercise-only and comprehensive care programs, have beneficial effects on cardiac mortality. However, with respect to total mortality, exercise-only programs show a statistically significant reduction, whereas the comprehensive care programs showed a trend in that direction. The literature reports that these programs are cost-effective and may reduce costs to the health care system, particularly when patients fully participate in maintaining the required level of exercise over the long term.

This summary is based on a comprehensive health technology assessment report available from CCOHTA's web site (www.ccohta.ca): Brown A, Taylor R, Noorani H, Stone J, Skidmore B. **Exercise-based cardiac rehabilitation programs for coronary artery disease: a systematic clinical and economic review**.

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Executive Summary

The Issue

Coronary artery disease (CAD) imposes a large burden on health and health care resources in industrialized countries. Cardiac rehabilitation (CR) with an exercise component is often offered to patients with CAD. Exercise-based CR can be delivered either as an exercise-only program (EX CR) or as part of a comprehensive CR program (CCR). CCR involves exercise in combination with other secondary measures such as CAD risk factor management, patient education and psychosocial interventions.

Objectives

- To systematically review the clinical and cost-effectiveness evidence for CR with an exercise component for secondary prevention of CAD
- To discuss the impact of the evidence on the future development of CR services for the secondary prevention of CAD

Methods

The review of clinical effectiveness was an update of a 2001 Cochrane systematic review of the effectiveness of CR with an exercise component, which covered literature to Dec. 31, 1998. Reviewed studies were randomized controlled trials (RCTs) of CR with an exercise component (either EX CR or CCR) versus usual care, with a follow-up period of six months or more post-randomization. The study population was men and women of all ages, in hospital and community-based settings, who had documented CAD, i.e. had experienced a myocardial infarction (MI), had undergone coronary artery bypass graft surgery, had undergone percutaneous transluminal coronary angioplasty or who had angina pectoris due to CAD, defined by angiography. Trials of patients with congestive heart failure were excluded. The quality of the trials was assessed using a modified Jadad scale. A quantitative meta-analysis was carried out using Stata v.6 software.

The inclusion/exclusion criteria for the studies in the economic review were the same as that for the clinical review, with one exception: RCT and non-RCT based studies were both included. Substantial heterogeneity in study design and patient characteristics prevented study results from being pooled quantitatively.

For the review of health sector impact, there was a comprehensive search of the literature as well as consultation with clinical experts.

Results

Ninety-nine of 1000 potentially relevant citations appeared to meet the review inclusion criteria. From assessing the full text of these 99 articles, five new EX CR trials and five new CCR trials were identified in addition to those in the 2001 Cochrane review. The total number of trials analyzed in our meta-analysis was 46.

Our meta-analysis of clinical studies found that CCR showed a trend toward reduction in total mortality, although this was not statistically significant at the 95% confidence level (RR 0.87, 95% CI 0.74 to 1.02). However, cardiac mortality was significantly reduced (RR 0.80, 95% CI 0.65 to 0.99). EX CR significantly reduced both total mortality (RR 0.76, 95% CI 0.59 to 0.98) and cardiac mortality (RR 0.73, 95% CI 0.56 to 0.96). Health-related quality of life (HRQoL) outcomes were not pooled, but there was evidence of a consistent improvement in HRQoL across the nine trials reporting this outcome, although few trials showed improvement above that measured in the usual care groups. Meta-regression analysis failed to demonstrate the presence of any significant sub-group effects. Sub-groups analyzed included: EX CR or CCR, duration of program, intensity of program, follow-up period, all post MI or other than just MI patients, gender, age, trials pre- or post-1995 and quality of trials.

In the review of economic evidence, 64 of 614 potentially relevant studies were retrieved for full text assessment. Six were ultimately included in the review; three full economic evaluations and three cost studies. Only one included study was RCT-based. The study, an economic evaluation located in Canada, concluded that an eight-week supervised exercise plus counselling program cost US$9,200 per QALY and US$21,800 per life-year gained during the year of follow-up. Another Canadian-based economic evaluation found that it costs less than US$15,000 per year of life saved for a supervised CR program for men. A US study found that it cost US$4,950 per year of life saved through CR. The cost studies, based in Sweden and the US, concluded that CR may be cost-saving compared to standard care for patients with CAD, due to lower rehospitalization rates and lower mean patient costs.

Conclusions

The clinical evidence supports the findings of the previous Cochrane review that CR with exercise reduces cardiac mortality and total mortality (although the trend for CCR on total mortality was not significant). CCR has a somewhat more positive effect overall on risk factors than EX CR. The few studies that measured HRQoL show a non-significant trend that CR with exercise enhances quality of life relative to usual care. Although recent trials have increasingly recruited patients who have had revascularization or angina, the representation of women and the elderly in the trials remains poor. The benefit of CR on mortality tends to diminish in the long-term (i.e. 10 years or more), possibly due to reduced exercise behaviour.

The three full economic evaluations all suggested CR that includes exercise is cost-effective, and the three cost studies all suggested CR with exercise may reduce costs to health care systems due to reduced rehospitalization and drug utilization. Although the cost studies suggest that cost savings over time would result from switching to CR from standard care, in the short term there would likely be a significant budget impact. For example, at an average cost of C$1,000 per patient, making supervised CR standard practice for Canadian CAD patients could increase short run annual expenditures in Canada by C$225 million.

Our analysis of health sector impact found that Canadian CR programs that include exercise may be under-subscribed; only 10% of eligible patients attend. We estimated the need for CR services in Canada to be 250,000 “places” for the year 2001.

1. Introduction

Cardiovascular disease is the leading cause of death in Canada, accounting for close to 80,000 deaths in 1998.[1,2] It is also the leading cause of hospitalization for men and women (excluding childbirth). Over 50% of all cardiovascular deaths are due to coronary artery disease (CAD), [2] which accounted for a total cost of $7.8 billion in Canada in 1993.[1]

Cardiac rehabilitation (CR) programs have been promoted as a way to enhance recovery following acute cardiac events and to encourage behaviour aimed at the secondary prevention of CAD. The Canadian Association of Cardiac Rehabilitation (CACR) has defined CR as *"the enhancement and maintenance of cardiovascular health through individualized programs designed to optimize physical, psychological, social, vocational and emotional status. This process includes the facilitation and delivery of secondary prevention through heart hazard (i.e. risk factor) identification and modification in an effort to prevent disease progression and the recurrence of cardiac events."* [3] The term "heart hazard," rather than the more generally recognized term "risk factor," was used in this definition to reflect the direct causal relationship between diabetes, hypertension, dyslipidemias, tobacco abuse, physical inactivity and so on, in the initiation and proliferation of vascular disease.[3,4] Hereafter, we will use "risk factor" in this context.

CR is a complex intervention that often consists of three elements. First, CR can involve education and risk factor management. This can include providing a patient with information on the pathology of cardiac disease, the mechanism of drug action, resumption of physical and sexual activity, vocational advice, dietary advice, smoking cessation and other lifestyle changes. Second, there may be psychological interventions such as stress management through relaxation therapy and counselling techniques, and the management of depression. Third, rehabilitation usually includes exercise training.[5]

The relative emphasis that different individual CR programs place on each of these three elements can vary widely. Current guidelines advocate that programs should be "individualized," i.e. allocation and focus of interventions should be made on the basis of individual need.[5] Nevertheless, it is widely agreed that exercise training should form the basis of CR; it is, therefore, the focus of this systematic review. Reviews of the effectiveness of education-based and psychological interventions have been published elsewhere.[6,7]

CR is not a new therapy but its uptake has not been consistent.[4] The reasons for this variation in utilization are varied and complex.[8-11] One of the strongest predictors of attendance in CR programs is referral and endorsement of the program by the patients' physicians and caregivers.[10,12]

It is estimated that, as of December 2002, there are over 25,000 patients enrolled in more than 120 formal CR programs in Canada (Marilyn Thomas, Canadian Association of Cardiac Rehabilitation, Winnipeg: personal communication, 2002 Dec.). This represents approximately 10% of the overall eligible cardiac population, based on data from Health Canada.[13,14] The programs are situated all across Canada with the majority in Ontario and Quebec, as would be expected from population demographics.

The availability and use of CR programs in Canada varies widely, not only from province to province, but also from region to region. CR programs also differ in the duration and type of patient care services they offer. Most programs in Canada are currently running at or near capacity and have waiting lists for program admission that vary from weeks to months. Although there is heterogeneity, the majority of programs still adhere to the "standard" 12-week format of CR.[15-17] This format includes supervised exercise three times per week for 12 weeks, or a total of 36 exercise sessions. Patients may also receive education classes and/or supervision and management of risk factors.

Previous systematic reviews of the effectiveness of exercise-based rehabilitation for cardiac patients have distinguished between two types of exercise rehabilitation: "exercise-only rehabilitation" (EX CR) and exercise in conjunction with psychological (such as stress management); and educational (such as risk factor management) interventions, usually termed "comprehensive cardiac rehabilitation" (CCR).[3,4] A number of systematic reviews and meta-analyses of randomized controlled trials (RCTs) of exercise-based rehabilitation have shown reductions in mortality and improvements in both morbidity and CAD risk factor profile compared with usual medical care.[18-21]

The most recent meta-analysis involved 8,440 CAD patients [with previous myocardial infarction (MI), revascularization or angina] in 36 trials. It was published in the Cochrane Library in 2001 and covered literature to December 31, 1998. This meta-analysis found that EX CR reduced all-cause mortality by 27% and cardiac mortality by 31%.[21] Similarly, CCR reduced all-cause mortality, although to a lesser degree (13%), and reduced cardiac mortality by 26%.[21] A number of other systematic reviews of CR have also endorsed its benefits.[6,7] In addition, case-control studies have suggested a positive benefit of CR programs on cardiac risk factors.[22]

A number of concerns, however, have been raised regarding the applicability of the meta-analyses and systematic reviews available to date. The trials included have been small and often of poor methodological quality.[7] Many of these trials were conducted before implementation of current medical therapies, including thrombolysis. There has been insufficient evidence to conclude whether or not EX CR and CCR have equivalent effectiveness. Perhaps the main limitation has been the fact that the majority of trials have been conducted in low-risk, post-MI male patients, despite cardiovascular disease being the major cause of death and disability in women.[1] Finally, no systematic analysis of cost-effectiveness studies has been undertaken within these secondary reviews.

The focus of this systematic review is exercise-based CR (i.e. CR programs with an exercise component). This review will attempt to address many of the issues stemming from previous reviews, in addition to covering three years of trials since the Cochrane review.

2. Objectives

The objectives of this assessment are:

(1) to assess the evidence base for the clinical effectiveness of CR with an exercise component for secondary prevention of CAD through a meta-analysis of RCT evidence;

(2) to assess the evidence base for the cost-effectiveness of CR with an exercise component for secondary prevention of CAD through a systematic review of economic evaluations; and

(3) to discuss the impact of this evidence on the possible future direction and development of CR services for secondary prevention of CAD in the Canadian health care system.

3. Clinical Effectiveness Review

Methods

The methods used in this review generally followed those of the 2001 Cochrane systematic review of the effectiveness of exercise-based CR.[21] In some instances the methods were modified.

a) Literature Search

Published literature was obtained by searching a number of databases (MEDLINE®, EMBASE®, HealthSTAR, Allied and Complementary Medicine™, Manual, Alternative and Natural Therapy® (MANTIS™), PASCAL, SciSearch® and SPORTDiscus) using the DIALOG® system. Retrieval was limited to the publication years 1999 onward with no language restrictions. Database alerts/updates were established on Current Contents Search®, EMBASE® Alert, MEDLINE®, PASCAL and SciSearch®; the Current Contents Search® and SciSearch® updates were discontinued August 2001. Results from these alerts were considered for inclusion in the review until the end of February 2002. CINAHL and PubMed also yielded a large number of records, many of which were duplicates of the original DIALOG® search. Searches were performed and updated throughout the duration of the project on the CD ROM version of The Cochrane Library.

Grey literature was obtained through searching a number of specialized rehabilitation databases (e.g. National Rehabilitation Information Center and PEDro), as well as the web sites of health technology assessment and related agencies and their associated databases. Clinical trial registries, including the National Research Register and the *meta*Register of Controlled Trials, were also searched for information on current or completed trials. The Google™ search engine was used to search for Internet material. Further information was obtained by hand-searching the bibliographies of selected papers, and through contacts with appropriate experts and agencies.

b) Selection Strategy

Studies were included or excluded on the basis of the following criteria:

Table 1: Inclusion/Exclusion criteria

Study Design	Randomized Controlled Trials
Participants	Included were men and women of all ages, in hospital-based and community-based settings, who had experienced an MI, or who had undergone a coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA), or who had angina pectoris or CAD defined by angiography. Studies predominantly involving participants with heart transplants, heart valve surgery, heart failure, pacemakers and congenital heart disease were excluded.
Interventions	Included were inpatient, outpatient, community or home-based exercise-based RCT interventions (either EX CR or CCR programs) with a follow-up period of six months or more post-randomization.
Comparator	Included studies had a usual care component, such as drug therapy, instead of an exercise-based program.
Note: Observational studies were not included to be consistent with the Cochrane review. Studies only available in abstract form were considered but not included in the quantitative analysis due to insufficient data.	

c) Outcome Measures

The outcome measures sought were: all-cause mortality; cardiac mortality; non fatal MI; revascularization (CABG, PTCA); modifiable primary risk factors (smoking behaviour, blood pressure and blood lipid levels); and health-related quality of life [HRQoL; including the Short-Form 36 measure (SF-36) and the quality of life post-myocardial infarction measure (QLMI)].

d) Data Extraction and Quality Assessment

Two reviewers (RT and HN) independently selected trials to be included in this review. Disagreements were resolved by consensus between the authors. Once the trials were included in the review, RT and HN independently extracted the data.

Trial quality was independently assessed (by RT and HN) with respect to the method of randomization, adequacy of allocation concealment, proportion of patients lost to follow-up and blinding of outcome assessment. The trials were scored using a modified Jadad scale; the higher the Jadad score, the higher the quality (range 0 to 5).[23]

e) Data Synthesis

Dichotomous outcomes for each trial were expressed as relative risks (RR) with 95% confidence intervals (CI). Continuous variables were expressed as the mean change from baseline to follow-up, and the standard deviation difference from baseline to follow-up for each comparison group. Where standard deviation differences were not reported in the source papers, allowance has been made for within-patient correlation from baseline to follow-up measurements by using the correlation coefficient between the two (see Cochrane Heart Group web site www.epi.bris.ac.uk/cochrane/heart.htm for details, and Follmann et al., 1992).[24] A weighted mean difference (WMD) and 95% CI were calculated for each trial.

Data from each trial were pooled using a fixed effects model, except where substantial heterogeneity existed according to the χ^2statistic. In that case, a random effects model was used. Stratified and meta-regression analyses were undertaken to relate the magnitude of intervention-effect to patient and intervention characteristics. All covariates were stated *a priori* and all analyses were performed using Stata v.6 software.

Results

The review was divided into two comparisons: EX CR versus usual care; and CCR versus usual care.

This comparison not only reflects the methods used in the previous Cochrane review, but also represents a potentially important difference in terms of resource consumption.

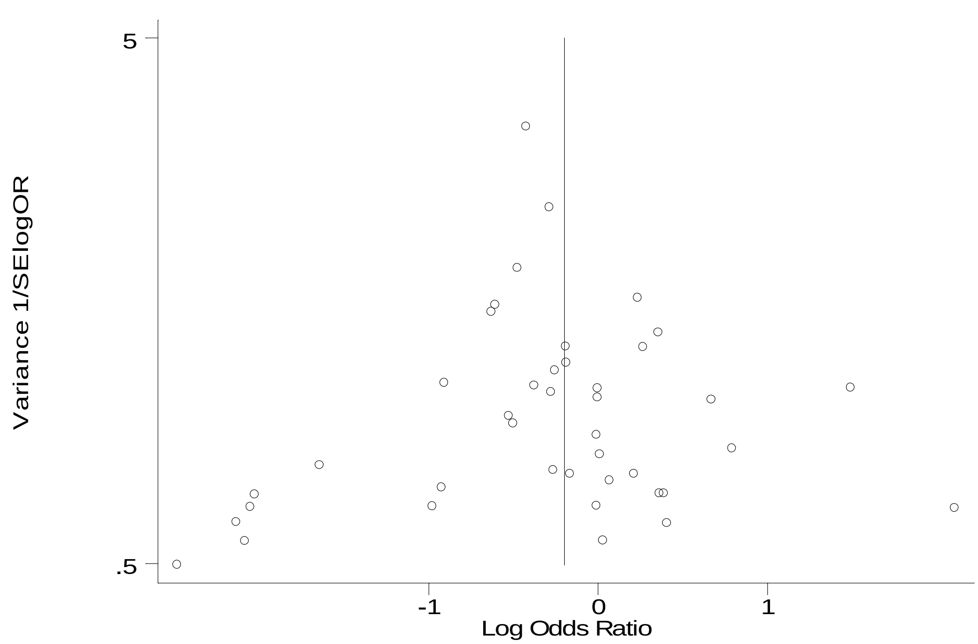
a) Trial Inclusion

A total of 36 RCTs were included in the original Cochrane review: 14 EX CR trials[25-38] and 22 CCR trials.[33,39-59] From the updated literature search, 12 new articles (reporting data from five EX CR trials[60-66] and five CCR trials[67-71]) met the selection criteria. The current study therefore includes 19 EX CR trials and 27 CCR trials.

In addition, we found longer follow-up reports of four trials originally included in the Cochrane review.[72-77] Two additional CCR trials by Schenck-Gustafsson et al.[78] and West et al.[79] were available only in abstract form and were therefore excluded. Finally, one paper was identified that provided a detailed overview of the protocol of a CCR RCT currently underway.[80]

The lack of funnel plot asymmetry for total mortality (the most frequent outcome reported across the trials) suggested little evidence of publication bias (see Figure 1). This visual assessment was confirmed by the Egger test (p = 0.319).[81]

Figure 1: Funnel plot for all trials reporting total mortality



b) Study Characteristics and Quality

The characteristics of the patients are summarized in Table 2.

Table 2: Summary of patient characteristics across trials

Parameter	EX CR trials *N* = 19 trials *n* = 2,984 patients	CCR trials *N* = 27 trials *n* = 5,693 patients
Mean sample size (range)	157 (37-651)	208 (38-1,479)
Mean age (range of means)	54 (50-70) yrs	56 (47-63) yrs
Mean % females (range)	4.9 (0-20)%	12.0 (0-35) %
Number of trials (%): Recruiting only post-MI patients Recruiting only CABG and PTCA patients Recruiting both	 14 (74%) 3 (16%) 2 (10%)	 16 (62%) 5 (19%) 5 (19%)
Mean follow-up in months (range)	24 (6-60)	26 (6-72)
Median Jadad score (range)	2 (1-5)	2 (1-5)

Most trials were of relatively low quality. Of the 46 trials, 17 (37%) provided details of randomization, nine (20%) provided details of adequate concealment and nine (20%) reported blinding of outcome assessment. Follow-up of 80% or more was achieved in 30 trials (65%). The overall median Jadad score was two (range 1 to 5). There was no evidence of an improvement in the quality of recent trials as compared with older trials.

c) Clinical Events

EX CR significantly reduced both all-cause mortality (RR 0.76, 95% CI 0.59 to 0.98) and cardiac mortality (RR 0.73, 95% CI 0.56 to 0.96), compared with usual care. CCR also significantly reduced cardiac mortality (RR 0.80, 95% CI 0.65 to 0.99), but the reduction in all-cause mortality was statistically non-significant (RR 0.87, 95% CI 0.74 to 1.02). Neither EX CR (RR 0.78, 95% CI 0.59 to 1.03) nor CCR (RR 1.07, 95% CI 0.85 to 1.35) had a significant effect on the subsequent occurrence of non-fatal MI. Similarly, neither EX CR nor CCR had a significant effect on the need for CABG (EX CR: RR 0.87, 95% CI 0.58 to 1.29; CCR: RR 0.81, 95% CI 0.59 to 1.10) or PTCA (EX CR: RR 0.57, 95% CI 0.28 to 1.16; CCR: RR 0.84, 95% CI 0.59 to 1.19).

Compared with usual care, exercise-based CR (pooling EX CR and CCR trials) was responsible for statistically significant RR reductions in all-cause mortality of 24% (95% CI 4% to 27%) and cardiac mortality of 23% (95% CI 9% to 35%). Taking the usual care baseline risk, this corresponds to a number needed to treat (NNT) of 66 (95% CI 35 to 273) and 49 (95% CI 26 to 120), i.e. 66 and 49 patients need to receive exercise-based CR to prevent one death from any cause and one cardiac death respectively, over an average of 28 months follow-up.[82]

d) Modifiable Primary CAD Risk Factors

We examined the impact of EX CR and CCR, compared with usual care, on the following modifiable CAD risk factors: cholesterol, triglycerides, blood pressure and smoking. No significant benefits were observed for EX CR; however, few EX CR trials reported on these outcomes (n = 1 to 5) and hence the precision of these results is likely to be low.

Statistically significant benefits were observed with CCR for a number of CAD risk factors ($p \leq 0.05$); however, only a few CCR trials reported on LDL cholesterol (n = 2) and systolic blood pressure (n = 4). CCR resulted in significant reductions of 0.71 mmol/L (95% CI = -0.83 to -0.60) for total cholesterol, 0.52 mmol/L (95% CI = -0.70 to -0.31) for LDL cholesterol, 0.29 mmol/L (95% CI = -0.44 to -0.14) for triglycerides and -3.5 mmHg (95% CI = -0.6.1 to -0.9) for systolic blood pressure.

e) HRQoL

A total of nine trials (20%) assessed HRQoL using a range of measures. Given the variation in both HRQoL outcome measures and methods by which their results are reported, data pooling was considered inappropriate for this outcome. Although most studies reported an improvement in HRQoL domain scores with EX CR and CCR, there were few studies in which this improvement exceeded that observed in the usual care control groups.

f) Long-Term Follow-Up

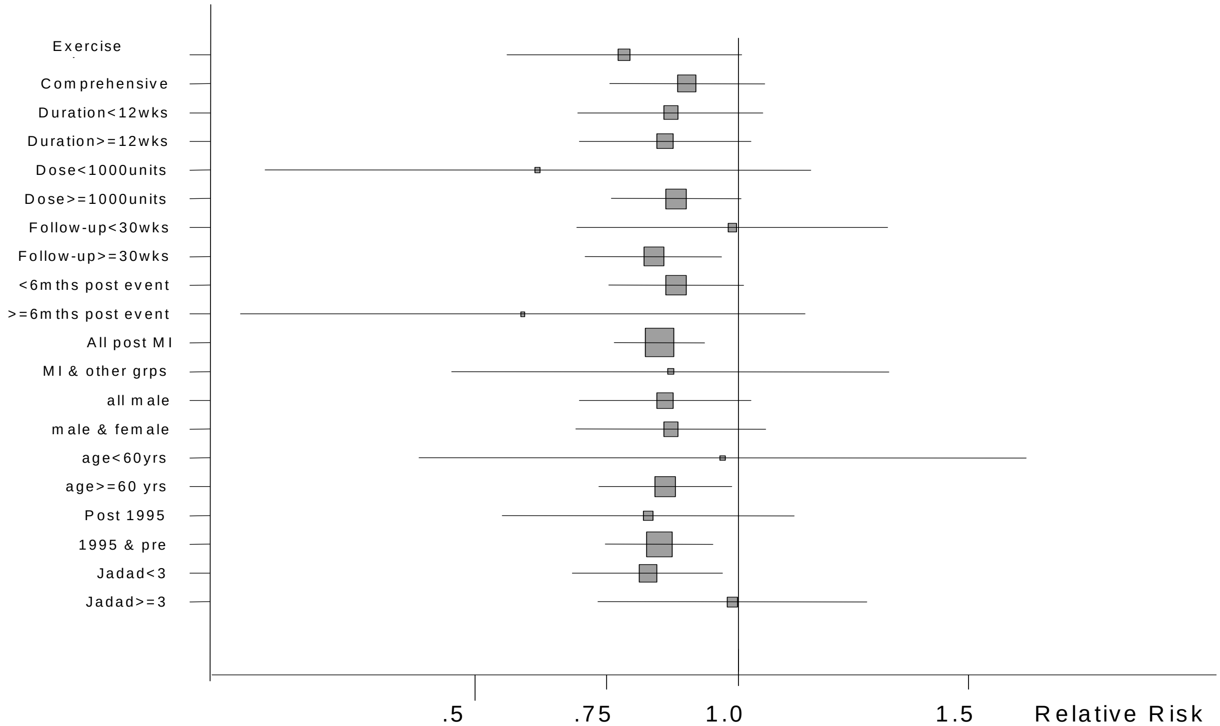
We identified four follow-up studies that reported on outcomes 10 years or more after initiation of CR.[73,75-77] None of the individual studies observed a significant reduction in total mortality at long-term follow-up, although Hamalainen et al. did report a significant reduction in cardiac deaths and sudden deaths at 10 and 15 years.[76,77]

g) Subgroup Analyses

Subgroup analyses were carried out on all trials that assessed the outcome of total mortality (both EX CR and CCR trials combined). The subgroups analysed are listed in Figure 2.

Although stratified analyses indicated that the effect size appeared to vary with the total amount of intervention and with various patient characteristics, none of these within-stratum comparisons found statistically significant differences (i.e. all of the 95% CIs overlapped in the pair-wise comparisons; Figure 2).

Figure 2: Stratified (sub-group) analysis for the total mortality outcome



Dose = (total duration of rehab in weeks) x (frequency of exercise sessions per week) x (duration of each session in minutes); for example, 12-week program with 3 sessions/week of 30 minutes = 1,080 dose units.

Discussion

This updated review supports the principal finding of the Cochrane review published in 2001, i.e. that exercise-based CR (pooling both EX CR and CCR trials) significantly reduces the RR of all-cause mortality and cardiac mortality.

Some differences in outcomes between EX CR and CCR trials were observed. For both EX CR and CCR, a significant reduction in cardiac mortality was observed; however, a significant reduction in all-cause mortality was observed only with EX CR. Significant benefits in a number of CAD risk factors were observed only with CCR. Evidence for a trend towards an improvement in a number of CAD risk factors was observed with EX CR; however, the effects were not statistically significant.

One method of determining which patients will benefit from a particular intervention is to examine the number-needed-to-treat (NNT). The closer the NNT is to 1.0 (i.e. every patient treated by the intervention will derive the intended benefit), the more clinically effective is the intervention.[82] The NNT of 66 for exercise-based CR to prevent all-cause mortality over an average of 28 months of follow-up compares favourably with the NNT per year for accepted CAD secondary prevention practices such as beta-blocker therapy post MI (NNT = 84),[83] anti-platelet therapy post MI (NNT = 306)[84] and statin treatment for cholesterol (NNT = 11 to 56).[85-87]

This updated review provides a number of additional findings. First, there is currently insufficient evidence to conclude that CR with an exercise component enhances the HRQoL of cardiac patients more than usual care. Second, the benefits of exercise-based CR appear to be consistent across cardiac patient groups that include post-MI, post-CABG, post-PTCA and angina patients. However, female and elderly patients remain poorly represented. Third, the trials with long-term follow-up (i.e. 10 or more years) suggest that the overall mortality benefit of CR is likely to diminish, or even disappear over time. This temporally related treatment attenuation effect may be associated with reductions in exercise behaviour. However, the number of trials with long-term follow-up remains small.

The introduction in recent years of more intensive cardiac-drug therapy and revascularization has called into question the "added value" of CR relative to such interventions. However, we observed no statistical evidence of a difference in the treatment effect between studies pre- and post-1995 (95% CIs for the pooled effect estimate overlap). Thus, the beneficial effects of CR on mortality appear to have been retained with the advent of new technologies.

Potential limitations of our review include the generally poor quality of RCTs included in the review, and variation regarding information on the dose of intervention (i.e. details on the frequency, duration and intensity of exercise varied between trials).

4. Review of Economic Evidence

Methods

a) Literature Search

All databases searched for the clinical objective were also searched for the economic objective. The electronic search of economic objectives covered publication years 1995 onward with no language restrictions. Bibliographies of relevant articles were hand-searched, giving access to articles published prior to 1995. In addition to The Cochrane Library and other grey literature sources consulted in the clinical search, we also performed and updated searches throughout the duration of the project on the CD ROM version of the Health Economic Evaluations Database (HEED).

The descriptors and keywords used to describe the clinical condition and intervention were also used for the economic searches. To avoid eliminating economic evaluations based on decision theoretic models, we did not use a filter limiting retrieval to RCTs in the economics search. Instead, an economic filter was applied to limit results to economic articles. Therefore, RCT-based and non-RCT-based economic articles were included in the search.

b) Selection Strategy

An economic article was eligible for inclusion if it met each of the following criteria.

Study design: Included were full economic evaluations (comparative analysis of both the costs and consequences of alternative courses of action). These could be cost benefit studies (consequences measured in dollars), cost-effectiveness studies (consequences measured in natural units), cost utility studies (consequences measured in derived units like quality adjusted life years) and cost minimization studies (with proof that the intervention and comparator are equally effective).[88]

Or

Cost studies examining costs at the micro level.

Population: adult patients who have CAD (post-MI, post-PTCA, post-CABG, angina pectoris or CAD defined by angiography).

Intervention: CR programs with an exercise component (EX CR or CCR) and comparator being usual care.

Primary outcomes: must be presented as an incremental measure of the implication of moving from the comparator to the intervention. In other words, an Incremental Cost-effectiveness Ratio, or an Incremental Net Benefit measure, i.e. cost per quality adjusted life year (QALY), cost per year of life saved, cost per medical event averted.

Or

If a cost study, comparative costs are expressed in dollars or in terms of real resources.

c) Data Extraction

Two individuals (AB and HN) broadly applied the inclusion criteria to the title of each citation, as well as to the abstract and key words (if available). Where disagreements or uncertainty occurred, the citation was retained for the next step in the process. The remaining citations were identified for retrieval as full text articles. Two reviewers (AB and HN) then applied the inclusion criteria to the articles obtained in full text from this list. An inclusion/exclusion form was used. If an article received a "yes" for all questions, it was accepted for inclusion in the review. Disagreements between the reviewers were resolved by consensus. The same two reviewers used a data extraction form to independently extract and document relevant information.

d) Analysis

There was substantial heterogeneity in the included studies in terms of study design and other characteristics (see Tables 4 to 7). No attempt was made to pool the results quantitatively; instead, a qualitative analysis was undertaken. Laupacis and colleagues have developed cost-effectiveness ranges for consistent decision making.[89] Although designating an intervention as "cost effective" is somewhat arbitrary, these can be useful indicators.

Results

a) Search Results

A total of 614 potentially relevant articles were identified. Of these, 550 were excluded, 75 of which were excluded at the abstract review stage due to duplication. Although there was no language restriction in the electronic search strategy, 67 non-English articles were excluded on the basis that CR is a form of conventional medicine and there is little evidence of language bias in conventional medicine (as opposed to alternative medicine).[90] Of the 64 full length articles retrieved for further analysis, six were included for review.[91-96]

b) Study Selection and Data Extraction Results

All six studies included for review were comparative, i.e. compared patients undergoing a CR program with patients who were not. Three of these studies were full economic evaluations[92,95,96] and three were cost studies.[91,93,94] Only one article was RCT-based.[96]

The full economic evaluation studies included for review[92,95,96] were of two types.

- Cost-effectiveness analysis (CEA): consequences measured in natural units such as life-years gained (LYG).
- Cost-utility analysis (CUA): consequences measured using a preference score (e.g. time trade-off or standard gamble) from which QALYs are estimated.

Characteristics of these studies are provided in Table 3.

Table 3: Study characteristics — full economic evaluations

Author	Source	Intervention	Study Design	Geographic Location	Clinical Outcome Source
Lowensteyn (2000)[95]	Journal article	Supervised and unsupervised exercise programs	Decision theoretic CEA	Canada	Simulation using the Cardiovascular Disease Life Expectancy model applied to the Canadian Heart Health Survey
Ades (1997)[92]	Journal article	Exercise-based & comprehensive programs	Decision theoretic CEA	US	Meta-analysis of RCTs of CR
Oldridge (1993)[96]	Journal article	8 weeks supervised exercise plus counselling	RCT-based CUA & CEA	Canada	A 12 month clinical trial of patients post acute MI, with anxiety and/or depression

Cost-effectiveness results for these studies are presented in Table 4. For the Lowensteyn study,[95] the source for costs was an average of Ontario and Quebec health insurance plan fees from 1996. Costs for the first year of a supervised exercise program were estimated at US$605 and for all subsequent years, US$367. For the Ades study,[92] cost data were obtained from survey responses obtained from 626 operating centres in the US, most of which were hospital based (78%), and most of which provided 12 week/36 session programs (94%). The average cost of a conventional program of CR was determined to be US$1,305. In the Oldridge study,[96] program costs (e.g. rent, staff salaries, equipment) and costs borne by patients (e.g. transportation) were included.

Table 4: Cost-effectiveness results — full economic evaluations

Author	Study Perspective	Currency	Currency Year	Point Estimate of Cost-effectiveness
Lowensteyn (2000)[95]	Not stated directly - appears to be societal	$US	1996	Less than $15,000 per year of life saved for a supervised program for men
Ades (1997)[92]	Patient or insurance payer	$US	1995	$4,950 per year of life saved
Oldridge (1993)[96]	Not stated directly - appears to be societal	$US	1991	$9,200/QALY gained during the year of follow-up $21,800 per life year gained

Study characteristics of the three cost studies[91,93,94] are provided in Table 5; cost results are provided in Table 6.

Table 5: Study characteristics — cost studies

Author	Source	Intervention	Study Design	Geographic Location	Cost Source
Bondestam (1995)[93]	Journal article	Low intensity exercise and counselling	Non-randomized matched study of rehospitalizaton rates	Sweden	A primary care rehabilitation program for patients 65 years and over with acute MI
Ades (1992[91]	Journal article	Comprehensive CR program	Non-randomized cost analysis adjusted by analysis of covariance	US	Patients surviving MI or CABG at the Medical Center Hospital of Vermont
Levin (1991)[94]	Journal article	Comprehensive CR program	Cost analysis	Sweden	Patients younger than 65 years at a post-MI clinic

Table 6: Cost results — cost studies

Author	Study Perspective	Currency	Year	Cost Results
Bondestam (1995)[93]	Primary health care provider	Not applicable	Around 1993	Over the one-year follow-up period, mean number of days for rehospitalization was 2.1 for the intervention group and 5.4 for the control group.
Ades (1992)[91]	Hospital	$US	Around 1992	Over the mean follow-up period of 21 months, per capita hospitalization was $739 lower in the CR group.
Levin (1991)[94]	Swedish National Health Insurance System	Swedish Krona	Around 1991	Over the five-year follow-up period, mean patient cost was SEK 73,500 lower (about C$11,500) in the rehabilitation group.

Discussion

Our review of economic evidence identified three full economic evaluations.[92,95,96] These studies all found CR to be cost-effective by current commonly accepted standards. Two of the studies were carried out in Canada,[95,96] which supports their applicability to the Canadian context. The three cost studies identified[91,93,94] all found that, over time, CR programs with an exercise component save costs and/or resources for the health care system.

Table 7 compares CR cost-effectiveness evidence with other procedures, including other options available after acute coronary events.[92,97,98] The table includes the cost-effectiveness ratios of the three full economic evaluations included in the review.[92,95,96] In terms of cost-effectiveness measures, CR compares well with other medical treatments in general, and in particular with treatments available after acute coronary events.

Table 7: Cost-effectiveness ratios for selected medical interventions

Intervention	Comparator	Cost-effectiveness Ratio
Smoking cessation program[92]	No therapy	US$220 per LYG* (1991)
Education to promote cholesterol reduction[98]	No intervention	US$3,475 per LYG** (1999)
Cardiac rehabilitation[92] (included study - Ades et al. 1997)	Usual care	US$4,950 per LYG (1995)
Coronary artery angioplasty (one vessel, severe angina)[92]	Medical care	US$8,700 per QALY† (1993)
Lipid lowering (simvastatin) for secondary prevention[92]	No therapy	US$9,630 per LYG (1996)
Cardiac rehabilitation[95] (included study - Lowenstyn et al. 2000)	Standard care	US$15,000 per LYG (1996)
Cardiac rehabilitation[96] (included study - Oldridge et al. 1993)	Usual care	US$21,800 per LYG (1991) US$9,200 per QALY (1991)
CABG[98]	PTCA	US$26,570 per LYG** (1999)
Tissue plasminogen activator[98]	Treatment with streptokinase	US$35,257 per LYG** (1999)
Thrombolytic reperfusion (t-PA, anterior MI, age 41-60)[92]	Streptokinase	US$49,900 per LYG (1993)
Captopril (in 50 year old patients surviving MI)[97]	No captopril	US$76,000 per QALY (1998)
Coronary artery angioplasty (one vessel, mild angina)[92]	Medical care	US$126,400 per QALY (1993)

*LYG = life-year gained
**Converted at US$1= C$1.55
† QALY = Quality adjusted life-year

A major limitation of our economic analysis, however, was the limited economic evaluation data from which to determine the cost-effectiveness of CR. Only one of the studies included in the economic review was RCT-based.[96] The apparent cost-effectiveness of CR programs in relation to more technologically oriented, acute care focused therapies warrants further analysis. A prospective RCT in a Canadian setting, with an economic evaluation performed alongside, would further clarify the economic issues.

5. Policy Implications

Need for CR Programs

Population information from Health Canada indicates that the rate of hospital discharges for cardiovascular disease from 1979 to 1994 stayed relatively constant at approximately 1,600 per 100,000.[13,14] Based on expected population increases, this translates to 500,400 hospital discharges for cardiovascular disease in 2001 and 530,500 by 2011. Based on a 50% compliance rate,[99] the need for CR services in Canada can be estimated at 250,000 patients in 2001 and 270,000 patients by 2011.

Impact on the Health Sector

Some have argued that if CAD prevention and treatment services are to be truly effective, they must be fully integrated along the spectrum of disease.[100-102] This integrated approach would link primary care, secondary prevention, diagnostic monitoring and CR. The current approach to client and patient care in CAD would be replaced with care that:

- fully recognizes the role of risk factors in the genesis and progression of CAD;
- respects the need to treat risk factors to scientifically validated targets; and
- emphasizes and reinforces a co-operative and collaborative multidisciplinary approach to CAD care.[103]

Furthermore, changes to the current provision of CR services would need examination.

- At the present time, the majority of patients attending CR programs are relatively low-risk, younger males (age < 60). However, evidence suggests that providing CR services to higher-risk cardiac populations can be safe and can confer similar improvements in functional capacity, strength and risk factors as those that accrue to lower risk populations.[104-108] Providing CR services to high and very high-risk populations may improve the cost-effectiveness of CR.
- There is evidence from RCTs that clinical outcomes can be improved when risk factor levels are significantly reduced. To extend this benefit to the usual care setting, patients in CR programs would be treated to the same risk factor target levels that have been established in RCTs.
- A direct link between risk factors and the likelihood of future cardiac events has been established[109,110] Stratification of patients with cardiovascular disease, based on their risk factor profile and other factors such as co-morbidity, can assist in identifying higher risk patient populations who are likely to benefit from CR.
- Evaluating patients before hospital discharge to identify associated risks would allow for appropriate and cost-effective follow-up, with high-risk patients perhaps being assigned to comprehensive, facility-based CR programs, and low-risk patients being referred to home-based CR programs.
- The use of clinical/critical paths or patient care algorithms has demonstrated organizational and clinical benefits.[111,112] Routinely integrating evidence-based clinical paths into CR programs has the potential to improve outcomes, reduce costs and lessen the dependence of cardiac patients on acute care institutions.

Implications for Policy Makers

The clinical and cost-effectiveness evidence in this review generally supports the provision of exercise-based CR for post-MI and revascularization patients. The benefit of CCR, however, was not shown to be statistically significant with respect to total mortality, although it did improve cardiac mortality. The body of evidence for females and older individuals remains relatively sparse.[3,6,99,113] Our review has demonstrated that the “added value” of CR over usual care persists in spite of recent advances in drug therapy and revascularization.

Suggestions for Future Research

- Current trials should track patients over time, to assess the long-term impact of CR.
- The focus of future trials should be directed towards identifying the patients who gain the most from CR, and matching the degrees and types of interventions to patient needs and projected benefits.
- Future trials should increase recruitment of under-represented populations, e.g. the elderly, women, ethnic groups and higher risk patients.
- Future trials must improve reporting of methods, to allow for assessment of quality.
- Compared to previous reviews, more trials that included validated HRQoL outcomes were identified in this update. However, a variety of different measures were used, making it difficult to compare across studies or to pool studies. Although previous HRQoL reviews have suggested patients can benefit from CR programs,[114] there remains a need for future CR trials to collect HRQoL using accepted outcome measure(s), such as the SF-36 and EuroQol 5D (EQ-5D).
- A recent 19-year follow-up of CR reports loss of mortality benefit of CR over time.[73] Given that this loss of effect may be the result of a decrease in exercise behaviour, this change in behaviour requires further study. There is also a need for research into ways to improve and maintain compliance with CR.
- The majority of CR trials continue to take place in hospital/secondary care settings. Other settings (home/community-based CR) should be explored to assess their cost-effectiveness. These settings may improve patient compliance.
- The apparently paradoxical, although non-significant, trend of improved clinical outcomes in EX CR patients compared to CCR patients seen in this review begs further exploration.
- Currently there is no consensus regarding the delivery of CR services. There is a need to conduct appropriately powered RCTs with concurrent economic evaluations to determine the most cost-effective combination(s) of program, duration, intensity and frequency of visits with respect to exercise, patient education and risk factor modification.
- There is a need for an appropriately powered RCT of CCR versus usual care in low, moderate, high and very high-risk patients.
- The highest incidence of index cardiac events occurs in the patients with the highest risk of ischemic heart disease. The difference between these high-risk persons and cardiac patients is often minimal. There is a need for appropriately powered RCTs to determine whether aggressive intervention in high-risk IHD persons (i.e. targeted primary prevention), through existing CR programs, is cost-effective.

6. Conclusions

The systematic review of clinical evidence supports the findings of the previous Cochrane review, in that CR that includes exercise has beneficial effects on cardiac mortality and total mortality (although the trend for CCR on total mortality was not significant). It appears that CCR has a somewhat more positive effect overall on risk factors than EX CR. Few studies have examined the impact of CR on HRQoL, and in those that have there was a non-significant trend that CR that includes exercise enhances quality of life relative to usual care. Although recent trials have increasingly recruited patients who have had revascularization or angina, the representation of women and the elderly in the trials remains poor. The long-term (i.e.10 years or more) mortality benefit of CR tends to diminish. This may be associated with a reduction in exercise behaviour.

The results of the included economic studies were consistent, in that the three full economic evaluations all suggested CR that includes exercise is cost-effective. Also, the three cost studies all suggested CR that includes exercise may reduce costs to health care systems due to reduced rehospitalization and drug utilization. Although the cost studies suggest that cost savings over time would result from switching to CR from standard care, in the short term there would likely be a significant budget impact. For example, at an average cost of $1,000 per patient, making supervised CR standard practice for Canadian CAD patients could increase short-run annual expenditures in Canada by $225 million.

Our analysis of health sector impact found that Canadian CR programs that include exercise may be under-subscribed; only 10% of eligible patients attend. We estimated the need for CR services in Canada to be 250,000 "places" for the year 2001.

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