SPECIAL ARTICLE

Exercise-Based Rehabilitation for Patients with Coronary Heart Disease: Systematic Review and Meta-analysis of Randomized Controlled Trials

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PURPOSE: To review the effectiveness of exercise-based cardiac rehabilitation in patients with coronary heart disease.

METHODS: A systematic review and meta-analysis of randomized controlled trials was undertaken. Databases such as MEDLINE, EMBASE, and the Cochrane Library were searched up to March 2003. Trials with 6 or more months of follow-up were included if they assessed the effects of exercise training alone or in combination with psychological or educational interventions.

RESULTS: We included 48 trials with a total of 8940 patients. Compared with usual care, cardiac rehabilitation was associated with reduced all-cause mortality (odds ratio [OR] = 0.80; 95% confidence interval [CI]: 0.68 to 0.93) and cardiac mortality (OR = 0.74; 95% CI: 0.61 to 0.96); greater reductions in total cholesterol level (weighted mean difference, −0.37 mmol/L [−14.3 mg/dL]; 95% CI: −0.63 to −0.11 mmol/L [−24.3 to −4.2 mg/dL]), triglyceride level (weighted mean difference, −0.23 mmol/L [−20.4 mg/dL]; 95% CI: −0.39 to −0.07 mmol/L [−34.5 to −6.2 mg/dL]), and systolic blood pressure (weighted mean difference, −3.2 mm Hg; 95% CI: −5.4 to −0.9 mm Hg); and lower rates of self-reported smoking (OR = 0.64; 95% CI: 0.50 to 0.83). There were no significant differences in the rates of nonfatal myocardial infarction and revascularization, and changes in high- and low-density lipoprotein cholesterol levels and diastolic pressure. Health-related quality of life improved to similar levels with cardiac rehabilitation and usual care. The effect of cardiac rehabilitation on total mortality was independent of coronary heart disease diagnosis, type of cardiac rehabilitation, dose of exercise intervention, length of follow-up, trial quality, and trial publication date.

CONCLUSION: This review confirms the benefits of exercise-based cardiac rehabilitation within the context of today's cardiovascular service provision. **Am J Med. 2004;116:682–692.**

Cardiac rehabilitation has been defined as the "coordinated sum of interventions required to ensure the best physical, psychological and social conditions so that patients with chronic or post-acute cardiovascular disease may, by their own efforts, preserve or resume optimal functioning in society and, through improved health behaviours, slow or reverse progression of disease" (1). It is a complex intervention that may involve a variety of therapies, including risk factor education, psychological input, and drug therapy. Nonetheless, international clinical guidelines consistently identify exercise therapy as a central element of cardiac rehabilitation (1–4). Four previous meta-analyses of the effects of exercise-based interventions in patients with coronary heart disease reported a statistically significant benefit in patients receiving exercise therapy compared with usual medical care, with a reduction in total and cardiac mortality ranging from 20% to 32% (5–8).

Still, there are concerns about the applicability of these results with regard to policy formation on the current provision and planning of cardiac rehabilitation services. Randomized controlled trials have generally been small and often of questionable methodological quality, raising concerns that the true benefit of exercise rehabilitation may be overestimated (9,10). Early trials enrolled almost exclusively low-risk, middle-aged men after myocardial infarction. The exclusion or underrepresentation of women, elderly people, and other cardiac groups (e.g.,

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postrevascularization and angina pectoris) not only limits the applicability of the evidence to contemporary cardiovascular practice but also fails to consider those who may benefit most from rehabilitation (8). Moreover, previous meta-analyses have not reported outcomes of secondary prevention, which, through risk factor modification and enhancement of patient's health-related quality of life, is important in cardiac rehabilitation. Finally, the widespread introduction of a variety of drug therapies as part of the routine management of the cardiac patient—therapies that were not available at the time of the earliest trials (11)—may offset the magnitude of benefit associated with rehabilitation.

Thus, the aims of this study were to update the systematic review of the effects of exercise-based cardiac rehabilitation in patients with coronary heart disease, and to address previous concerns regarding the applicability of this evidence to routine clinical practice.

METHODS

Literature Search

Randomized controlled trials were identified from previously published systematic reviews and meta-analyses (5–8). This list of studies was updated by searching a number of clinical databases, including MEDLINE, EMBASE, CINAHL, and SciSearch, up to March 2003. The Cochrane Library was also searched. The search strategy was developed to maximize sensitivity of article identification and was not restricted by language. It used both controlled vocabulary (e.g., Medical Subject Headings [MeSH]) and key words ('*coronary heart disease* and [synonym]' and '*rehabilitation* or *exercise* or [synonym]').

Grey literature was obtained by searching specialized rehabilitation databases, such as those of the National Rehabilitation Information Center and PEDro, as well as the websites of health technology assessment and related agencies and their associated databases. Citation lists of relevant papers were checked. Clinical trial registries, including the National Research Register and the *meta*Register of Controlled Trials, were also searched for information on current or recently completed trials. The search engine Google was used to search for a variety of materials on the Internet. Further information was sought by hand-searching the bibliographies of selected papers and through contacts with appropriate experts and agencies.

Study Selection and Data Abstraction

Two reviewers independently scanned all the titles and abstracts and identified potentially relevant articles to be retrieved. Where there was uncertainty, full-text copies of papers were obtained. Studies were considered eligible if they were randomized controlled trials with follow-up of 6 months or more; included patients with coronary heart disease who had a myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention), or angina pectoris or coronary heart disease defined by angiography; involved any form of supervised or unsupervised structured exercise program undertaken in an inpatient-, outpatient-, community- or home-based setting (exercise training alone [exercise-only cardiac rehabilitation] or in combination with psychosocial or educational interventions [comprehensive cardiac rehabilitation] was considered); and comprised a usual care group that did not receive any form of structured exercise training or advice but that could include standard medical care such as drug therapy.

Outcomes included the following: all-cause and cardiac mortality, nonfatal myocardial infarction, revascularization, modifiable cardiac risk factors (blood lipid levels, blood pressure, smoking), and health-related quality of life (assessed by recognized and validated measures).

Two reviewers independently selected trials to be included: disagreements were resolved by consensus. Two reviewers independently extracted the data once the trials were formally included in the review using a standardized form. Where multiple time points were reported, the latest follow-up point was extracted.

Quality Assessment

The quality of trials, as reported in the source papers, was assessed independently in terms of the method of randomization, adequacy of allocation concealment, blinding of outcome assessment, and proportion of patients lost to follow-up. Quality was scored overall using the Jadad scale (12).

Statistical Analysis

Binary outcomes for each trial are expressed as odds ratios and 95% confidence intervals. Continuous variables are expressed as the mean ($\pm$ SD) change from baseline to follow-up. Weighted mean differences and 95% confidence intervals were calculated for each continuous variable in each trial (13). If the standard deviation for change was not reported in the source papers, allowance was made for within-patient correlation from baseline to follow-up measurements by using the correlation coefficient between the two (http://www.epi.bris.ac.uk/cochrane/heart.htm) (14). Data from each trial were pooled as appropriate using a fixed-effects model, except where substantial heterogeneity existed according to the chi-squared statistic, and a random-effects model was used (15).

Using stratified meta-analyses, we tested six a priori hypotheses that there may be differences in the effect of cardiac rehabilitation on total mortality across particular subgroups: coronary heart disease case mix (myocardial infarction–only trials vs. other trials); type of cardiac rehabilitation (exercise-based cardiac rehabilitation vs. comprehensive cardiac rehabilitation); 'dose' of exercise intervention ([dose = duration in weeks * number of sessions * number of sessions per week – dose of 1000

units] vs. dose >1000 units); follow-up period (≤12 months vs. >12 months); trial quality (Jadad score ≤3 vs. >3); and year of publication (before 1995 vs. 1995 or later). Additionally, these prespecified characteristics were examined by univariate and multivariate regression models (meta-regression); exercise dose, year of publication, follow-up period, and trial quality were modeled as binary and continuous variables. All analyses were performed using either Stata, version 6 (Stata Corp., College Station, Texas) or RevMan, version 4.2 (Wintertree Software Inc., Oxford, United Kingdom) software. The funnel plot and the Egger test were used to examine publication bias (16).

RESULTS

Over 5000 titles were retrieved from the various search sources and 425 full papers were identified for possible inclusion. Studies were excluded for a variety of reasons: nonrandomized design (18%), inappropriate patient group(s) (9%), inappropriate intervention (22%), the control group received an exercise intervention (14%), inappropriate outcome(s) (21%), inadequate follow-up (14%), and preliminary results available only in abstract form (2%) (17,18). One trial published after the search cutoff date was included as the unpublished trial manuscript was previously made available to us by the study authors (19). After identification of duplicate publications, 48 eligible studies remained, which provided information on a total of 8940 patients with coronary heart disease (Table) (19–66).

Study Characteristics and Quality

Nineteen trials were judged to be exercise-only trials and 30 were judged to be comprehensive cardiac rehabilitation trials (Table); one trial randomly assigned patients to both exercise-only cardiac rehabilitation and comprehensive cardiac rehabilitation (56). The majority of trials (30 studies, 63%) were undertaken in Europe, either as single or multicenter studies. Trial sample sizes varied widely from 37 to 1479 patients (median, 112 patients), with a median intervention duration of 3 months (range, 0.25 to 30 months) and a follow-up of 15 months (range, 6 to 72 months).

Patients with myocardial infarction alone were recruited in 32 trials (67%); the remaining trials recruited either exclusively postrevascularization patients (i.e., coronary artery bypass graft and percutaneous coronary intervention) or both groups of patients. The ages of patients in the trials ranged from 48 to 71 years. Although over half of the trials (27 studies, 54%) included women, on average women accounted for only 20% of the patients recruited.

Across the 29 studies that reported exercise details, patients undertook an average of 3.7 sessions of 53 minutes per week at an intensity of 76% maximum oxygen uptake (or maximal heart rate). Across the comprehensive cardiac rehabilitation trials, the majority included some combination of risk factor education or modification and psychological intervention.

Table. Selected Characteristics of the 48 Trials

Characteristic	Number (%) or Median* (Range)
Exercise-only trials	19 (39)†
Sample size	112 (37–1479)
Publication date	
1970–1979	2 (4)
1980–1989	17 (35.5)
1990–1999	21 (44)
2000–2003	8 (6.5)
Study location	
Europe	30 (63)
North America	13 (27)
Asia/Australia	5 (10)
Sex	
Men only	21 (44)
Women only	1 (2)
Both	26 (52)
Unspecified	1 (2)
Age (years)	55 (48–71)
Diagnosis	
Post-myocardial infarction only	32 (67)
Revascularization only	8 (6.5)
Both	8 (6.5)

* Median of study means:
† Forty-nine trials, of which one trial included both exercise-only rehabilitation and comprehensive cardiac rehabilitation arms.

Trial quality was poorly reported. Only 16 studies (33%) provided details of randomization with adequate details of concealment in only five studies (10%); blinding of outcome assessment was reported in eight studies (17%) and follow-up of 80% or more was achieved in 33 studies (69%). The median Jadad score was 2 (range, 1 to 5).

Outcome Results

Clinical events. Cardiac rehabilitation was associated with a significant reduction in all-cause mortality (odds ratio [OR] = 0.80; 95% confidence interval [CI]: 0.68 to 0.93) and total cardiac mortality (OR = 0.74; 95% CI: 0.61 to 0.96) (Figure 1). There was no significant difference in the rates of nonfatal myocardial infarction (OR = 0.79; 95% CI: 0.59 to 1.09), coronary artery bypass grafting (OR = 0.87; 95% CI: 0.65 to 1.06), or percutaneous coronary intervention (OR = 0.81; 95% CI: 0.49 to 1.34) with cardiac rehabilitation (Figure 2).

Modifiable risk factors. Cardiac rehabilitation was associated with a significant reduction in total cholesterol (weighted mean difference, –0.37 mmol/L [–14.3 mg/dL];

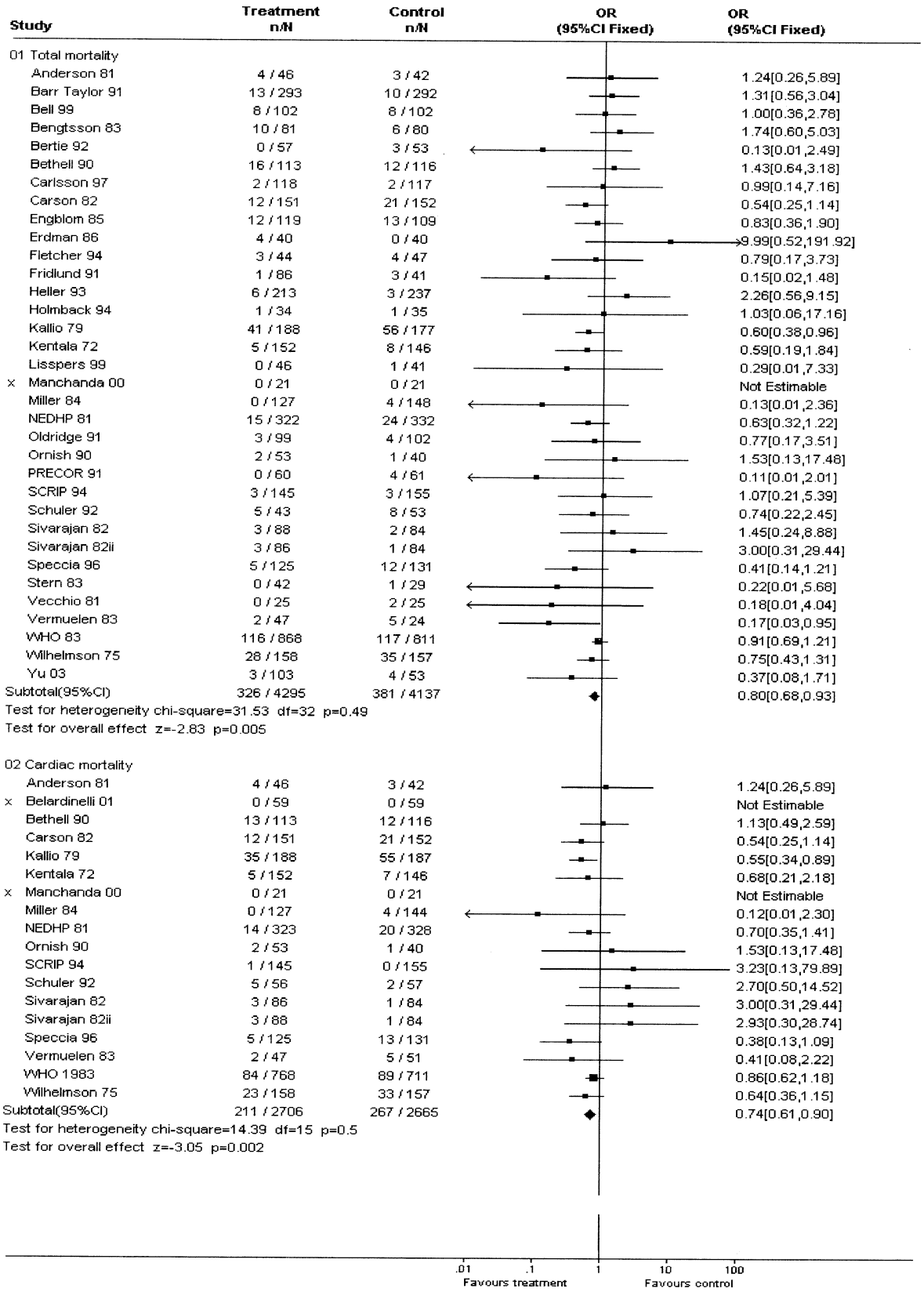

Figure 1. Pooled odds ratios (OR) and 95% confidence intervals (CI) for total and cardiac mortality in patients randomly assigned to exercise-based cardiac rehabilitation versus usual care.

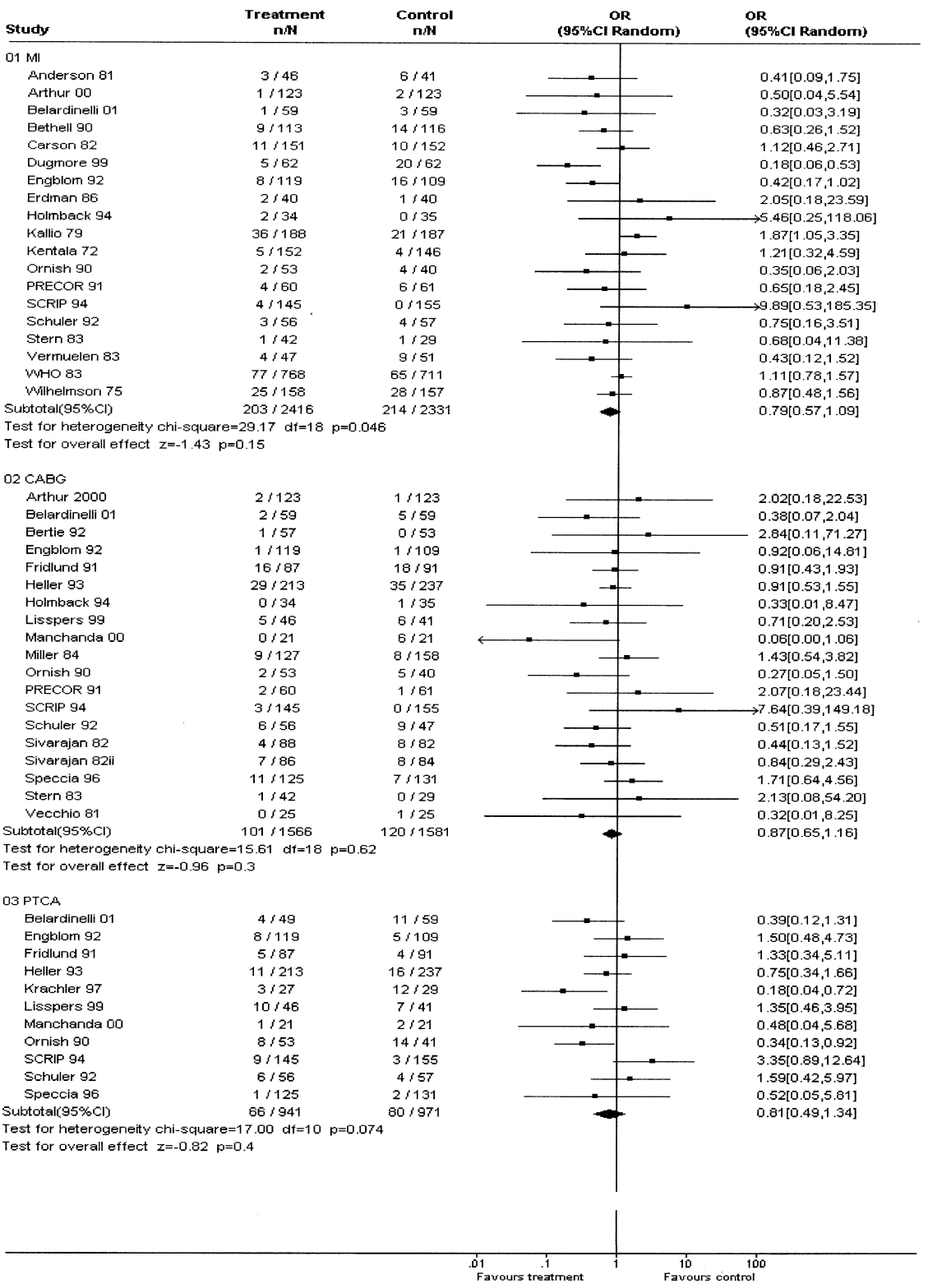

Figure 2. Pooled odds ratios (OR) and 95% confidence intervals (CI) for recurrent myocardial infarction (MI), percutaneous coronary angioplasty (PTCA), and coronary artery bypass grafting (CABG) in patients assigned randomly to exercise-based cardiac rehabilitation versus usual care.

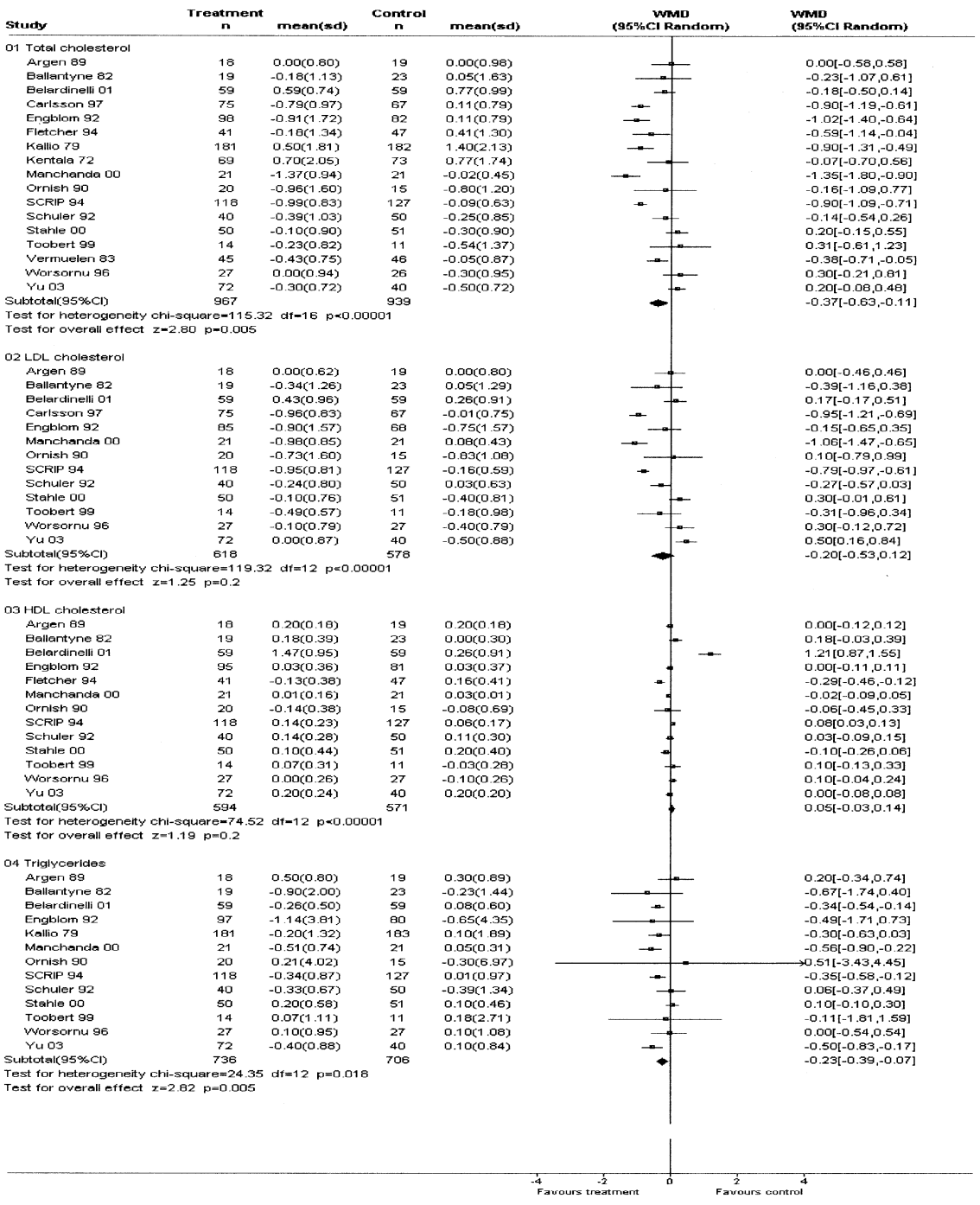

Figure 3. Pooled change in blood lipid levels (in mmol/L) at follow-up in patients assigned randomly to exercise-based cardiac rehabilitation versus usual care. To convert to mg/dL, for cholesterol (total, HDL, and LDL) multiply by 38.6; for triglycerides, multiply by 88.5. CI = confidence interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein; WMD = weighted mean difference.

95% CI: −0.63 to −0.11 mmol/L [−23.4 to −4.2 mg/dL]) and triglyceride (−0.23 mmol/L [−20.4 mg/dL]; 95% CI: −0.39 to −0.07 mmol/L [−34.5 to −6.2 mg/dL]) levels (Figure 3). There was no significant difference in low-density (−0.20 mmol/L [−7.7 mg/dL]; −0.53 to 0.12 mmol/L [−20.4 to 4.6 mg/dL]) and high-density (−0.05 mmol/L [−1.9 mg/dL]; 95% CI: −0.03 to 0.14 mmol/L [−1.1 to 5.4 mg/dL]) lipoprotein cholesterol levels.

Systolic blood pressure was reduced significantly with cardiac rehabilitation (weighted mean difference, −3.2

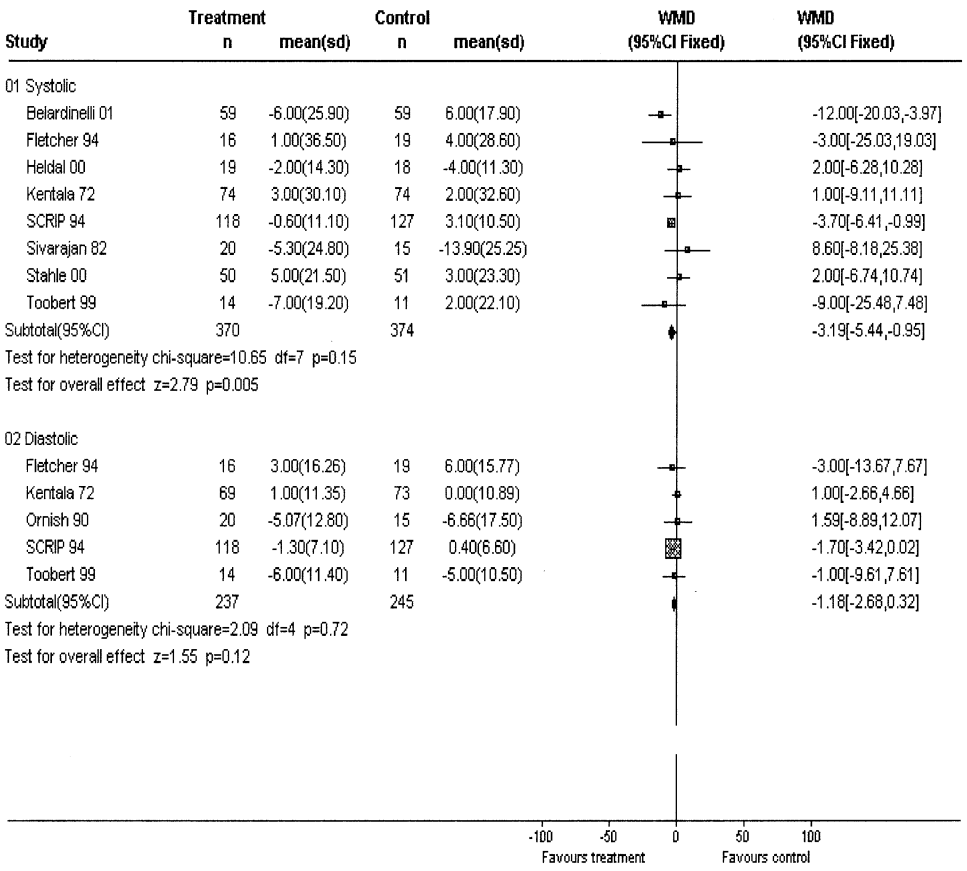

Figure 4. Pooled change in blood pressure (in mm Hg) at follow-up in patients assigned randomly to exercise-based cardiac rehabilitation versus usual care. CI = confidence interval; WMD = weighted mean difference.

mm Hg; 95% CI: –5.4 to –0.9 mm Hg), but there was no difference in diastolic blood pressure (–1.2 mm Hg; 95% CI: –2.7 to 0.3 mm Hg) (Figure 4).

At follow-up, the proportion of patients who reported smoking was reduced significantly with cardiac rehabilitation (OR = 0.64; 95% CI: 0.50 to 0.83) (Figure 5).

Health-related quality of life. Twelve trials assessed health-related quality of life using a range of outcome measures (19,24, 32,33,35,39,46,49,54,56,58,60), but, given the variation in outcome measures and methods of reporting results, a meta-analysis was not undertaken. Although all trials demonstrated an improvement in quality of life with cardiac rehabilitation, an improvement was also reported consistently in control patients. Only in two trials did the magnitude of improvement in quality of life with cardiac rehabilitation appear to exceed that of controls (32,56).

Subgroup Analyses

Stratified meta-analyses showed that the total mortality effect of cardiac rehabilitation varied within the subgroups: myocardial infarction–only trials (24 trials; OR = 0.81; 95% CI: 0.70 to 0.93) versus other trials (eight trials; OR = 0.92; 95% CI: 0.57 to 1.51); exercise-only cardiac rehabilitation (12 trials; OR = 0.76; 95% CI: 0.59 to 0.98) versus comprehensive rehabilitation (20 trials; OR = 0.84; 95% CI: 0.72 to 0.99); exercise intervention dose ≤1000 units (six trials; OR = 0.81; 95% CI: 0.50 to 1.32) versus <1000 units (eight trials; OR = 0.75; 95% CI: 0.55 to 1.02); follow-up period ≤12 months (12 trials; OR = 0.91; 95% CI: 0.61 to 1.35) versus >12 months (12 trials; OR = 0.80; 95% CI: 0.69 to 0.92); Jadad score ≤3 (12 trials; OR = 0.81; 95% CI: 0.61 to 1.35) versus >3 (four trials; OR = 0.93; 95% CI: 0.43 to 2.03); and publication before 1995 (26 trials; OR = 0.84; 95% CI: 0.73 to 0.97) versus 1995 or later (six trials; OR = 0.62; 95% CI: 0.38 to 1.04). The overlap in 95% confidence intervals of each within-stratum comparison suggests that none of these subgroup differences were statistically significant. These findings were confirmed by both univariate and multivariate meta-regression analyses.

Publication Bias

There was no significant publication bias as evidenced by either funnel plot asymmetry or Egger test ($P = 0.32$).

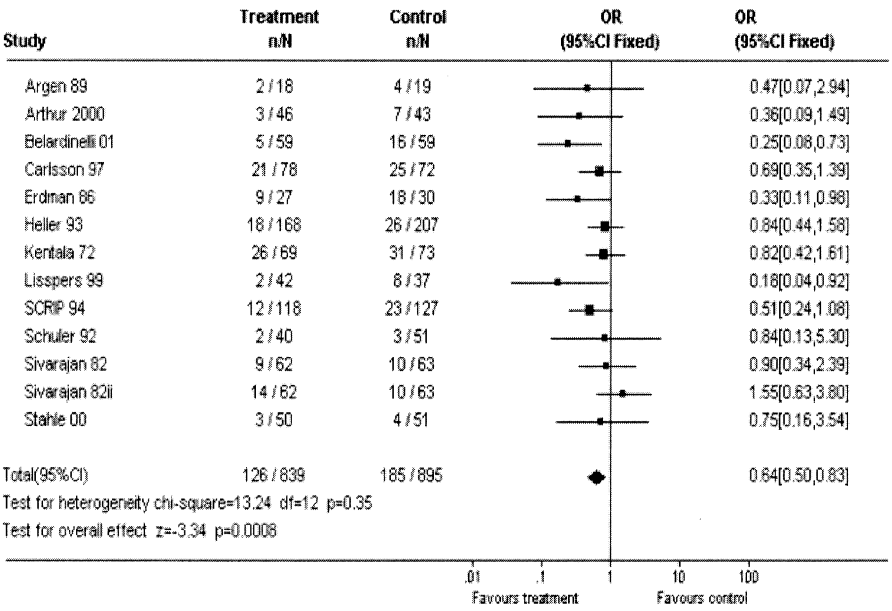

Figure 5. Pooled odds ratios (OR) and 95% confidence intervals (CI) for smoking at follow-up in patients assigned randomly to exercise-based cardiac rehabilitation versus usual care.

DISCUSSION

This systematic review confirms the findings of previous meta-analyses that exercise-based cardiac rehabilitation reduces both cardiac and total mortality but not the risk of recurrent myocardial infarction or revascularization (5–8). In fact, our review shows that the mortality effects of exercise therapy appear to be consistent across a number of coronary heart disease groups (e.g., post–myocardial infarction, postrevascularization, angina) as well as a range of exercise-based intervention delivery strategies. Trials in this review assessed exercise therapy alone and also in combination with educational and psychological cointerventions, and also across a range of exercise 'doses' (a composite measure based on the overall duration of the exercise program plus the intensity, frequency, and length of exercise sessions). There was no difference in mortality effect between exercise-only cardiac rehabilitation and comprehensive cardiac rehabilitation, or by exercise dose or duration of follow-up. Our findings are in contrast to the earlier review of Oldridge and colleagues who reported a greater reduction in all-cause death with rehabilitation trials of follow-up lasting more than 36 months (5). Although we observed improvements in several primary cardiac risk factors with cardiac rehabilitation, the effect of cardiac rehabilitation on health-related quality of life remains unclear.

The precise mechanism(s) by which exercise therapy improves mortality in patients with coronary heart disease has not been elucidated fully (67). Exercise training has been shown to have direct benefits on the heart and coronary vasculature, including myocardial oxygen demand, endothelial function, autonomic tone, coagulation and clotting factors, inflammatory markers, and the development of coronary collateral vessels (68,69). However, our findings support the hypothesis that reductions in mortality may also be mediated via the indirect effects of exercise through improvements in the risk factors for atherosclerotic disease. We found that the effect of comprehensive rehabilitation on mortality was no greater than that of exercise-only rehabilitation, which may suggest that these indirect effects may need time to become effective and that the follow-ups in studies were too short to allow observation of such effects.

This review has several potential limitations, notably the poor methodological quality of many trials. Few trials provided details of the process of randomization, allocation concealment, or blinding of outcome assessment. As expected, we observed that poorer quality studies were associated with greater reductions in all-cause mortality. Nevertheless, these differences were not statistically significant. Furthermore, the quality of trials did not appear to have improved over the last decade.

Despite substantial differences in the duration of follow-up (range, 6 to 69 months), we pooled results across studies. This decision was supported by our observation that the reduction in all-cause mortality was relatively consistent with cardiac rehabilitation, regardless of the duration of follow-up. The inability to identify unpublished studies may have led to overestimation of treatment effects (16). We found no evidence of publication bias.

We were unable to demonstrate a clear benefit of exercise therapy on health-related quality of life, which may be explained by several factors. First, given the heterogeneity of health-related quality-of-life outcome measures used and their reporting, we did not synthesize the results by formal numerical pooling. Only two of the 12 trials that assessed health-related quality of life had a sample size in excess of 250 patients, meaning that they were powered to detect a modest health-related quality-of-life difference between cardiac rehabilitation and control. Second, all but one trial used generic measures that lack sensitivity to change with cardiac treatments, particularly in comparison with disease-specific measures (70,71). Finally, we limited our assessment of health-related quality of life to validated measures.

We believe that our findings have important implications for both the current policy on delivery of cardiac rehabilitation service as well as the direction of future research. Previous meta-analyses have been criticized on the grounds that they preceded most of the present treatments for coronary heart disease, such as acute thrombolytic therapy, beta-adrenergic blockers, and aggressive lipid management. They also focused almost entirely on patients following myocardial infarction (5,6). It has therefore not been clear if the benefits of exercise therapy after myocardial infarction would be sustained in the present era of cardiovascular therapies and across the contemporary range of coronary heart disease case mix. Our review shows that trials conducted in last decade have continued to report benefits of cardiac rehabilitation. Moreover, post–coronary artery bypass grafting, post–percutaneous transluminal coronary angioplasty, and angina patients are increasingly represented in this evidence base, an encouraging sign that cardiac rehabilitation should be made routinely available to a broader group of patients with coronary heart disease, including patients with heart failure, many of whom have underlying coronary heart disease and respond well to cardiac rehabilitation exercise training (72,73).

With a few exceptions, the trials identified by this review have examined exercise therapy delivered in a supervised manner, often in a formal health care setting, such as the hospital. Given the current shortfall in the provision of cardiac rehabilitation in many countries (74,75) and the increasing drive towards cost containment, future research should examine the relative efficacy and costs of cardiac rehabilitation delivery in non–health care settings, such as the home, especially for low- to moderate-risk and older patients (19). These studies also need to consider patients across the range of coronary heart disease diagnoses, sexes, ages, ethnicities, and economic classes.

In conclusion, this review confirms the benefits of exercise-based cardiac rehabilitation in terms of cardiac and all-cause mortality, as well as demonstrates improvements in a number of primary risk factors that appear to be sustained in the present era of cardiovascular therapy provision. These benefits are not limited to particular coronary heart disease patient subgroups or particular models of exercise intervention.

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