Technology Assessment

Technology Assessment Program

Randomized Trials of Secondary Prevention Programs in Coronary Artery Disease: A Systematic Review

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FINAL REPORT

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RANDOMIZED TRIALS OF SECONDARY PREVENTION PROGRAMS IN CORONARY ARTERY DISEASE: A SYSTEMATIC REVIEW

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SUMMARY

Background: While it is well established that cardiac rehabilitation programs employing supervised exercise training improve outcomes in survivors of myocardial infarction, the effects of secondary prevention programs which are not primarily exercise-based are unclear.

Objectives: To determine whether secondary prevention programs for patients with established coronary artery disease (CAD) improve health outcomes. To characterize secondary prevention programs which have been evaluated in the literature and to identify any program-related factors which influence effectiveness for patients with established coronary artery disease (CAD). Of note, secondary prevention programs which consisted of exercise training alone were not included in this review.

Design: Randomized clinical trials (RCTs) of secondary prevention programs in patients with CAD were identified by searching Medline 1966-2004; the Cochrane Central Register of Controlled Trials, Issue 4, 2004; Embase 1980-2004; CINAHL 1982-2004; SIGLE 1980-2004; the Cochrane Effective Practice and Organization of Care Study Registry; bibliographies of published

studies, and via contact with experts in the field and references provided by the Centers for Medicare and Medicaid Services and authors of the primary studies. Studies were excluded if the program being evaluated consisted of supervised exercise training only; studies were selected and data extracted independently by 2 investigators, and summary risk ratios were calculated using the random effects model. Each intervention was classified *a priori* into one of 3 groups: (1) *Comprehensive Cardiac Rehabilitation* (those interventions which consist of exercise training plus group education and counseling sessions about coronary risk factor management), (2) *Group Cardiac Rehabilitation without exercise component* (programs which include group education and counseling sessions about coronary risk factor management, but without a structured exercise component), or (3) *Individual Counseling* (programs, usually delivered by specially trained nurses, which involve individual education and counseling sessions with individual follow-up, either in person or by telephone, to encourage coronary risk factor optimization). Primary study authors were contacted for additional details about their programs. The association of program

characteristics with the main outcomes were examined using a forward step-wise meta-regression.

Results: A total of 46 RCTs (18 821 patients with CAD) were identified. The summary RR was 0.87 (95% CI 0.79-0.97) for all-cause mortality in the 29 trials (13 857 patients) reporting this outcome, but this result differed over time with a RR of 0.97 (95% CI 0.82-1.14) for 12 month all-cause mortality in the 19 trials (9393 patients, p for heterogeneity=0.95, I-squared=0%) reporting this timeframe and a RR of 0.53 (95% CI 0.31-0.92) for all-cause mortality at 24 months in the 4 trials (1367 patients, p for heterogeneity=0.44, I-squared=0%) reporting this timeframe. The summary RR was 0.83 (95% CI 0.72-0.96) for recurrent myocardial infarction and 0.84 (95% CI 0.74-0.97) for hospitalization rates over a median follow-up of 12 months. There were no appreciable differences between the 3 types of secondary prevention programs we examined in their effects on mortality, hospitalizations, or recurrent myocardial infarctions. None of the program characteristics demonstrated a significant effect on all-cause mortality or on recurrent myocardial infarctions- indeed, the mortality benefit seen with short-term interventions (less than 10 hours of patient-provider contact time) was similar to the overall

pooled result: RR 0.80, 95% CI 0.68 to 0.95, in 4307 patients from 9 trials. For hospitalizations, programs with increased degrees of individualization exerted greater impacts ($p<0.001$ in meta-regression, RR 0.74, 95% CI 0.65 to 0.85). Secondary prevention programs had positive impacts on processes of care: patients randomized to these programs were more likely to be prescribed efficacious medications and 22 out of 27 trials evaluating cholesterol profiles demonstrated improvements with these programs compared to usual care (in 14 trials the improvements were statistically significant, with effect sizes in the small to moderate range). Eighteen of the 30 trials evaluating quality of life or functional status reported statistically significantly better outcomes in those patients exposed to the intervention programs, although the effect sizes were generally small. None of these trials were double-blind and Jadad quality scores were clustered around 2. Physicians adopted a coordinating role in only 4 (9%) programs. Only one quarter of the programs were based on specific guidelines. Around one third offered standardized programs, though the greatest proportion of these programs (43%) had some individualization to the degree expected with usual care.

Conclusions: Secondary prevention programs improve processes of care, enhance quality of life/functional status, reduce hospitalizations, reduce recurrent myocardial infarctions, and reduce mortality in patients with established CAD. There is inadequate data to conclusively comment on the incremental benefits of specific components contained within these programs. Though most programs are likely to involve specialist health professionals, physicians adopt an active coordinating role in only a small minority of programs. Programs with more individualization are more effective at reducing hospitalizations and even short-term programs (less than 10 hours of provider-patient contact) demonstrate mortality benefits.

INTRODUCTION

Although cardiovascular death rates in North America have declined over the past two decades,[1] cardiovascular disease remains the most common cause of death (38% of all deaths in the United States in 2002), hospitalization, and physician office visits (over 80 million visits in 2002), and accounts for a large portion of total health care costs in the United States (estimated direct and indirect costs for 2005 are over $393 billion).[2] Using data from the National Health and Nutrition Examination Survey (NHANES 1999-2002), it is estimated that over 70 million Americans have one or more types of cardiovascular disease and over 13 million have known coronary artery disease (CAD), however, the proportion with undiagnosed disease is likely several fold higher.[2] Indeed, it is estimated that a United States citizen suffers a coronary event every 26 seconds, with 41% dying within a year.[2] Of course, CAD is not a North American phenomenon and atherosclerotic cardiovascular disease is the leading cause of death worldwide.[3] A case-control study in nearly 30,000 subjects from 52 countries confirmed that 9 known coronary risk factors (Box 1) account for over 90% of the

population attributable risks for CAD in both men and women, in all age subgroups, and across all regions.[4]

Control of the CAD epidemic will require a multifaceted strategy that targets the 9 modifiable risk factors identified in the INTERHEART study and includes both primary prevention strategies (some designed for the general population and some targeting only high risk populations) and secondary prevention strategies (targeted at those with established CAD).[5] Despite the abundant evidence base for CAD prevention,[6] health outcomes studies consistently demonstrate suboptimal control of cardiovascular risk factors due to gaps in the application of this evidence to clinical practice that contribute to sub-optimal patient outcomes.[7-15] Furthermore, even when some therapies proven to be efficacious in preventing morbidity and mortality in patients with coronary disease are prescribed, patient compliance may be poor (from 43% to 75% at one year).[16,17] Secondary prevention programs are increasingly advocated as a means to improve management and outcomes for patients with CAD.

What are Secondary Prevention Programs?

In this report, we employ the American Heart Association and the American Association of Cardiovascular and Pulmonary

Rehabilitation definition of a secondary prevention program as one that “incorporates a multifaceted and multidisciplinary approach to overall cardiovascular risk reduction in patients with established coronary artery disease”.[18] Secondary prevention programs may include a number of components to achieve the overall goal of assessing and modifying cardiovascular risk factors in at-risk patients. In order to examine the effects of different types of secondary prevention programs, we a priori defined the following program types: (1) Comprehensive Cardiac Rehabilitation (programs that include exercise with group education and counseling sessions about coronary risk factor management), (2) Group Cardiac Rehabilitation without exercise component (programs that include group education and counseling sessions about coronary risk factor management, but no structured exercise component), or (3) Individual Counseling (programs, usually delivered by specially trained nurses, involving individual education and counseling sessions and individual follow-up, either in person or by telephone, to encourage coronary risk factor optimization).

Rationale for this Review:

While numerous reviews have shown that cardiac rehabilitation programs improve outcomes in MI survivors,[19-23] these conclusions were based largely on trials which tested supervised exercise programs versus no exercise post-MI. As activity levels are inversely proportional to cardiovascular mortality and exercise training confers substantial physiologic and clinical benefits,[24] it is not surprising that trials of exercise programs found positive treatment effects. However, few of the trials included in these reviews evaluated secondary prevention programs that were not primarily exercise-based. To address this gap in the literature, we performed a systematic review- in the 12 trials we identified (with 9803 patients), we found that multidisciplinary non-exercise based programs improved processes of care (namely prescription of proven efficacious secondary prevention therapies) and risk factor profiles, and reduced hospitalizations by 16% (95% confidence interval [CI] 6% to 24%), but did not have an appreciable impact on rates of death (RR 0.91, 95% CI 0.79-1.04) or recurrent myocardial infarction (RR 0.94, 95% CI 0.80-1.10).[25]

As current guidelines recommend that secondary prevention programs should not be restricted to supervised exercise programs

but should rather address the full range of modifiable risk factors,[18] we conducted the current systematic review to expand our earlier work and to determine whether comprehensive secondary prevention programs (in contradistinction to exercise-only or similar single modality programs) prevent coronary events and/or death in patients with CAD.

Systematic reviews incorporating meta-analyses can determine the effectiveness of interventions. However, in pooling different studies the particular characteristics of different interventions tend to be “lost in the mix”[26] and meta-analyses cannot explain why some interventions are more effective than others.[27] To gain a comprehensive overview of the literature on secondary prevention programs, we therefore derived a survey to collect a wide range of additional quantitative and qualitative data on program characteristics from primary study authors. Finally, to identify to what degree program characteristics affect outcomes, we performed a meta-regression to examine the association of *a priori* defined co-variates with our main outcomes.

METHODS

Searching for relevant studies:

We searched the following electronic databases to identify human randomized trials published in English: Medline 1966-2004; Cochrane Central Register of Controlled Trials, Issue 4, 2004; Embase 1980-2004; CINAHL 1982-2004; and, SIGLE 1980-2004. In order to identify recent publications, we also searched PubMed from January 2004 to December 2004 and conducted a cited reference search for our previous systematic review [25] in Web of Science (1999 to 2004). The searches (see Appendix A for listing of search strategy strings and results) were based on the following terms: case management, comprehensive health care, disease management, health services research, home care services, clinical protocols, patient care planning, quality of health care, rehabilitation, nurse led clinics, special clinics, and myocardial ischemia. To identify any studies missed by the literature searches, we hand-searched reference lists of all identified studies, as well as the reference list of a recent related review.[23] Finally, we screened references provided by the Centers for Medicare and Medicaid Services and content experts, including authors of the primary studies.

Selection of studies and abstraction of data:

For the systematic review, two of the investigators (AC and FM) independently reviewed the titles and abstracts of all citations to identify any studies reporting the impact of secondary prevention programs on death, MI, or hospitalization rates in patients with CAD (clinically manifest as angina, MI, or coronary revascularization). The full texts of all potentially relevant articles were obtained and reviewed by both investigators using pre-standardized data abstraction forms and *a priori* defined eligibility criteria. Any discrepancies were resolved by consensus.

All outcome data were extracted by AC and FM independently, and double-checked by BV. Outcomes were assigned according to the intention-to-treat principle and we accepted the definitions for each outcome used by the investigators in the primary studies. Original investigators were contacted to clarify the published data: 27 of the 31 study authors contacted provided further data.

Studies were excluded if they: were not randomized, were primary prevention studies (ie. restricted to patients without documented CAD), evaluated single-modality interventions (such as exercise-only programs, yoga interventions, or telephone follow-up),

tested interventions delivered to hospitalized patients rather than outpatients, did not include a “usual care” arm, or tested interventions that were not provided by health professionals (such as letter reminders, self help groups, self-directed interventions, or general health promotion interventions). Studies in which patients with multiple diseases were enrolled were included if the outcomes for patients with coronary heart disease were reported separately or if that data was provided by the study principal investigator when contacted.

Two of the investigators (AC and FM) assigned each reported intervention independently to one of 3 *a priori* defined groups: (1) *Comprehensive Cardiac Rehabilitation* (programs which included exercise with group education and counseling sessions about coronary risk factor management), (2) *Group Cardiac Rehabilitation without exercise component* (programs which included group education and counseling sessions about coronary risk factor management, but no structured exercise component), or (3) *Individual Counseling* (programs, usually delivered by specially trained nurses, involving individual education and counseling sessions and individual follow-up, either in person or by telephone, to

encourage coronary risk factor optimization). Patient education was a key component of all 3 types of interventions (see Tables 1 and 5 for a more detailed description of the program in each included trial). Data on the methodological quality of the trials were also independently extracted and verified.

Statistical analyses:

Analyses were performed using RevMan 4.2 (The Cochrane Collaboration 2004). Our primary outcome was all-cause mortality. Secondary outcomes that were meta-analyzed were recurrent myocardial infarctions and hospitalizations. We attempted to obtain data on all-cause hospitalizations wherever possible; however for some trials, even after contact with the primary study authors, we could only obtain data on cardiovascular hospitalizations. We defined "hospitalization rate" as the number of patients in each trial arm who were hospitalized at least once (thus, each patient could only contribute one event to these analyses).

As the outcomes were relatively common, risk ratios were calculated and the I^2 statistic was used to assess for heterogeneity in each outcome of interest. Studies were combined using the DerSimonian and Laird random effects model. Analyses were

conducted for each of the three types of programs: comprehensive cardiac rehabilitation, cardiac rehabilitation (without exercise component), and individual counseling. For the primary analysis, we used data from the longest follow-up period reported in each trial. We also conducted analyses using the various follow-up periods reported (6, 12, 24, 36, 48, 56, 60, and 72 months).

Due to a lack of consistency in how they were measured and/or reported (ie. different trials used different scales or measurements and while some trials reported mean/median results for continuous variables others transformed these same variables into binary variables for analyses and reporting), we described, but did not meta-analyze, the following outcomes: effects on major cardiovascular risk factors (cholesterol, smoking, blood pressure), use of proven efficacious therapies, patient quality of life, and patient functional status or symptom scores. These were evaluated and categorized as: statistically significant benefit seen in the intervention arm versus the control arm; trend towards better outcomes in the intervention arm which did not reach statistical significance; or, no appreciable difference between the intervention and control arms. In order to standardize the reporting of results for non-dichotomous outcomes

(such as change in cholesterol or blood pressure levels, quality of life, or functional status scores), we calculated standardized effect sizes by dividing the absolute difference between intervention and control arms by the standard deviation in the control arms. By convention, effect sizes <0.20 are considered trivially small, 0.50 moderate, and >0.80 large.

Exploring the impact of program components on clinical outcomes: A meta-regression

The effectiveness of an intervention is not just a consequence of a small number of macro characteristics, such as program type. Other program characteristics and the context in which the intervention is introduced are also likely to influence its provision and possibly its effectiveness [26].

A meta-regression was therefore undertaken to identify the association of several components of programs (see Tables 5a,b,c) with our main outcomes: all-cause mortality, recurrent myocardial infarctions, and all-cause hospitalizations.

To provide more details regarding program characteristics and given the paucity of details in published reports, in order to conduct the meta-regression we had to contact primary study authors for

further data on program characteristics (see Appendix C for the standardized email survey items sent to the primary study authors, Figure 10 for outline of survey steps, and Appendix D for summary of missing data before/after the survey). All 46 trials were screened by 2 investigators independently to extract the characteristics outlined in Appendix C. Further details were required for 34 of the trials- we could not trace 3 of the primary study authors (even using Google searches). Overall response rate to the survey was 87% (27/31), resulting in 36 additional variables being identified.

Since we had a larger number of studies than most meta-analyses, we decided to do a forward step-wise multiple meta-regression rather than the univariate meta-regression that one is often restricted to with smaller numbers of studies. The following co-variates were considered in the regression: location of study intervention (i.e. hospital, community, etc.), time to commencement after index event, mean length of study, number of intervention sessions, degree of individualization, presence of prescribing nurse or pharmacist, type of physician involvement, supplementary telephone support, and theoretical basis for treatment (i.e. stage of change, cognitive, etc.). As there have been no previous meta-

regressions of secondary prevention programs, these co-variates were selected based on: the factors identified as being potentially salient during the Medicare Coverage Advisory Committee Meeting, the terms used in the Medicare Coverage Advisory Committee evaluative questions, the common dimensions along which secondary preventions programs tend to differ, and what data on programs would realistically be available. Due to the expected large disparity in values for continuous variables, the variables *time to commencement after index event* and *number of sessions* were analyzed on the logarithmic scale.

RESULTS

Study selection and evaluation:

Overall we identified 6,345 citations from electronic databases (n=6,207), reference lists (n=45), and the Centers for Medicare and Medicaid Services (n=93). We reviewed 254 full manuscripts for potential inclusion. We excluded 196 of these studies after detailed evaluation; the reasons for exclusion are detailed in Figure 1 and Appendix A (a full list of excluded studies is included in Appendix B).

Disagreement among the reviewers regarding eligibility of the studies occurred on 16 occasions for a kappa value of 0.81. All disagreements were resolved by consensus.

Of the randomized trials eligible for inclusion,[28-85] 9 were reported in more than one publication. Two trials reported different endpoints in two separate publications.[28,29,57,58] One trial[30] reported the outcomes for all patients enrolled (only 56% of whom had cardiac disease) and, in a separate publication[31], provided details of event rates in the subgroup of patients with cardiac disease. The WHO Trial[32] included 24 collaborating centers; however, the original investigators excluded 7 sites because of poor

subject follow-up, and 4 sites due to significant differences at baseline between the intervention and control arms. We included the 3-year outcome data from the remaining 13 sites as one trial for the purposes of this analysis, an approach validated by the non-significant tests for statistical heterogeneity for all-cause mortality (Q=15.7, 11 df, p=0.16) and MI (Q=15.9, 11 df, p=0.15) and the fact that the summary risk ratios for both endpoints were identical under the random and fixed effects models. While the two Finnish centers in the WHO Trial published their results separately (and for multiple follow-up periods), we included only their 3-year outcome data with the other 11 WHO sites for consistency of data presentation.[33-35] In five cases, we identified studies that reported longer follow-up data from another relevant trial.[36-40]

Studies included in the systematic review:

Summary data from the 46 unique randomized trials eligible for this systematic review are presented in Table 1.[28-85] In all of the trials, patients randomized to the control groups received usual care (which was generally undefined). One trial [41] is presented twice in Table 1 because it had two intervention groups (comprehensive cardiac rehabilitation and group counseling) as well as a usual care

control arm. Although all of the control patients were included for the subgroup analyses in which this trial was relevant (comprehensive cardiac rehabilitation versus usual care, and group cardiac rehabilitations versus usual care), for the overall analyses (in which all 3 types of secondary prevention programs in the 46 trials were pooled, we only included the control arm patients once).

Our search retrieved 34 trials not included in our previous systematic review (that was limited to the pre-1999 literature)[25] and 26 trials not included in a more recent systematic review of cardiac rehabilitation (that was based on an earlier Cochrane review and limited to the pre-2003 literature on exercise interventions)[22,23].

Quantitative data synthesis:

All-cause mortality: Only one of the 29 trials reporting this outcome found a statistically significant survival benefit with the intervention (Table 2, Figures 2-4). The summary RR for all 29 trials reporting all-cause mortality (13 857 patients) was 0.87 (95% CI 0.79-0.97), using the data from the entire follow-up period in each trial (which ranged from 6 months to 6 years), with no significant statistical heterogeneity between trials (p=0.95, I-squared=0%). Pooling the data at the 12 month follow-up visit in each trial (or as close to 12

months as possible), the summary RR for all 29 trials was 0.90 (95% CI 0.79-1.01), with no significant statistical heterogeneity between trials (p=0.90, I-squared=0%).

Although there was no appreciable difference in the treatment effects with any of the 3 types of secondary prevention programs (Table 2, Figures 2-4), there were differences in effect over time. While the RR for all-cause mortality was 0.97 (95% CI 0.82-1.14) in the 19 trials (9393 patients, p for heterogeneity=0.95, I-squared=0%) reporting 12 month outcome data, the RR for all-cause mortality was 0.53 (95% CI 0.31-0.92) in the 4 trials (1367 patients, p for heterogeneity=0.44, I-squared=0%)[40,41,43,77] reporting 24 month outcome data. Furthermore, pooling the data from the 5 trials (2273 patients)[28,39,40,42,71,72] reporting follow-up data from at least 5 years after initiation of the intervention program demonstrates that programs had a sustained beneficial effect: the RR for all-cause mortality was 0.76 (95% CI 0.62-0.92) at 5 years with no appreciable heterogeneity between the trials (p=0.93, I-squared=0%).

Re-infarction Rate: One of the 17 trials reporting this endpoint (Table 2, Figures 5-7) detected a significant difference between intervention and control patients and the summary RR for

re-infarction rate at longest follow up for all 9526 patients was 0.83 (95% CI 0.72-0.96) with no significant heterogeneity (p=0.39, I-squared=6%). At 12 months, or as close as possible to 12 months, (17 trials, n=9258), the RR of re-infarction was 0.80 (95% CI 0.65-0.99) in patients randomized to secondary prevention programs. There was no significant statistical heterogeneity among trials at 12 months (p=0.24, I-squared=18%). There was no appreciable difference in the treatment effects with any of the 3 types of secondary prevention programs (Table 2, Figures 5-7), neither were there any differences in effect over time.

Hospitalization Rate: Two of the 13 trials (5751 patients) reporting hospitalization rates detected a significant difference between intervention and control patients. The summary random effects RR for hospitalization rates for all 5751 patients was 0.85 (95% CI 0.78-0.93)- (Figure 8). There was no significant statistical heterogeneity between trials (p=0.24, I-squared=20%) despite the fact that some trials reported data on all-cause hospitalizations and some on only cardiovascular hospitalizations. Median length of follow-up in these trials was approximately 12 months.

Restricting our analysis to the 9 trials (3653 patients) which reported all-cause hospitalization rates revealed a summary random effects RR of 0.84 (95% CI 0.74-0.97). Restricting our analysis to the 7 trials (3233 patients) which reported cardiovascular hospitalization rates revealed a summary random effects RR of 0.76 (95% CI 0.58-0.98).

Sensitivity Analyses: Analyses failed to reveal any effect of publication year on the observed results (data not shown).

Publication Bias: There was no evidence of publication bias (see Funnel Plot in Figure 9 for our primary outcome of all-cause mortality). The results of Begg's Test (p=0.41) and Egger's Test (p=0.88) confirm this.

Processes of Care: Twenty-seven trials tested the impact of these disease management programs on cardiovascular risk factors. Twenty two demonstrated better cholesterol profiles in patients randomized to the interventions, although the differences were statistically significant in only 14 trials and the effect sizes were generally small to moderate (Table 3). Of the 20 trials that assessed the use of proven efficacious medications, 8 demonstrated statistically significantly better application of at least one of these

therapies in the intervention patients, 2 demonstrated better prescribing in intervention patients but did not achieve statistical significance, and 10 failed to demonstrate any appreciable difference between intervention and control patients (Table 3). It should be noted that in many cases the failure to demonstrate improved processes of care with the intervention was because of improved risk factor management in control patients. For example, in one study that followed patients for over 4 years, 55% of controls had been exposed to comprehensive secondary prevention clinics by the close of the study.[37]

Other Endpoints: Eighteen of the 30 trials evaluating quality of life or functional status reported statistically significantly better scores in those patients exposed to the intervention programs, although the effect sizes were generally small (Table 3). Only 7 of these trials[30,44,49,50,65,66,105] described the costs of the intervention- while 2[30,50] reported that their intervention was cost-saving, only 1 performed formal cost-effectiveness analyses (and demonstrated an incremental cost per quality-adjusted life year of £1097). Another trial did not report costs, but did report that patients in the intervention arm had fewer visits to physicians as outpatients,

fewer emergency room visits, less laboratory testing, and fewer total hospital days in follow-up than control patients.[83] Another trial reported statistically significantly lower inpatient bed days in intervention arm patients over 4 years of follow-up compared to controls (Dr. M. Vale, personal communication, January 10 2005).[81]

Methodologic Quality:

None of these trials were double-blind (not surprising considering the nature of the intervention) and very few described randomization procedures or accounted for discrepancies between recruitment and follow up sample sizes. As a result, Jadad quality scores were clustered around 2 (Table 4). None of the trials reported side effects with the secondary prevention programs beyond the adverse clinical outcomes described below.

Exploring the impact of program components:

Program Descriptions (Table 5a,b,c and Appendix E):

Physicians adopted a coordinating role in only 4 programs (9%); conversely, 8 programs (17%) had no physician involvement. In the majority of interventions (52%) physicians only supervised exercise stress tests or exercise sessions. Most programs (78%) utilized professionals who were either specialists in cardiac

rehabilitation or in the cardiac area. Only 15% of these programs reported being based on one or more theory of behavioral change; these included social cognitive, learning, and motivational theories. Only one quarter of the interventions were based on stated guidelines. The relatively recent emergence of guidelines for cardiac prevention and rehabilitation may account for this small proportion.

Around one third of interventions were standardized in terms of components and content. Hence, all patients received a virtually identical program. The greatest proportion of programs (43%) had the level of individualization that would be expected with usual care, i.e. with inclusion and intensity of a limited range of prescribed exercise regimes based on exercise stress test results or, with counseling interventions, programs involving direct interactions with health professionals but little formalized or detailed patient assessment. However, 23% reported individualizing the components patients received and/or the content of these components based on assessments substantially more involved than is typical for usual care. This heightened level of individualization reflected significant and formalized individual assessment of needs, goals and preferences, and alteration thereon of program components offered

and/or the specific content of a component. Five programs individualized both the components offered to patients and the contents of interventions within each component. The vast majority of programs (87%) did not include pharmacist or nurse prescribing of medications. Only 39% of these interventions incorporated telephone support of patients.

Meta-Regression: None of the program components described in Table 5 demonstrated a significant effect on all-cause mortality or on recurrent myocardial infarctions. While the lack of a significant effect for particular program components may be seen as a disappointing result, the converse is important to emphasize: namely, shorter programs and programs delivered by non-specialists were just as effective as longer programs and programs delivered by specialists (Figures 11 and 12 respectively). For example, programs containing 10 hours or less of direct or telephone-based contact between patients and health professionals were effective at reducing all-cause mortality (RR 0.80, 95% CI 0.68 to 0.95, n=4307 in 9 trials) and were at least as effective as longer programs (Figure 11). Further, interventions that were based in non-hospital settings were effective in reducing all-cause mortality (RR 0.76 95% CI 0.63 to

0.92; n=2628 in 3 trials) and compared well with hospital-based programs (RR 0.90, 95% CI 0.79 to 1.03, n=9057 in 21 trials).

For hospitalizations, programs with increased degrees of individualization had greater impacts ($p<0.001$ in the meta-regression, RR 0.74, 95% CI 0.65 to 0.85, for those programs classified as having individualized components consistent with, or greater than, usual care), as did programs with nurse prescribing ($p=0.007$), although it should be noted in the latter case that there was only one study (of those reporting on all-cause hospitalizations) that had a prescribing nurse- see Figures 13 and 14.

DISCUSSION

In summary, the weight of the published randomized trial evidence suggests that comprehensive secondary prevention programs positively impact on processes of care (risk factor profiles, use of proven efficacious therapies) which are closely linked to subsequent morbidity and mortality in patients with CAD.[86] Pooling the data from those trials which reported subsequent rates of MI reveals a statistically significant 17% relative risk reduction in recurrent MIs over a median follow-up of 12 months. The majority of these programs also demonstrate improved symptom scores, exercise tolerance, or quality of life in participants. The mortality benefit derived from participation in the secondary prevention programs we identified became apparent with longer follow-up (47% at 2 years and 24% at 5 years). This is not surprising given that the natural history of atherosclerotic CAD dictates that changes in coronary risk factors would not be expected to produce immediate improvements in atherosclerotic plaque stability or coronary artery diameter. There was a statistically significant 15% relative risk reduction in hospitalizations (driven by a statistically significant 24% reduction in cardiovascular hospitalizations) over a median follow-up

of 12 months. These early beneficial effects on hospitalizations mirror the findings of a recent systematic review of multidisciplinary strategies for patients with heart failure which found that such interventions reduce hospitalizations by 25% within 6 months of implementation.[87]

Some comprehensive lifestyle modification programs under consideration by the Medicare Coverage Advisory Committee were not included in our analysis as they had not been evaluated in randomized controlled trials. However, our analyses extend the evidence base from these other programs to show significant benefits on hard clinical endpoints. Though none of the papers included were replication studies (i.e. tested interventions found to be effective previously in different settings), subsequent studies have confirmed that the Ornish multi-component cardiac rehabilitation program [71] can be successfully taught and implemented at various sites in the United States [88] and should be cost-saving.[89] However, while this economic analysis suggests that cost reductions in the order of 30% to 60% for care within the first year are possible, the analyses are based on observational data (two concurrent cohorts followed for one year in one study, matched claims data analyses in another

study, and two studies comparing actual costs after participation in the Ornish Program versus predicted costs) rather than randomized trial evidence.[89] A recent analysis of direct health care costs at 30 cardiac rehabilitation centres in the United Kingdom's NHS for the fiscal year 2000-2001 reported an average cost of £486 per patient who completed a cardiac rehabilitation program (with most of the cost, or £354 per patient, being attributed to staff salary costs).[90] However, citing an average cost is misleading since program costs varied widely across centres (depending on duration of interventions and staff to patient ratios amongst other factors) and the investigators demonstrated that economies of scale could be achieved in that costs were projected to fall by 0.25% per patient for every 1% increase in patient throughput. Although very few of the trials we identified for this review reported costs, the reality is that the 1-2 year follow up period of many of these trials is too short anyway to fully evaluate the cost-effectiveness of secondary prevention programs and while studies with 5 and 10 year time horizons are ongoing, more studies that include long term measurement of outcomes and costs are needed.

Previously published systematic reviews of cardiac rehabilitation in survivors of myocardial infarction have reported survival benefits in the order of 20-24%. However, most of the trials included in those overviews evaluated single modality exercise-based interventions and thus were not included in our overview. For example, a recently published meta-analysis reported a statistically significant 20% reduction in all-cause mortality in 8432 patients; however, closer inspection of this report reveals that 40% of the data in the mortality analysis came from 13 trials that evaluated exercise-only programs and from 2 trials which were excluded from our systematic review because of lack of a usual care control arm.[23] Activity levels are inversely proportional to cardiovascular mortality and exercise training confers substantial physiologic and clinical benefits (including changes in endothelial function, autonomic tone, inflammatory markers)[24,91]. It is thus not surprising that trials comparing exercise training to no exercise found greater treatment effects than the trials included in our review which evaluated secondary prevention programs that were not primarily exercise-based. However, the selection of programs included in our review was driven by current guideline recommendations and the request of

the Medicare Coverage Advisory Committee that secondary prevention programs should not include comparisons of supervised exercise programs versus no exercise (a control arm that is no longer "usual care").[18,26] Our systematic review demonstrates that a wide variety of secondary prevention programs delivered by health care providers, in addition to having beneficial effects on patient risk factor profiles and quality of life/functional status, provide tangible reductions in clinically relevant endpoints such as hospitalization and death.

As a corollary to this review and in recognition of the interest of some in defining the impact of exercise-only programs, we conducted a systematic review of 17 trials (2566 patients) comparing supervised exercise training programs with no exercise and incorporated this data into a meta-comparison of exercise-based rehabilitation programs versus programs which did not incorporate an exercise training component.[92] While we demonstrated that supervised exercise training reduced mortality by 28% (95% CI 5% to 46%) compared to controls who did not receive exercise training, this degree of benefit was not statistically significantly different from the benefits seen with secondary prevention programs that did not

incorporate a structured exercise component (mortality reduction 13%, 95% CI 1% to 24%).

Why didn't the trials reporting 12 month outcome data (including over 9000 subjects) demonstrate a statistically significant survival benefit? First, 12 months was clearly too short to show a marked impact on mortality- this conclusion is not only supported by knowledge of the pathophysiology of atherosclerotic CAD but also by data demonstrating a significant survival benefit in those studies reporting outcomes over 2 years or more. It should be emphasized that studies which did evaluate coronary angiographic lesions at baseline and after 12 months did report statistically significant regression rates in patients compliant with comprehensive lifestyle modifications within 12 months even without significant changes in metabolic profiles or medication usage.[39,71] Second, the patients included in these studies were at sufficiently low risk over the first year after enrollment that the likelihood of detecting a beneficial effect was remote- indeed, the control event rates in these trials were substantially lower than those in other trials enrolling patients with clinically overt CAD. Third, the incremental benefit of secondary prevention programs over usual care may be very small in the

settings in which the trials were carried out (where management in the “usual care” arm may be atypically close to optimal already). Indeed, secondary prevention programs are likely to be most beneficial in those settings where usual care is sub-optimal. Finally, it is possible that the labeling of patients with one disease for special attention in a disease-specific management program may have led to sub-optimal care for their co-morbid conditions and, as a result, no real difference in all-cause mortality.[93]

The overall effectiveness of secondary prevention programs should also be interpreted in the context of the unexplained inconsistencies in effectiveness between different types of programs. We attempted to ‘open the black box’ to identify what the key characteristics of successful programs were, which components were most influential, or how particular program or setting characteristics influenced patients and health outcomes. However, although we obtained detailed data from the vast majority of primary study authors, our meta-regression did not find any factors which significantly drove the results for all-cause mortality or recurrent MIs. The particular mechanisms of effect of interventions remain poorly understood. Translation of the theoretical benefits of secondary

prevention programs into real-world patient benefit is also dependent on suitable patients being referred to, accessing, and completing the programs. Health outcomes research has consistently demonstrated that even in publicly funded health care systems where access is free, only a minority of patients (less than one quarter to one half) ultimately access these programs.[10,90,94] Moreover, those groups that are less likely to be referred, to attend, and to complete programs are often those in greatest need of additional support and risk reduction, such as women, the elderly, low income groups, and ethnic minorities.[90] These groups were underrepresented in the studies reviewed.

Generalizability of the trial data:

The trials included in this review enrolled relatively young patients- some even excluded patients over the age of 65 (see Tables 1 and 6). This raises potential concerns about the generalizability of our findings to this increasingly large segment of the population that is especially vulnerable to CAD. However, there is evidence that elderly patients derive similar benefits from secondary prevention programs as younger patients.[95-98] While it is now less common for programs to have age-based restrictions for

entry, older adults are frequently excluded from programs due to a lack of program capacity to address their complex health needs or limited resources.[99,100] The effectiveness of programs for older patients may therefore be dependent not only on program content but also on program capacity to provide effective care to patients who have multiple co-morbidities.

Women were also underrepresented in the studies reviewed (Table 7) and data were not available to examine results by gender. This imbalance is significant because although CAD remains the leading cause of death for women in most of the developed world [101], it is often erroneously viewed as principally being a “disease of men”. Gender differences in the investigation and management of CAD have been evident for many years.[102] Consequently, the need for improved and more responsive management of CAD in women has now been recognized by international guidelines.[102] While there is no evidence of any gender-based barriers to program benefit, women are consistently identified as being less likely to access programs.[94,103] To increase the strength of evidence supporting the benefits of programs to women, more women should

be included in studies, and studies should examine the effectiveness of programs in males versus females.

Finally, as with any intervention that is efficacious in trial settings, the applicability of this evidence to the “real-world setting”, where compliance is likely to be highly variable and generally lower than that observed in trial participants, is a potential concern. This may lead some to conclude that the results we report should be viewed as a “best case scenario” for the impact of secondary prevention programs. However, this view neglects the fact that randomized trial participants assigned to the control arm often also receive care which is better than typical usual care. Indeed, as we pointed out earlier, the incremental benefit of secondary prevention programs over usual care may be very small in the settings in which these trials were carried out, where management in the “usual care” arm was often close to optimal already. Indeed, it is likely that secondary prevention programs will be more beneficial in other settings that are more akin to the “real world” of current clinical practice where usual care is sub-optimal.

Limitations of this Review:

As with all systematic reviews, this study has a number of potential limitations. The most obvious arise from the primary data (lack of blinding in outcome ascertainment, lack of detail on whether randomization was conducted properly or whether allocation concealment was achieved, and our inability to identify unpublished studies- although we did not find any evidence for publication bias) and, as all tend to result in over-estimation of any treatment effects,[104] these factors should be taken into account when interpreting our summary estimates. Our interpretation of these trials and the generalizability of the programs are hampered by our inability, even with additional unpublished data from 87% of the trials and the use of meta-regression, to determine the incremental benefits of the various components of each intervention. Determining the optimal mix of interventions, including their frequency and duration, should be a priority for future research studies in this field. While some may criticize our choice of primary endpoints as being too broad to detect differences in “cardiac” morbidity and mortality, we believe that it is most appropriate to look at all-cause mortality or hospitalization as interventions to reduce resource use in one area

can have unanticipated effects in another. Finally, we are unable to make a definitive comment on the cost-effectiveness and economic impact of the programs tested in these trials due to the paucity of relevant data and the likelihood that costs for program delivery will vary widely between different areas and different types of programs (depending on duration of the programs and staff-patient ratios in particular).

CONCLUSION

In summary, although there was substantial variability in the interventions offered and the studies enrolled highly selected populations, secondary prevention programs do improve processes of care, coronary risk factor profiles, and functional status/quality of life. Though the optimal mix of interventions, including their frequency and duration, are unclear, these programs do reduce hospitalizations, subsequent myocardial infarctions, and mortality in patients with known CAD. While these programs appear to reduce health care resource use, their cost-effectiveness has been inadequately evaluated thus far in the literature. Thus, we believe that any policy decisions to implement secondary prevention programs on a wide scale should be accompanied by plans to rigorously evaluate long-term clinical and economic outcomes in participants and non-participants.

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Box 1: Modifiable coronary risk factors (adapted from reference 4)

Modifiable Risk Factor	**Prevalence in cases with myocardial infarction**	**Population Attributable Risk (99% CI)**	Odds Ratio (99% CI) adjusted for age, gender, and smoking
Smoking	65%	36% (34% to 39%)	**2.3 (2.1-2.4)**
Dyslipidemia	33%	54% (50% to 59%)	**3.9 (3.4-4.4)**
Diabetes Mellitus	18%	12% (11% to 14%)	**3.1 (2.8-3.4)**
Hypertension	39%	23% (22% to 25%)	**2.5 (2.3-2.7)**
Abdominal Obesity	46%	34% (30% to 37%)	**2.2 (2.1-2.5)**
Psychosocial Factors	-	29% (23% to 36%)	**2.5 (2.2-2.9)**
Daily consumption of fruits and vegetables	36%	13% (10% to 17%)	**0.7 (0.6-0.8)**
Regular physical activity	14%	26% (20% to 32%)	**0.7 (0.7-0.8)**
Regular alcohol consumption	24%	14% (9% to 20%)	**0.8 (0.7-0.9)**
All of the above combined	-	**90% (88% to 92%)**	**129.2 (90.2-185.0)**

In the INTERHEART Study, “dyslipidemia” was defined as ApoB/ApoA1 Ratio in top quintile vs. lowest quintile; “abdominal obesity” was defined as waist/hip ratio > 0.90 in men and >0.83 in women; “psychosocial factors” was defined as positive exposure to depression, perceived stress at work or home, moderate or severe financial stress, low locus of control, and/or major life events; “regular physical activity” was defined as moderate or strenuous exercise for at least 4 hours per week; “regular alcohol consumption” was defined as 3 or more times per week.

Table 1: Description of studies included

Study	Sample Size	Study Population (Location)	Mean Age	% Male	Key Components of Intervention	Duration of Intervention
Comprehensive Cardiac Rehabilitation (19 trials, 4208 patients)						
Sivarajan et al. (1982)	258 (170 in control and comprehensive secondary prevention arms)	Patients younger than 70 years discharged after AMI (USA)	57	>80%	Exercise program plus group education/counseling sessions about risk factor management	3 m
Vermeulen et al. (1983)	98	Males 40-55 yrs, discharged after AMI (Netherlands)	49	100%	Multidisciplinary team (details not given) involved in exercise rehabilitation, social and psychological supports for patients	1.5-2 m
Bengtsson (1983)	87	Patients aged <65 years, one year after AMI (Sweden)	56	85%	Rehabilitation program involving physical assessment and training by physiotherapy and counseling	3 m
World Health Organization* (1983)	1,735	Males < 65 yrs, discharged after AMI (Europe)	53	100%	Multidisciplinary team (components differed at each center) involved in patient health education and supervised exercise program	36 m
Ornish et al. (1990) with longer term f/u reported in Ornish et al. (1998)	28	Patients 35-75 yrs with confirmed CAD at least 6 weeks after cardiac event (USA)	58	84%	One week residential program followed by 2 x weekly support meetings relating to low-fat vegetarian diet, stress management, exercise and social support	12 m/60 m
Oldridge et al. (1991)	201	Patients discharged with diagnosis of AMI and evidence of anxiety or depression (Canada)	52	89%	Exercise prescription, supervised training and behavioral counseling	2 m
PRECOR (1991)	182	Males <65 years, discharged after AMI (France)	51	100%	Two intervention arms, one of which was: Comprehensive cardiac rehabilitation (supervised exercise program, relaxation training, risk factor management, education)	1.5 m
Fridlund et al. (1991)	178	Patients <65 years discharged after AMI (Sweden)	56	87%	Nurse-led rehabilitation program addressing lifestyle, stress and social support.	6m
Engblom et al. (1992)	228	Patients younger than 65 years, discharged after CABG (Finland)	54	88%	Group education, individual counseling (with physician and dietician) about diet and	0.75 m

					physical activity, supervised exercise training	
Heidelberg Trial (Schuler et al. 1992 and Niebauer et al. 1997)	113	Males with CAD on angiography (Germany)	54	100%	Education about diet and exercise, exercise program with individual and group training sessions	12 m
Bell (1998)	353 (201 in control and comprehensive secondary prevention arms)	Patients $\leq$ 75 years discharged after AMI (UK)	60	78%	Comprehensive cardiac rehabilitation (supervised exercise program, group education sessions on risk factor management)	3 m
Johnston et al. (1999)	100	Patients $\leq$ 70 years hospitalized for 1st time myocardial infarction (UK)	56	65%	Nurse-led inpatient and outpatient cardiac rehabilitation program containing education, support for risk factor change and psychological effects.	1.5 m
Lisspers et al. (1999)	93	Patients <65 after PCI (Sweden)	53	37%	Comprehensive residential (health education, behavioral change) containing skills training, habit rehearsal on stress management, smoking, diet, exercise and smoking; followed by outpatient program of self observation and reporting of risk factors with follow up support.	12 m
Toobert et al. (2000)	28	Post menopausal female patients with documented CAD at least 6 weeks after cardiac event	64	0%	Residential program for women and spouse including support for low fat cookery, stress management, supervised exercise, and peer support sessions; followed by 2 x weekly community sessions.	9 m
Seki et al. (2003)	38	Male patients (>65 years) with CAD referred to hospital within past 6 months after MI, CABG or PTCA (Japan)	70	100%	Out patient program including supervised exercise sessions, and prescription, dietary and educational components.	6 m
Sundin et al. (2003)	132	Male patients <70 years after PCI, AMI or CABG (Sweden)	59	100%	Group-based multidisciplinary program addressing stress management, diet and exercise using lectures and skills training	12 m
Yu et al. (2003)	112	Obese patients attending cardiac rehabilitation after acute MI or after	62	79%	Exercise program with group education classes about risk factor modification	2.5 m

		percutaneous coronary intervention (China)				
Vestfold Heartcare Study (2003)	197	Patients discharged after acute coronary syndrome, CABG, PCI (85%); plus patients followed in clinic with stable CAD (15%) (Norway)	55	82%	Supervised exercise program, dietary advice, risk factor management education and individual plus group counseling involving a multidisciplinary team (physician, nurse, dietician, physiotherapist)	24 m
Marchionni et al. (2003)	270	Patients older than 45 years discharged after AMI (Italy)	69	71%	Supervised exercise training and education/counseling about risk factor management, optional monthly support groups	2 m
Group Cardiac Rehabilitation without exercise component (4 trials, 2671 patients)						
Stern et al. (1983)	106 (64 in control and group counseling arms)	Patients aged 30-69 years with recent MI (USA)	54	83%	Nurse and psychiatrist/social worker led group education and counseling sessions (12 sessions)	3 m
PRECOR (1991)	182	Males <65 years, discharged after AMI (France)	51	100%	Two intervention arms, one of which was: Group Counseling Program (group education and counseling led by physician, psychiatrist, and nutritionist)	1.5 m
Jones & West (1996)	2328	Patients discharged home within 28 days of AMI (United Kingdom)	62	73%	Nurse and psychologist regularly saw participants for education, counseling, and relaxation/stress management training	1.75 m
DIET (Masley et al. 2001)	97	Patients with known CAD and hyperlipidemia in specialty clinics (USA)	65	70%	Nurse-led education (group) and provision of written materials about diet and physical activity	12 m
Individual Counseling (24 trials, 11 942 patients)						
Ornish et al. (1983)	23	Patients 45-75 yrs with evidence of CAD as documented in hospital records (USA)	59	78%	Residential program in remote rural location of stress management and low fat dietary meals and training	1 m
SCRIP (Haskell et al. 1994)	300	Patients < 75 yrs referred for angiography for known or suspected CAD (USA)	56	86%	Nurse-managed patient education and algorithm-driven management of risk factors, exercise program, frequent telephone and clinic visits with nurse	48 m
DeBusk et al.	585	Patients $\leq$ 70 yrs discharged after AMI	57	79%	Nurse-managed patient education and	12 m

(1994) and Taylor et al. (1997)		(USA)			counseling, exercise program, frequent telephone contact, and algorithm-based lipid therapy	
Fitzgerald et al. (1994)	668	Patients > 45 yrs discharged from a general medicine in-patient service (2/3 with heart disease) and being followed at the general medicine clinic of a Veterans Affairs hospital (USA)	65	100%	Nurse-managed patient education, coordination of care, frequent telephone contact, and protocol-driven systematic assessments for unmet socio-medical needs	12 m
Naylor et al. (1994)	276 (142 with cardiac disease)	Patients > 70 yrs discharged from a tertiary care hospital with either CAD or heart failure (USA)	76	49%	Comprehensive discharge planning protocol with gerontologic nurse providing education, coordinating care, and maintaining telephone contact for 2 weeks	0.5 m
Cupples and McKnight (1994 and 99)	688	Patients <75 years with angina for at least 6 months identified from general practice records (UK)	63	59%	Individual nurse-led personalized health promotion program every 4 months	24 m
M-HART (Frasure-Smith et al. 1997)	1376	Patients discharged after AMI (Canada)	59	66%	Nurse contacted patients monthly by telephone, providing education and advice and screening patients for psychological distress- nurses referred patients to other health care resources as needed	12 m
Carlsson et al (1997)	168	Patients aged 50-70 years discharged after AMI (Sweden)	62	75%	Nurse-run education program (individual and group), exercise training program, nurse clinic visits	12 m
Carlsson (1998)	530	Patients aged 50-70 years discharged after AMI, CABG or PCI (Sweden)	62	79%	Individualized assessment and nurse counseling on risk factors and diet	12 m
Campbell et al. (1998), with longer term f/u reported in Murchie et al (2003)	1343	Patients <80 yrs old with documented CAD recruited from general practice records (United Kingdom)	66	58%	Regular follow-up at secondary prevention clinics run by nurses, promoting medical and lifestyle approaches to prevention	12 m
Jolly et al. (1999)	597	Patients with AMI or recent onset angina discharged from hospital or seen in a chest pain clinic (United Kingdom)	64	71%	Cardiac liaison nurse coordinated care between discharging service and family physician, patients given personal health record and prompts for follow-up	12 m
Naylor and	363 (202	Patients $\geq$ 65 years discharged from a	75	50%	Nurse-led patient education, coordination of	1 m

McCauley (1999)	with cardiac disease)	tertiary care hospital with either CAD or heart failure or after CABG/heart surgery (USA)			home care, at least 2 home visits, use of a standardized protocol to optimize medications, and weekly telephone contact for 1 month	
Allison et al. (1999)	152	Patients not treated with lipid lowering medication that completed cardiac rehabilitation after an acute coronary event (USA)	64	82%	Nurse-led follow up program every 6 weeks after start or change in lipid lowering therapy, including diet and exercise advice and lipid lowering medications.	6 m
Allison et al. (2000)	326	Patients attending emergency room with confirmed unstable angina (USA)	58	56%	Nurse-intervention including lipid management, referral to support services, counseling on risk factors and physician collaboration on abnormal results, 2 1-hour sessions at least 6 and 25 days after discharge	1 m
Moher et al. (2001)	1906	Patients 55-75 years identified in family practices with established CAD (UK)	66	68%	Nurse-led clinic providing support for risk factor change using electronic disease register and recall system	1 m
Stagmo et al. (2001)	241	Patients 50-69 years hospitalized in a CCU due to MI or previous CABG (Sweden)	62	78%	Hospital-based secondary prevention program	12 m
McHugh et al. (2001)	98	Patients on a waiting-list for elective CABG (UK)	62	76%	Shared nurse-led care program of monthly health education and motivational interviewing	7 m
Higgins et al. (2001)	105	Patients discharged after PCI (Australia)	48	90%	Nurse-led individualized education, risk factor goal setting and self-monitoring with telephone feedback, 3 home visits	12 m
Allen et al. (2002)	228	Patients $\leq$ 75 years discharged after CABG or PCI who had hypercholesterolemia (USA)	60	63%	Nurse practitioner case management in partnership with patient's primary provider (nurse-directed education and lifestyle modification advice, nurse clinic visits, nurse prescribed medications if necessary, f/u telephone calls)	12 m
COACH pilot (Vale et al. 2002)	245	Patients $\leq$ 75 years discharged after coronary revascularization procedure (Australia)	61	75%	Personal coaching by dietician via 5 telephone sessions and 5 mailings to achieve coronary risk factor targets (education, negotiated lifestyle plan,	6 m

					emphasis on follow-up with primary care provider and empowerment to ask for medication, repeated measurements)	
COACH (Vale et al. 2003)	792	Patients discharged from 6 hospitals after CABG, PCI, AMI, coronary angiography (Australia)	59	77%	Personal coaching (delivered by nurses or dieticians) via 5 telephone sessions and 5 mailings to achieve coronary risk factor targets (education, negotiated lifestyle plan, emphasis on follow-up with primary care provider and empowerment to ask for medication, repeated measurements)	6 m
ELMI Trial (Lear et al. 2003)	302	Patients discharged from 2 tertiary-care cardiac rehabilitation programs (Canada)	64	83%	Personal coaching by case manager delivered via telephone and in-person counseling sessions; if suboptimal coronary risk factors at 6 months, treatment algorithms with cover letter from cardiologist mailed to primary care physicians	12 m
Young et al .(2003)	146	Patients discharged home after AMI (Canada)	69	60%	Patient education, at least 6 home visits by nurse, nurse communication with primary care providers, and nurse-initiated referral for specialty care (based on standardized pathway)	2 m
REACH Trial (Lichtman et al. 2004)	756	Patients aged 30-80 years discharged from tertiary care hospital with documented coronary disease (USA)	64	71%	Nurse-based education and counseling about cholesterol and target levels delivered via telephone (4 calls in 9 m) and mailed educational materials about a variety of secondary prevention maneuvers	12 m

* As outlined in text, the results for 13 of the 24 collaborating centers in the World Health Organization Trial are included here. Reasons for the exclusion of the other 11 centers are given in the text.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; COACH = Coaching patients On Achieving Cardiovascular Health Study; DIET = Dietary Intervention and Evaluation Trial; ELMI = Extensive Lifestyle Management Intervention ; ETICA = Exercise Training Intervention after Coronary Angioplasty; M-HART = Montreal Heart Attack Readjustment Trial; MI = myocardial infarction; NEHDP = National Exercise and Heart Disease Project; NR = not reported; PCI = percutaneous coronary intervention; CCU = coronary care unit; REACH= Reinforcing Education About Cholesterol; SCRIP = Stanford Coronary Risk Intervention Project; UK = United Kingdom; USA = United States.

Table 2: Impact of interventions on all-cause mortality and recurrent myocardial infarctions.

Study	Length of Follow-up	All-cause mortality (#events/total # patients)			Recurrent Myocardial Infarctions* (#events/total # patients)		
		Intervention Arm	Control Arm	Risk Ratio	Intervention Arm	Control Arm	Risk Ratio
Comprehensive Cardiac Rehabilitation							
Sivarajan et al.	6 m	3/86	2/84	1.47 (0.25, 8.55)	NR	NR	NR
Vermeulen et al.	60 m	2/47	5/51	0.43 (0.09, 2.13)	4/47	9/51	0.48 (0.16, 1.46)
Bengtsson	12 m	10/81	6/90	1.85 (0.70, 4.87)	2/81	4/90	0.56 (0.10, 2.95)
WHO	36 m	146/893	161/842	0.86 (0.70, 1.05)	150/893	139/842	1.02 (0.82, 1.26)
Ornish et al. (90,98)	60m	2/28	1/20	1.43 (0.14, 14.70)	25/28	45/20	0.36 (0.07, 1.76)
Oldridge et al.	12 m	3/99	4/102	0.77 (0.18, 3.36)	NR	NR	NR
PRECOR** - comprehensive rehabilitation arm	24 m	0/60	4/61	0.11 (0.01, 2.05)	4/60	6/61	0.68 (0.20, 2.28)
Fridlund et al.	12 m	9/87	14/91	0.67 (0.31, 1.47)	4/87	14/91	0.30 (0.10, 0.87)
Engblom et al.	12 m	12/119	13/109	0.85 (0.40, 1.77)	8/119	16/109	0.46 (0.20, 1.03)
Heidelberg Trial	12 m 72 m	2/56 5/43	1/57 8/53	2.04 (0.19, 21.82) 0.77 (0.27, 2.18)	2/56 3/43	4/57 4/53	0.51 (0.10, 2.67) 0.92 (0.22, 3.91)
Bell	12 m	7/99	8/102	0.90 (0.34, 2.39)	NR	NR	NR
Lisspers et al.	12 m	0/46	1/41	0.30 (0.01, 7.12)	NR	NR	NR
Vestfold Heartcare Study	24 m	2/98	1/99	2.02 (0.19, 21.92)	4/99	3/99	1.33 (0.72, 1.05)
Marchionni et al.	12 m	7/180	3/90	1.17 (0.31, 4.41)	1/180	3/90	0.17 (0.02, 1.58)
Sub-Total:	***14 trials***	***208/1966***	***231/1835***	***0.86 (0.73, 1.03)***	***182/1637***	***202/1506***	***0.64 (0.43, 0.95)***
Group Cardiac Rehabilitation without exercise component							
Stern et al.	12 m	0/35	1/29	0.28 (0.01, 6.57)	3/35	2/29	1.24 (0.22, 6.94)
PRECOR** -counseling arm	24 m	5/61	4/61	1.25 (0.35, 4.43)	4/61	6/61	0.67 (0.20, 2.25)
Jones & West	12 m	79/1168	84/1160	0.93 (0.69, 1.26)	43/1168	48/1160	0.89 (0.59, 1.33)
Sub-Total:	***3 trials***	***84/1264***	***89/1250***	***0.94 (0.70, 1.25)***	***50/1264***	***56/1250***	***0.88 (0.61, 1.28)***

Individual Counselling							
SCRIP	12 m 24 m 36 m 48 m	1/145 1/145 2/145 3/145	0/155 2/155 2/155 3/155	3.21 (0.13, 78.06) 0.53 (0.05, 5.83) 1.07 (0.15, 7.49) 1.07 (0.22, 5.21)	5/145 5/145 5/145 6/145	0/155 3/155 6/155 11/155	11.75 (0.66, 210.69) 1.78 (0.43, 7.32) 0.89 (0.28, 2.86) 0.58 (0.22, 1.54)
DeBusk et al. and Taylor et al. (1997)	12 m	12/293	10/292	1.20 (0.52, 2.72)	10/293	20/292	0.50 (0.24, 1.05)
Fitzgerald et al.	12 m	35/333	35/335	1.01 (0.65, 1.57)	NR	NR	NR
Cupples & McKnight	24 m 60 m	13/342 47/342	29/346 65/346	0.45 (0.24, 0.86) 0.73 (0.52, 1.03)	NR NR	NR NR	NR NR
M-HART	12 m	38/692	27/684	1.39 (0.86, 2.25)	44/692	42/684	1.04 (0.69, 1.56)
Carlsson (1998)	12 m	2/118	2/117	0.99 (0.14, 6.92)	NR	NR	NR
Campbell et al.	12 m 56 m	22/673 100/673	25/670 128/670	0.88 (0.50, 1.54) 0.78 (0.61, 0.99)	13/540 100/673	12/518 125/670	1.04 (0.48, 2.26) 0.80 (0.63, 1.01)
Jolly et al.	12 m	15/277	23/320	0.75 (0.40, 1.42)	NR	NR	NR
Allison et al. (2000)	6m	2/158	2/168	1.06 (0.15, 7.46)	0/158	1/168	0.35 (0.01, 8.63)
COACH pilot	6 m	0/121	2/124	0.20 (0.01, 4.22)	NR	NR	NR
COACH	6 m 48 m	4/398 32/398	4/394 32/394	0.99 (0.25, 3.93)	NR NR	NR NR	NR NR
ELMI	12 m	1/151	3/151	0.33 (0.04, 3.17)	NR	NR	NR
Young et al.	14 m	8/71	11/75	0.77 (0.33, 1.80)	NR	NR	NR
Sub-Total:	***13 trials***	***295/3772***	***343/3831***	***0.86 (0.75, 1.00)***	***160/1961***	***199/1969***	***0.81 (0.66, 0.98)***
TOTAL -closest to 12m data -over entire study	**29 trials****	**442/7015** **587/7002**	**482/6859** **659/6855**	**0.90 (0.79, 1.01)** **0.87 (0.79, 0.97)**	**303/4742** **392/4862**	**327/4516** **451/4664**	**0.80 (0.65, 0.99)** **0.83 (0.72, 0.96)**

For trials with outcomes reported at various timepoints, the longest duration of follow-up data was used for generating the pooled sub-total estimates. The pooled total estimates are presented for both the “12 month or closest to 12 month data” as well as “longest duration of follow-up in each trial”. NR= not reported

***** Data for all trials except that of Campbell et al., DeBusk et al., and Allison et al. are for the combined endpoint of nonfatal and fatal myocardial infarction. The Campbell et al. trial only collected data on nonfatal reinfarction rate and total mortality (they were unable to dissect out causes of mortality). The Allison et al. and DeBusk et al. trials collected data on nonfatal myocardial infarction.

** Note that for PRECOR, there were 2 intervention arms and 1 control arm. The control arm data has been included only once in the “TOTAL” pooled estimate.

Table 3: Impact of interventions on other endpoints

Study	Major Cardiovascular Risk Factors			Use of proven efficacious therapies	Patient Quality of Life	Patient functional status or symptom scores
	Cholesterol	Smoking	BP			
Comprehensive Cardiac Rehabilitation						
Sivarajan et al.	NR	NR	NR	NR	NR	NR
Vermeulen et al.	++	0	NR	NR	NR	+
Bengtsson	NR	NR	++	NR	0	NR
WHO*	++	–	++	++	NR	0
Ornish et al. (90, 98)	++	NR	0	NR	NR	++
Oldridge et al.	NR	NR	NR	NR	+	0
PRECOR - comprehensive rehabilitation arm	NR	0	NR	NR	NR	++
Fridlund et al.	NR	0	NR	NR	++	++
Engblom et al.	0	++	0	0	++	NR
Heidelberg Trial -12 m f/u -72 m f/u	 ++ 0	 0 0	 NR NR	 0 0	 NR NR	 NR NR
Johnston et al.	NR	NR	NR	NR	++	++
Lisspers et al.	NR	++	NR	NR	NR	NR
Toobert et al.	0	+	+	NR	++	++
Seki et. al.	NR	NR	NR	NR	++	0
Sundin et al.	+	NR	NR	NR	NR	NR
Yu et al.	NR	NR	NR	NR	+	+
Vestfold Heartcare Study	0	++	0	0	++	++
Marchionni et al.	NR	NR	NR	NR	NR	++
Group Cardiac Rehabilitation without exercise component						
Stern et al.	NR	NR	NR	NR	++	NR
PRECOR -counseling arm	 NR	 0	 NR	 NR	 NR	 ++

Jones & West	NR	0	NR	0	0	0
DIET	+	NR	NR	NR	NR	NR
Individual Counselling						
Ornish et al. (83)	++	+	NR	NR	NR	++
SCRIP	++	++	+	++	NR	NR
DeBusk et al. and Taylor et al. (1997)	++	++	NR	++	NR	++
Fitzgerald et al.	NR	NR	NR	NR	NR	NR
Naylor et al. (94)	NR	NR	NR	NR	0	0
Cupples & McKnight	+	+	+	++	NR	++
M-HART	NR	NR	NR	NR	+	NR
huCarlsson et al. (1997)	NR	+	NR	NR	NR	NR
Carlsson (1998)	++	NR	NR	++	NR	NR
Campbell et al. -12m f/u -56 m year f/u	 ++ +	 0 0	 ++ +	 ++ 0	 ++ 0	 ++ 0
Jolly et al.	+	0	+	0	0	0
Naylor & McCauley (99)	NR	NR	NR	NR	+	+
Allison et al. (99)	+	++	NR	++	NR	NR
Allison et al. (2000)	+	0	0	0	NR	NR
Moher et al	++	++	++	0	0	NR
Stagmo et al.	+	NR	NR	+	NR	NR
McHugh et al.	++	++	++	NR	++	++
Higgins et al.	+	0	NR	NR	NR	++
Allen et al.	++	NR	NR	+	NR	NR
COACH pilot	++	NR	NR	0	NR	NR
COACH	++	0	++	++	++	++
ELMI	0	0	0	NR	0	0
Young et al.	NR	NR	NR	NR	NR	NR
REACH	0	NR	NR	0	NR	NR

Use of proven efficacious therapies" encompasses both increased prescription rate by clinicians and/or increased compliance by patients."
++ Statistically significant benefit seen in the intervention arm vs. control arm.
+ Trend towards better outcomes in the intervention arm, but didn't reach statistical significance.
0 No appreciable difference between the intervention arm and control arm.
NR Not reported in study.

Table 4. Methodologic Quality of Included Studies

Study	Described as Randomized	Method of Randomization Described and Appropriate	Description of Withdrawals or Losses to Follow-Up	Jadad Score	Allocation Concealment
Comprehensive Cardiac Rehabilitation					
Sivarajan et al.	Yes	No	Yes	2	Unclear
Vermeulen et al.	Yes	No	Yes	2	Unclear
Bengtsson	Yes	No	Yes	2	Unclear
WHO trial	Yes	Yes	No	2	Unclear
Ornish et al. (90, 98)	Yes	No	Yes	2	Unclear
Oldridge et al.	Yes	No	No	1	Unclear
PRECOR.,	Yes	No	Yes	2	Unclear
Fridlund et al.	Yes	No	Yes	2	Unclear
Engblom et al.	Yes	No	No	1	Unclear
Heidelberg Trial	Yes	No	Yes	2	Adequate
Bell	Yes	No	Yes	2	Unclear
Johnston et al.	Yes	No	Yes	2	Unclear
Lisspers et al.	Yes	No	Yes	2	Unclear
Toobert et al.	Yes	No	Yes	2	Unclear
Seki et al.	Yes	No	Yes	2	Adequate
Sundin et al.	Yes	No	No	1	Unclear
Yu et al	Yes	No	No	1	Unclear
Vestfold Heartcare	Yes	No	No	1	Adequate
Marchionni et al.	Yes	No	Yes	2	Unclear
Cardiac rehabilitation					
Stern et al.	Yes	No	No	1	Unclear
PRECOR.	Yes	No	Yes	2	Unclear
Jones and West	Yes	No	Yes	2	Adequate
D.I.E.T.	Yes	No	No	1	Unclear
Individual counseling					
Ornish et al. (83)	Yes	Yes	No	2	Unclear

SCRIP	Yes	Yes	Yes	3	Adequate
DeBusk et al.; Taylor et al. (97)	Yes	Yes	Yes	3	Adequate
Fitzgerald et al.	Yes	No	Yes	2	Unclear
Naylor et al. (94)	Yes	No	Yes	2	Unclear
Cupples and McKnight	Yes	Yes	Yes	3	Adequate
M-HART	Yes	No	Yes	2	Adequate
Carlsson et al.	Yes	No	Yes	2	Unclear
Campbell et al.	Yes	Yes	Yes	3	Adequate
Jolly et al.	Yes	No	Yes	2	Adequate
Naylor and McCauley (99)	Yes	Yes	Yes	3	Adequate
Allison et al. (99)	Yes	No	Yes	2	Unclear
Allison et al. (00)	Yes	Yes	No	2	Unclear
Moher et al.	Yes	Yes	Yes	3	Unclear
Stagmo et al.	Yes	No	Yes	2	Unclear
McHugh et al.	Yes	No	Yes	2	Unclear
Higgins et al.	Yes	No	Yes	2	Unclear
Allen et al.	Yes	Yes	Yes	3	Unclear
COACH pilot	Yes	No	Yes	2	Unclear
COACH	Yes	Yes	Yes	3	Unclear
ELMI	Yes	Yes	Yes	3	Unclear
Young et al.	Yes	Yes	Yes	3	Adequate
REACH	Yes	Yes	Yes	3	Unclear

*When there were several publications for the same study, quality assessment was done by using the primary publication. COACH = Coaching patients On Achieving Cardiovascular Health Study; DIET = Dietary Intervention and Evaluation Trial; ELMI = Extensive Lifestyle Management Intervention ; ETICA = Exercise Training Intervention after Coronary Angioplasty; M-HART = Montreal Heart Attack Readjustment Trial; NEHDP = National Exercise and Heart Disease Project; REACH= Reinforcing Education About Cholesterol; SCRIP = Stanford Coronary Risk Intervention Project.

Table 5a: Characteristics of Comprehensive Cardiac Rehabilitation Programs

Study	Location	Time to initiation (weeks)	Mean Length (weeks)	Total time (hours)	Individualization degree	Physician Involvement	Theo Basis	Nurs / Pharm Prescribing	Phone Support	Specialist Profs	Based on stated guidelines/ protocol
Sivarajan et al.	Hosp	0	13	14.5	3	ETT	X	X	X	•	X
Vermeulen et al.	Hosp	6	6	---	2	ETT	X	X	X	---	X
Bengtsson	Hosp	4	16	---	2	ETT	X	X	X	•	X
WHO	Hosp	2	156	---	4	Follow up	X	X	X	•	X
Ornish et al. (1990, 1998)	Comb	6	52	1040	3	Coord	X	X	•	•	•
Oldridge et al.	Hosp	6	8	12	2	ETT	X	X	X	•	X
PRECOR	Hosp	8	6	9	3	Teaching	X	X	X	•	X
Fridlund et al.	Hosp	0	26	52	3	Teaching	X	X	X	•	X
Engblom et al.	Hosp	0	52	59	2	ETT	X	X	X	X	X
Heidelberg Trial	Hosp	---	312	---	2	ETT	X	X	X	X	---
Bell	Hosp	8	---	---	2	ETT	X	X	X	X	X
Johnston et al.	Hosp	1	8	9	3	ETT	X	X	X	•	X
Lisspers et al.	Comb	2	52	140	2	ETT	•	X	•	•	X
Toobert et al.	Comb	26	104	117	3	Screening	X	X	X	•	X
Seki et al.	Hosp	204	26	26	3	Coord	X	X	X	•	X
Sundin et al.	Comb	---	52	51	2	ETT	•	X	X	•	X
Yu et al.	Comb	6	10	48	2	NONE	X	X	X	X	X
Vestfold Heartcare Study	Comb	6	104	50	2	Coord	•	X	X	•	•
Marchionni et al.	Comb	6	8	38	3	NONE	X	X	X	•	•

Table 5b: Characteristics of Group Cardiac Rehabilitation Without Exercise Component Programs

Study	Location	Time to initiation (weeks)	Mean Length (weeks)	Total time (hours)	Individualization degree	Physician Invovelment	Theo Basis	Nurs / Pharm Prescribing	Phone Support	Specialist Profs	Based on stated guidelines/ protocol
Stern	Hosp	52	12	13.5	2	ETT	X	X	X	X	X
PRECOR	Hosp	8	6	9	3	Teaching	X	X	X	•	X
Jones and West	Hosp	4	7	14	3	NONE	X	X	X	•	X
DIET	Comb	---	52	18	2	ETT	X	X	X	X	X

Table 5c: Characteristics of Individual Counseling Programs

Study	Location	Time to Initiation (weeks)	Mean Length (weeks)	Total time (hours)	Individualization degree	Physician Involvement	Theo Basis	Nurs / Pharm Prescribing	Phone Support	Specialist Profs	Based on stated guidelines / protocol
Ornish (1983)	Residential	6	3	37.5	3	Coord	X	X	•	•	X
SCRIP	Hosp	21	208	60	5	ETT	X	X	•	•	•
DeBusk et al .	Hosp	16	52	9	4	NONE	•	•	•	•	X
Fitzgerald et al.	Hosp	1	12	19	2	Screening	X	X	•	•	X
Naylor et al.	Hosp	0	2	4	4	ETT	X	X	•	•	X
Cupples and McKnight	GP	406	104	2	5	NONE	X	X	X	X	X
M---HART	Home	1	52	12	4	ETT	X	X	•	•	•
Carlsson et al. (1997)	Hosp	4	11	24	4	Follow up	X	X	X	•	X
Carlsson (1998)	Hosp	4	52	26	3	Follow up	X	X	X	•	X
Campbell et al.	GP	312	52	4.1	3	ETT	X	•	•	•	•
Jolly et al.	GP	0	52	---	3	ETT	•	X	•	•	X
Naylor and McCauley	Comb	0	4	4	3	ETT	X	X	•	X	X
Allison (1999)	Hosp	12	4	16	3	Follow up	X	•	X	•	•
Allison (2000)	Hosp	2	26	2	3	ETT	X	•	X	•	X
Moher et al.	GP	---	78	---	0	NONE	X	•	---	---	---
Stagmo et al.	Hosp	6	52	5.75	3	Follow up	X	X	X	•	•
McHugh et al.	Comb	---	---	---	5	ETT	•	X	•	•	•
Higgins et al.	Home	1	52	6	5	ETT	•	X	•	•	X
Allen et al.	Home	0	52	4.5	4	Lipid mment	X	•	•	•	X
COACH PILOT	Home	2	26	1.5	5	ETT	X	X	•	•	3
COACH	Hosp	2	24	1.5	2	ETT	X	X	•	•	X
ELMI	Hosp	8	16	40	3	NONE	X	X	•	•	•
Young	Home	1	8	6	3	NONE	X	X	X	•	X
REACH	Home	0	52	0.5	3	ETT	X	X	•	•	X

Table 6: Number of trials with age-based exclusion criteria

Upper age limit (years)	Number of studies
>79	2
75-79	8
70-74	6
65-69	8
60-64	0
55-59	1
No upper age-based criteria used	21

Table 7: Proportion of women in trials

Proportion of women	Number of studies
0 %	8
1%-10%	2
11%-20%	11
21-30%	13
31-40%	6
41-50%	3
51-60%	1
>61%	2

Figure 1: Flow of trials through the selection process

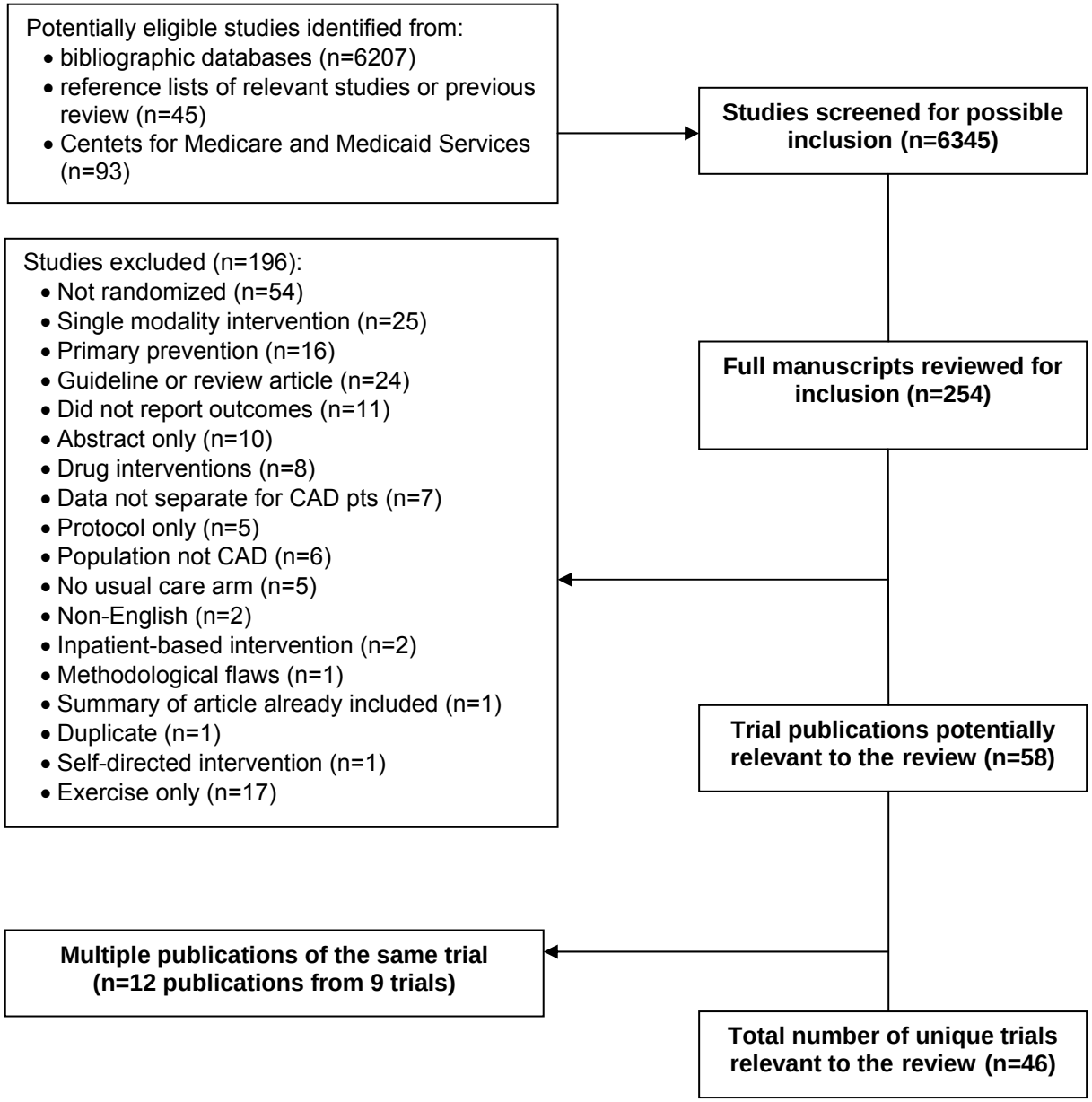


Figure 2: All-cause mortality in trials evaluating comprehensive cardiac rehabilitation

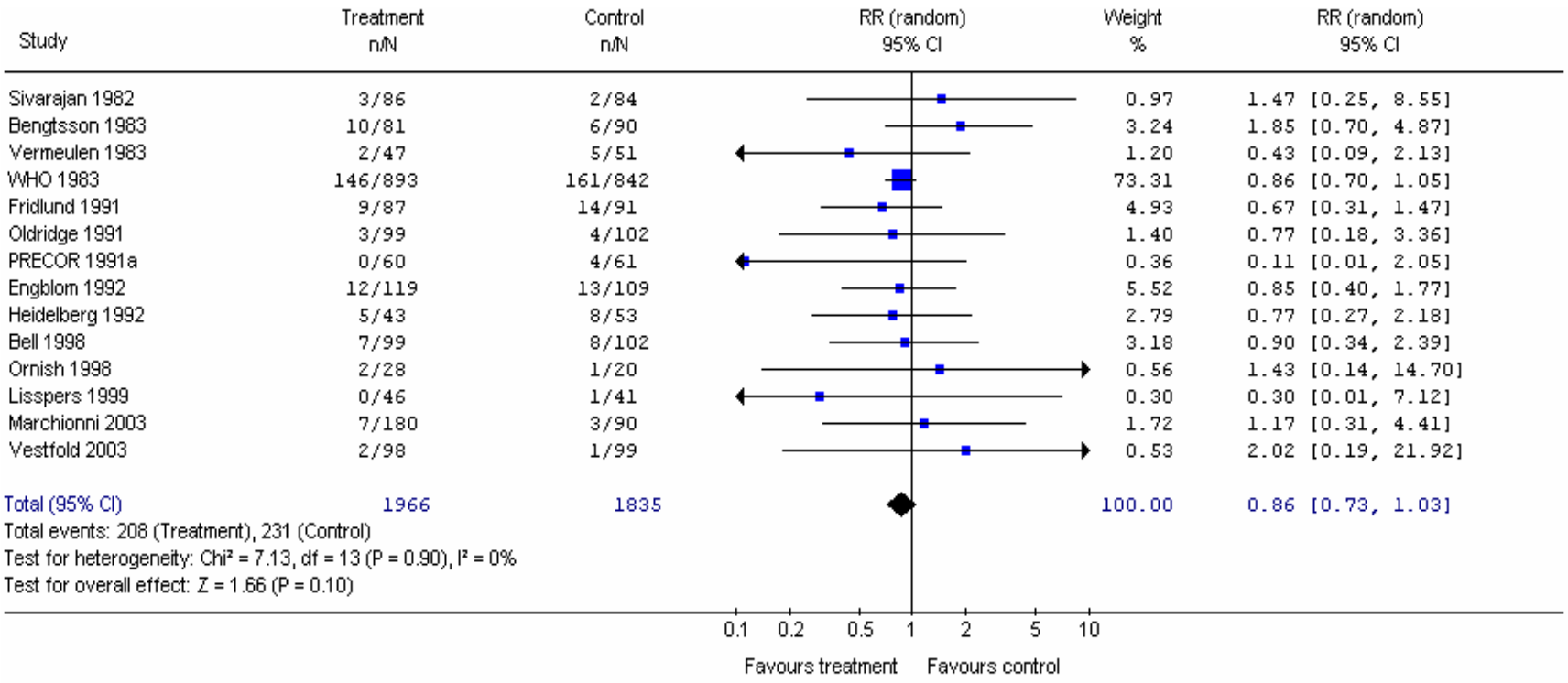


Figure 3: All-cause mortality in trials evaluating group cardiac rehabilitation without exercise component

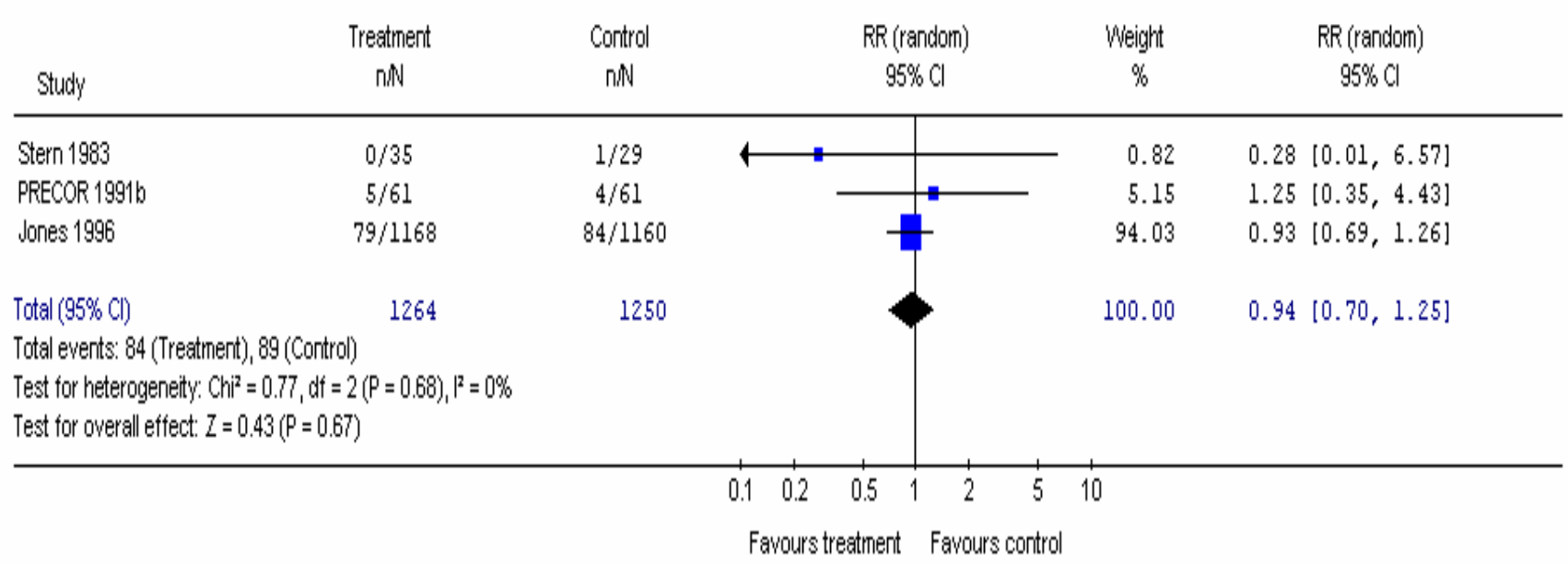


Figure 4: All-cause mortality in trials evaluating individual counseling

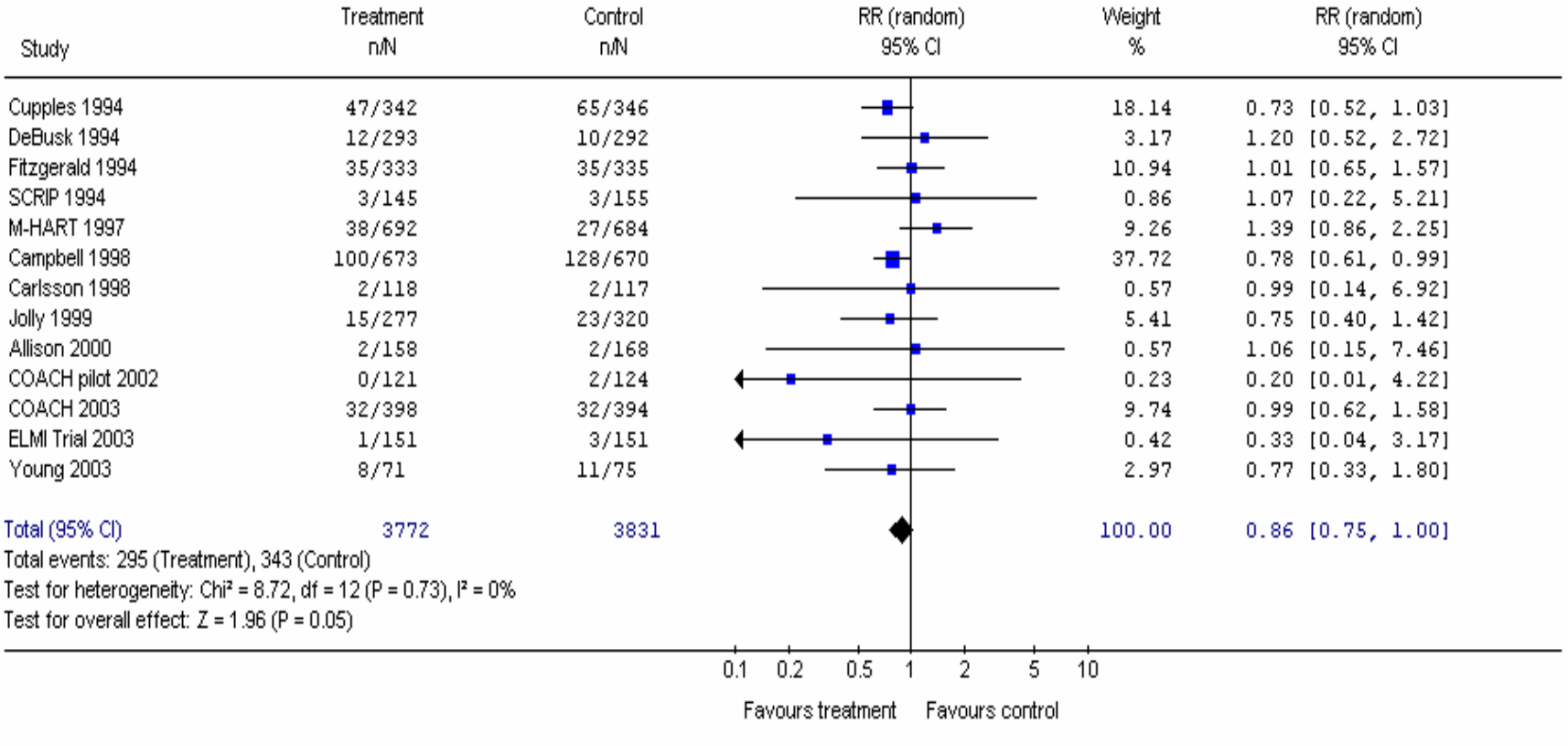


Figure 5: Recurrent myocardial infarctions in trials evaluating comprehensive cardiac rehabilitation

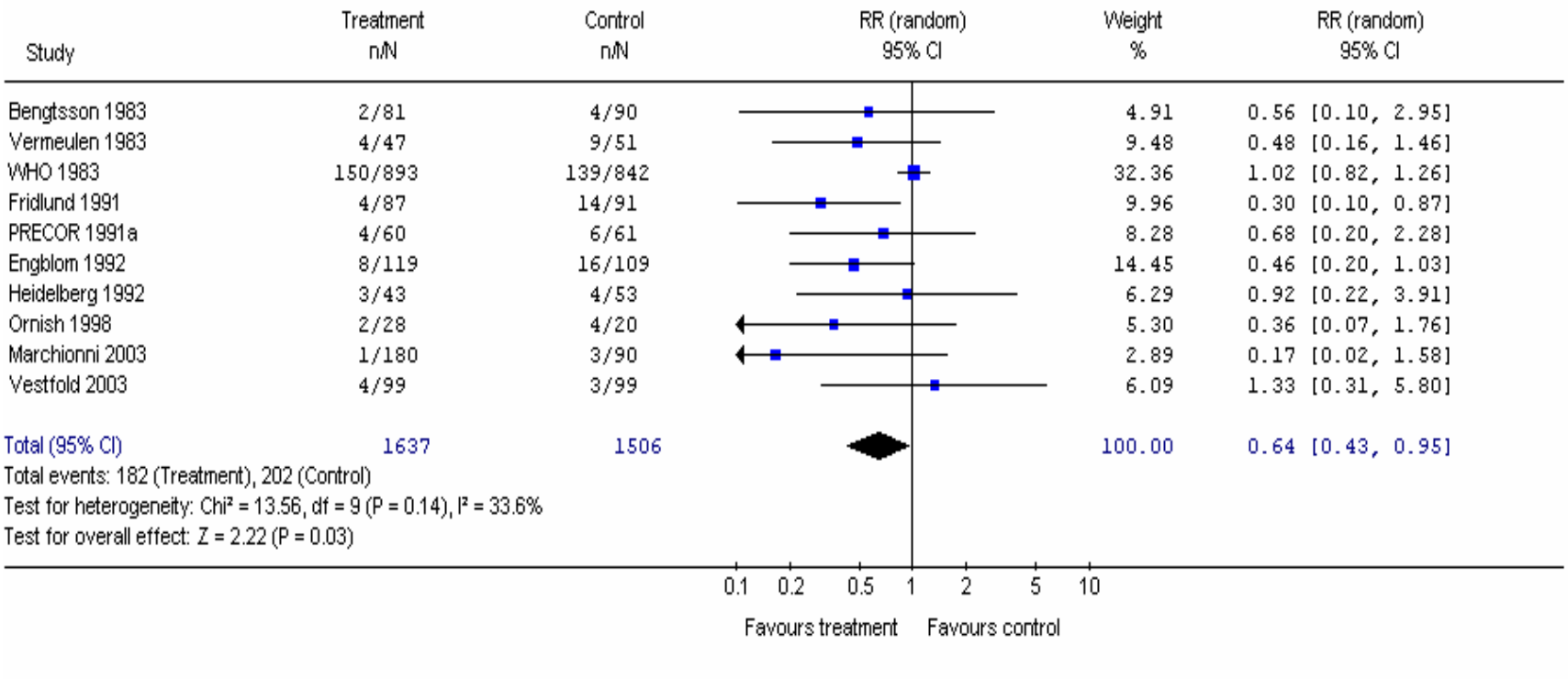


Figure 6: Recurrent myocardial infarctions in trials evaluating group cardiac rehabilitation without exercise component

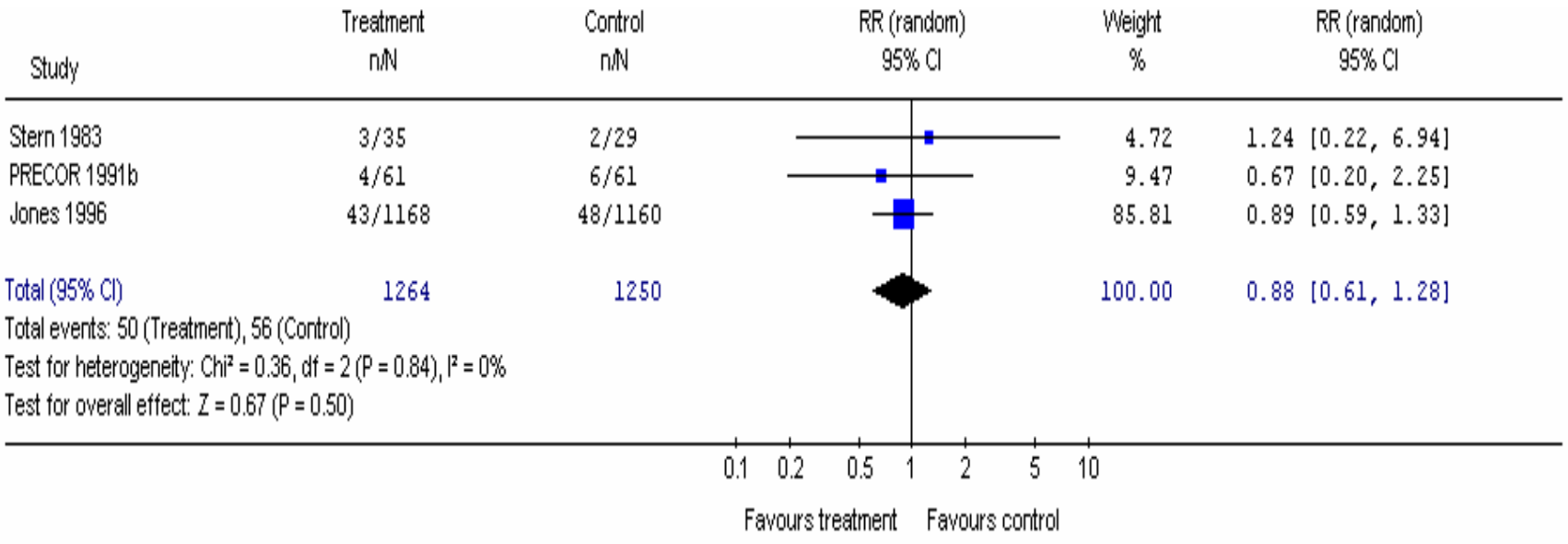


Figure 7: Recurrent myocardial infarctions in trials evaluating individual counseling

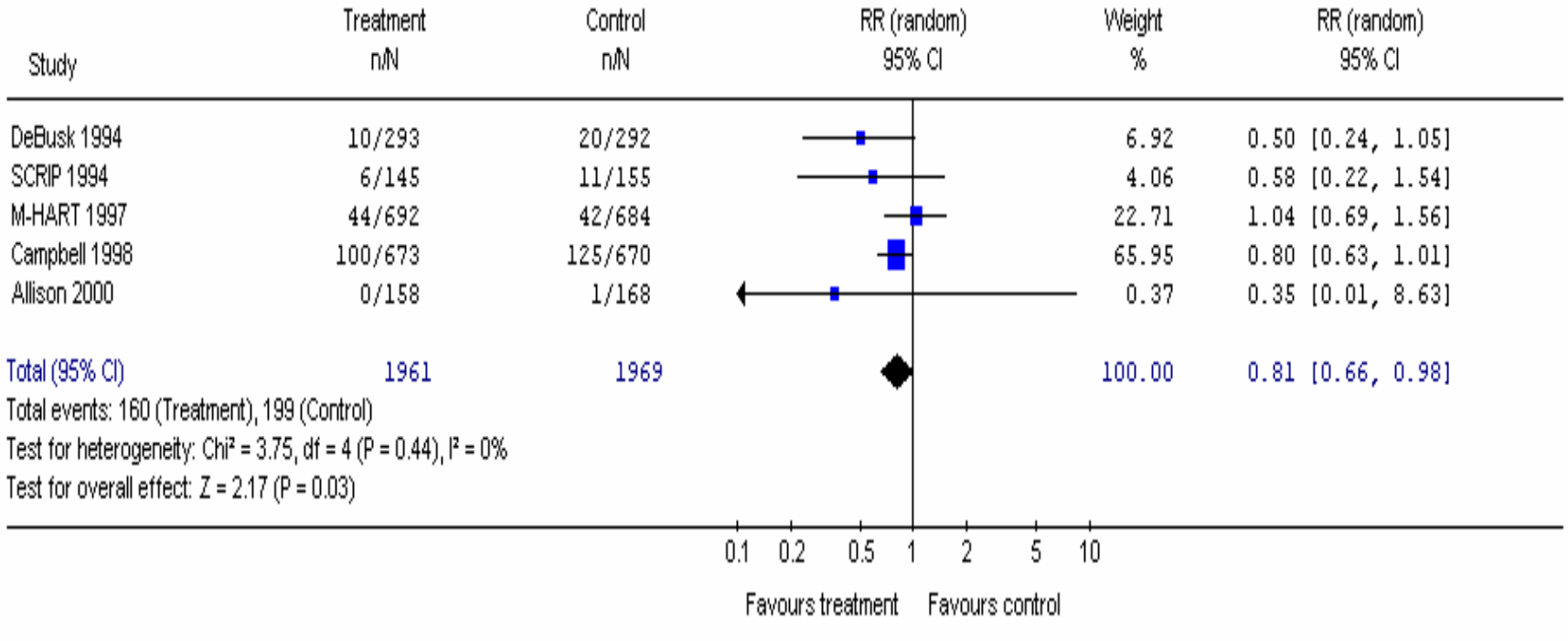
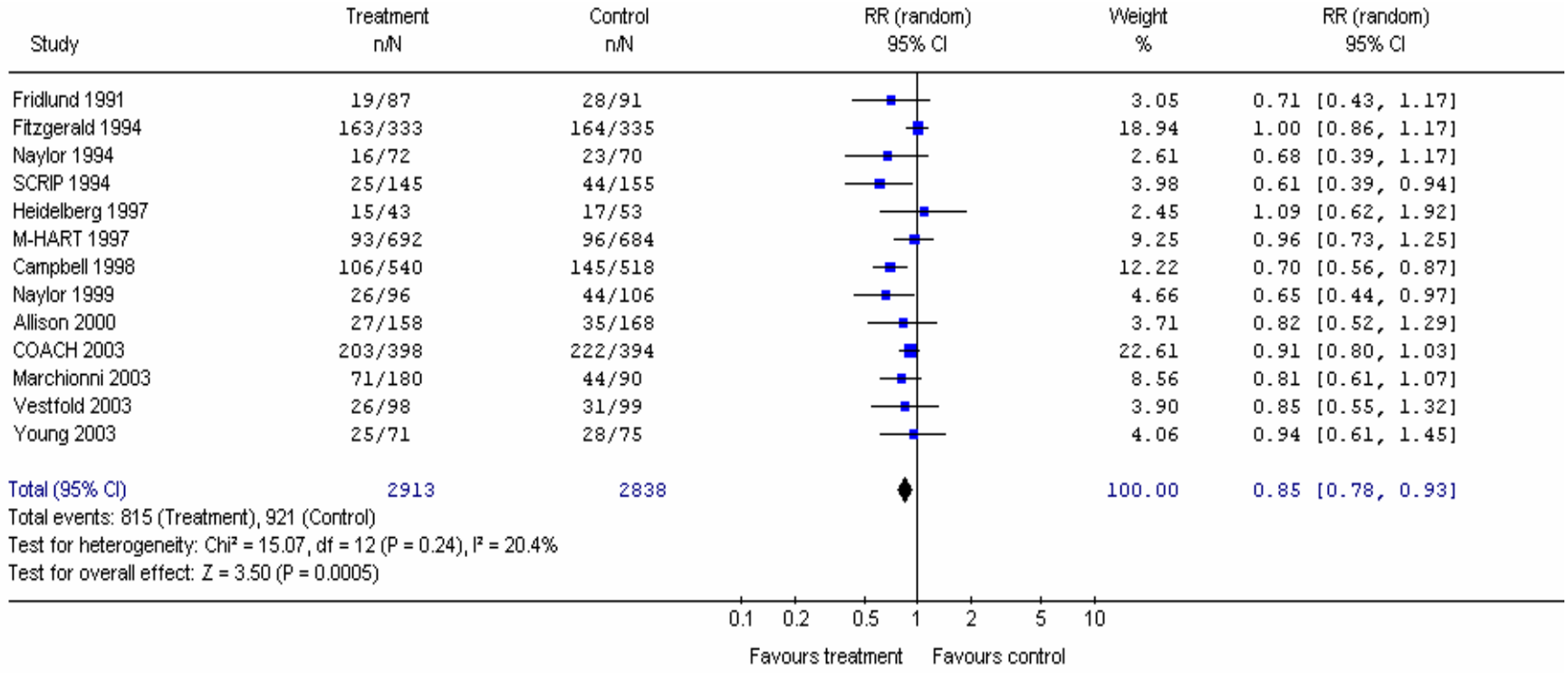


Figure 8: Hospitalization rates in trials evaluating secondary prevention programs



These data depict risk ratios for the number of patients requiring at least one hospitalization during follow-up. RR<1 are consistent with less hospitalizations in the intervention arm; RR>1 are associated with less hospitalizations in the control arm. Note that the data from some studies (SCRIP, Heidelberg, M-HART, Allison, and COACH) are "cardiovascular hospitalizations" while for the other studies it is "all-cause hospitalizations". The "all-cause hospitalization" summary RR was 0.84 (95% CI 0.74-0.97) in 9 trials (n=3653) and the "cardiovascular hospitalization" summary RR was 0.76 (95% CI 0.58-0.98) in 7 studies (n=3233).

Figure 9: Funnel Plot for all-cause mortality data

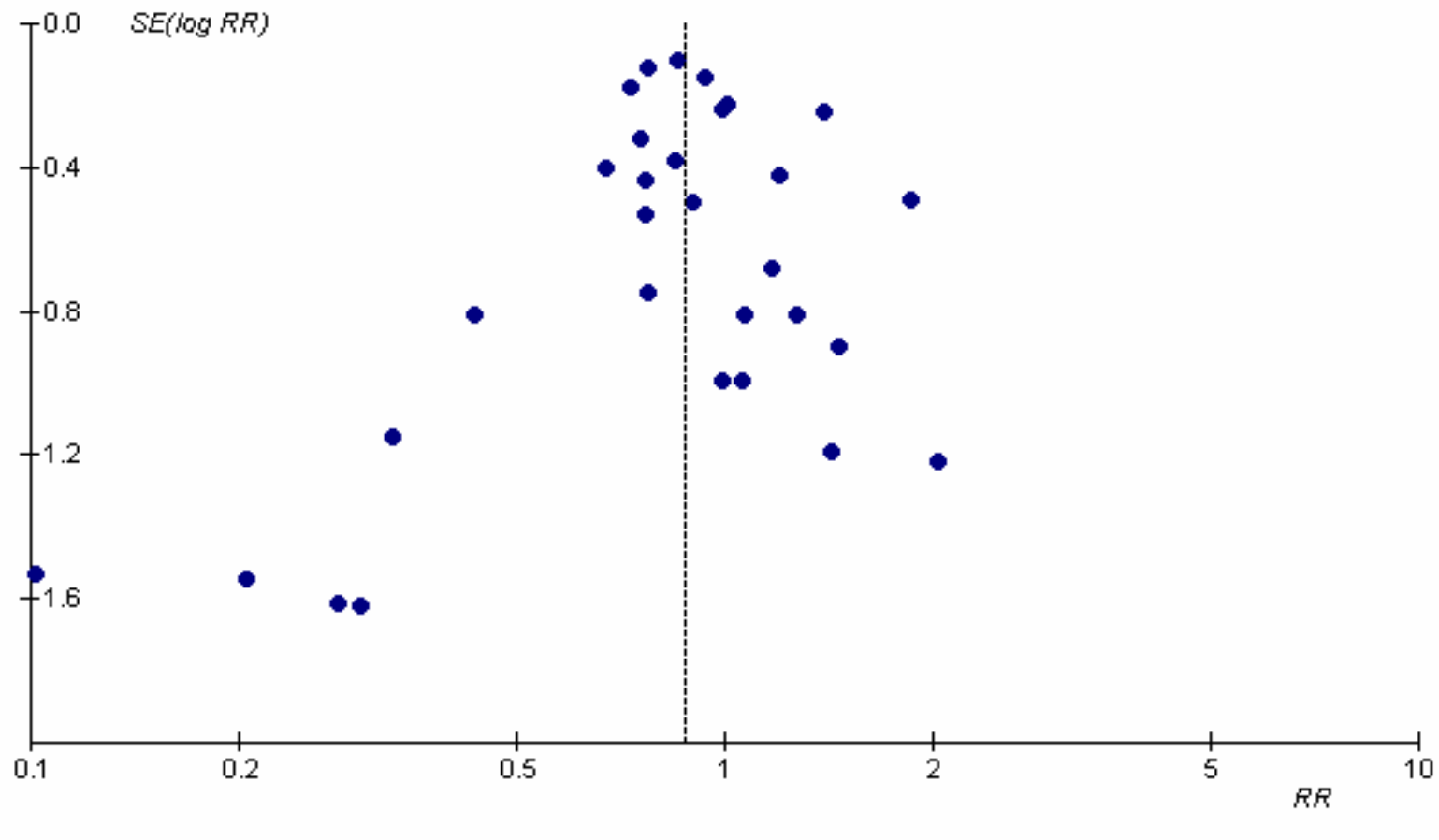


Figure 10: Survey steps

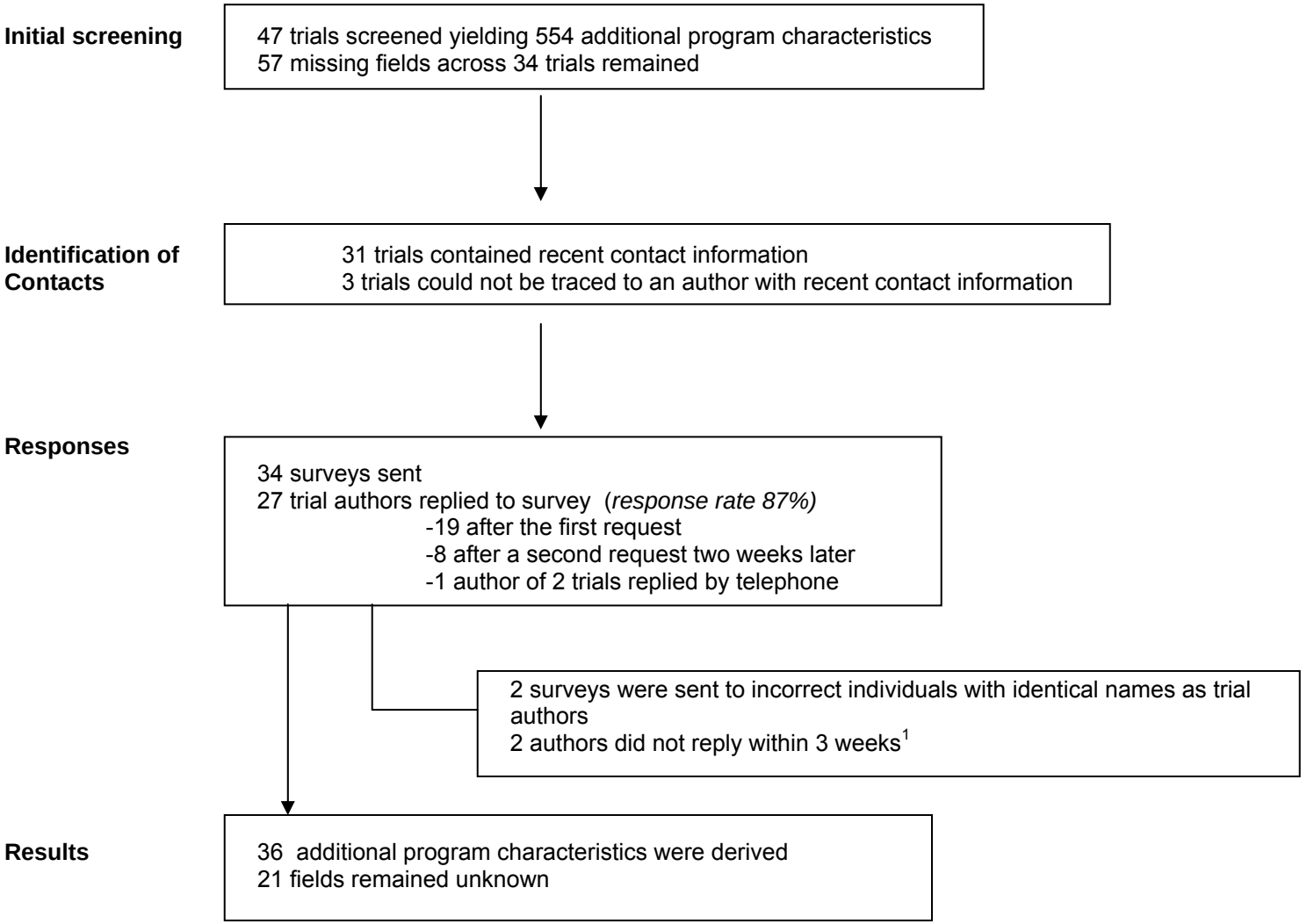


Figure 11: All-cause mortality stratified by length of program (expressed in hours)

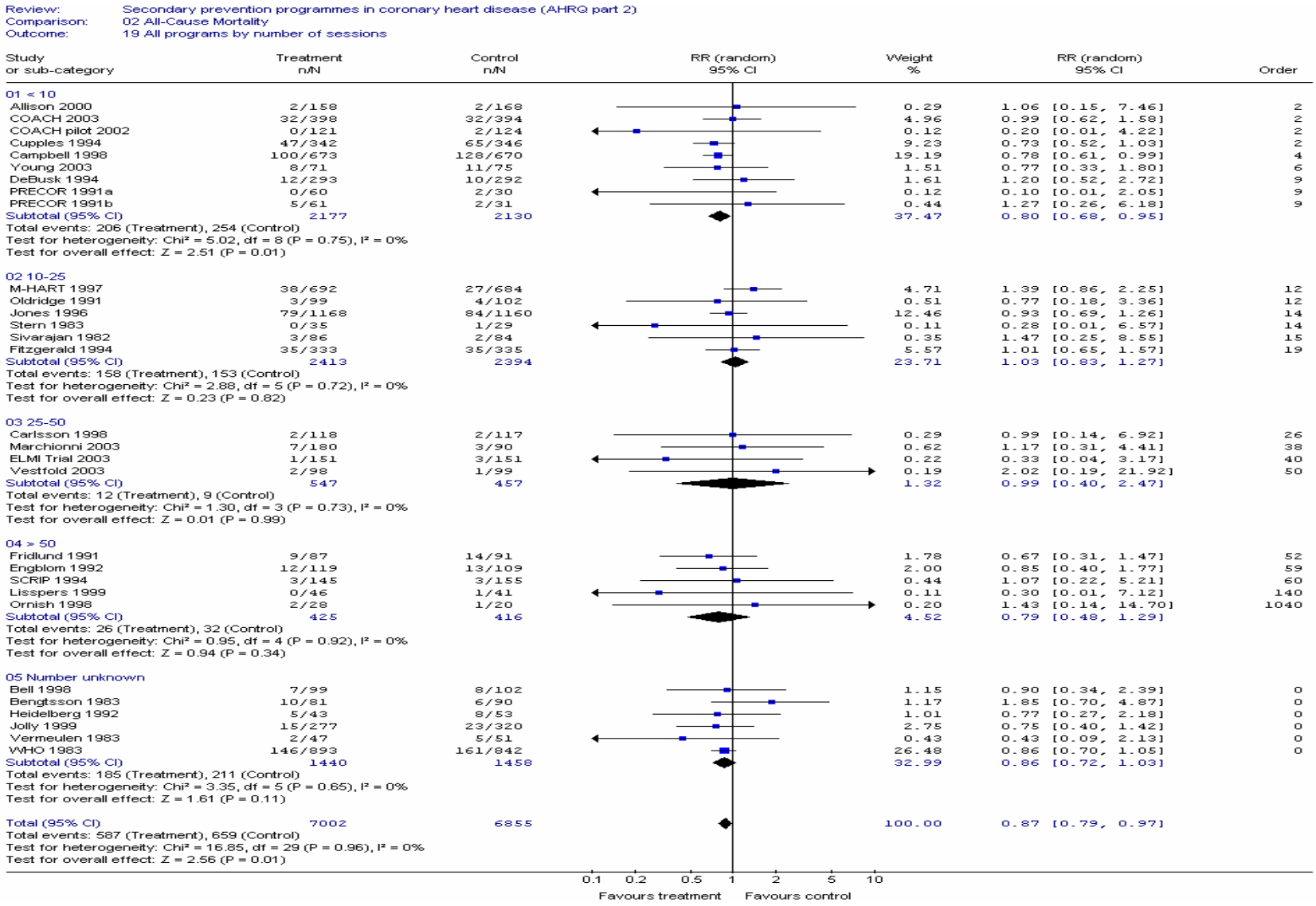


Figure 12: All-cause mortality stratified by degree of health care provider specialization

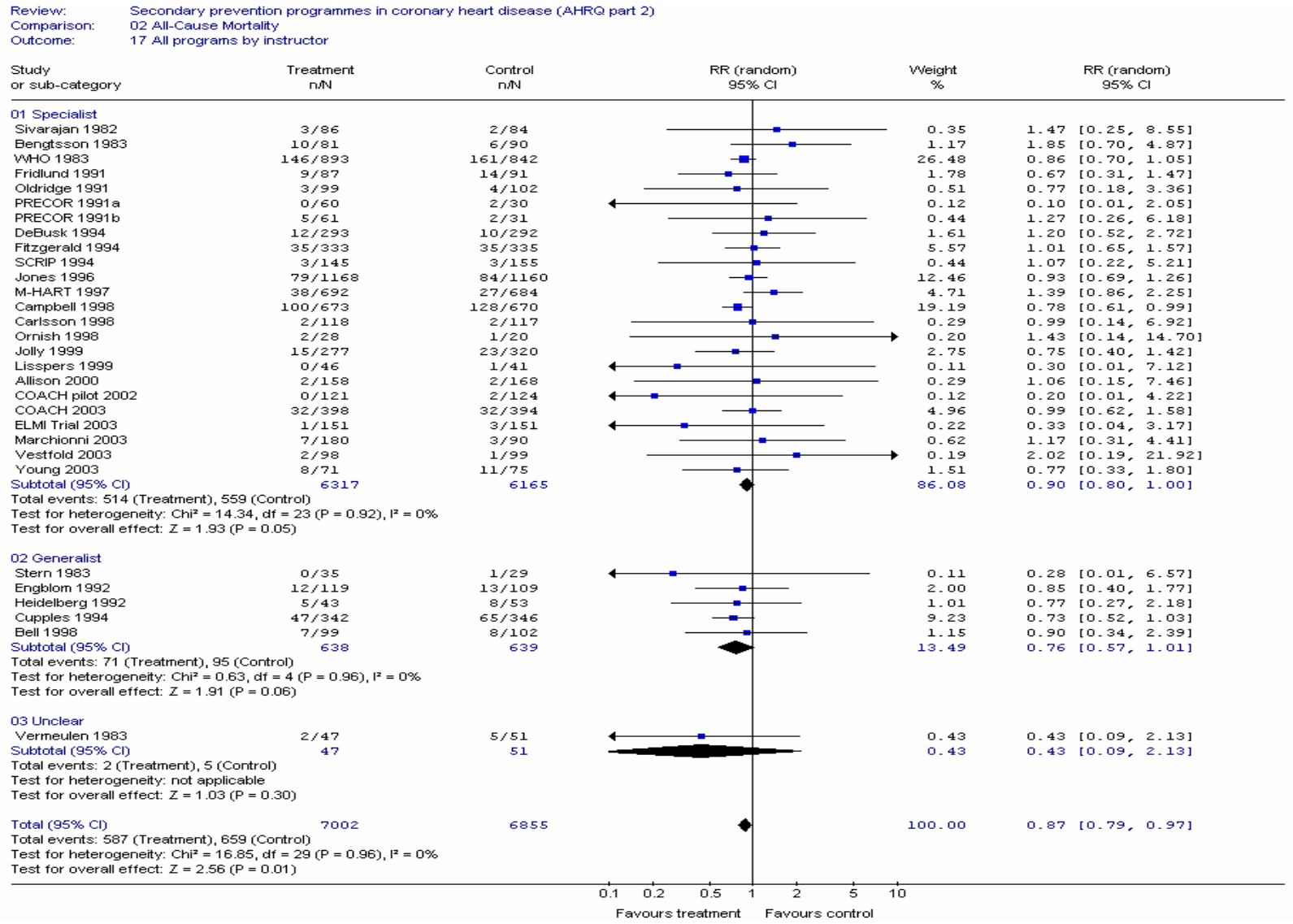


Figure 13: All-cause hospitalizations stratified by degree of individualization

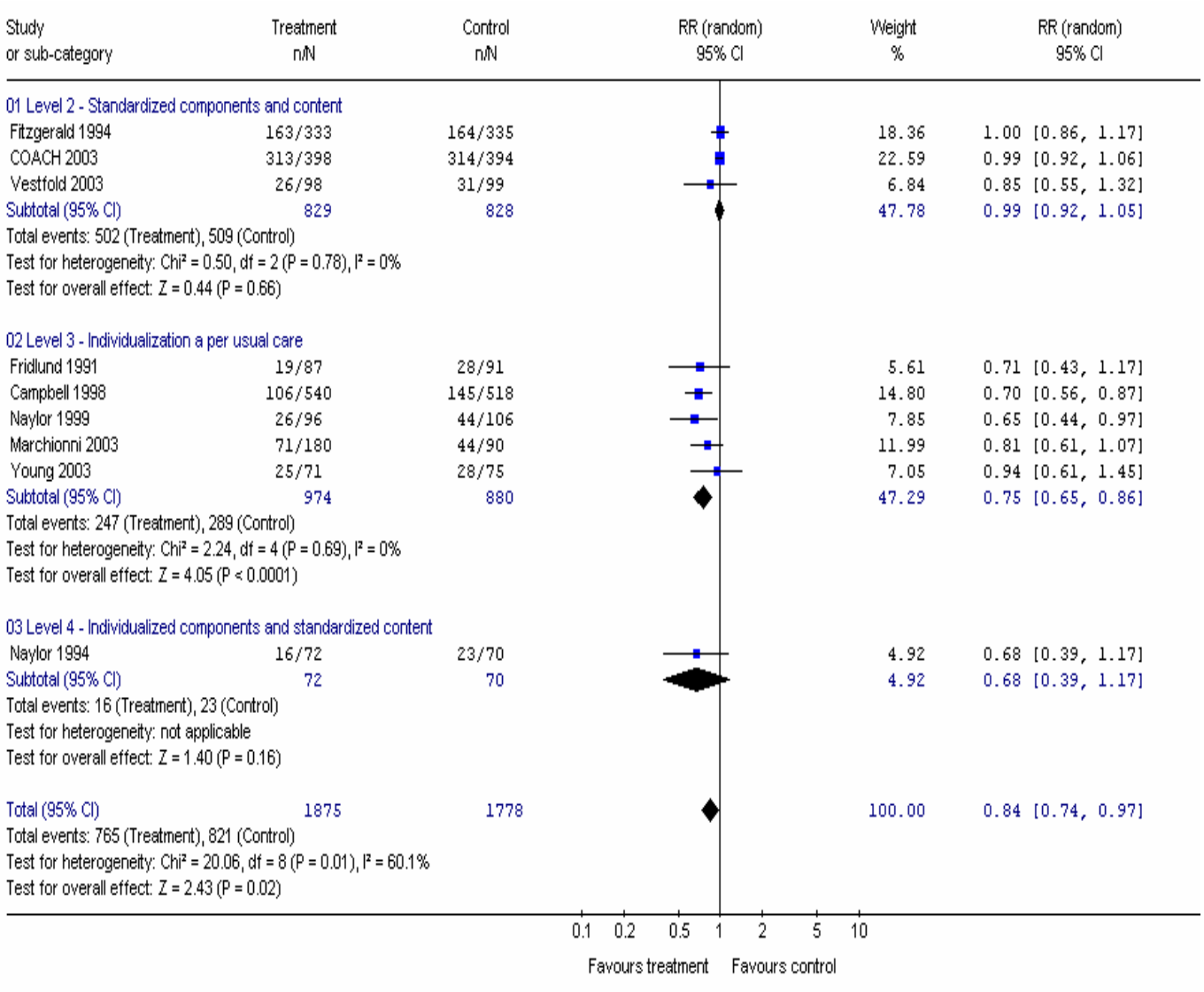
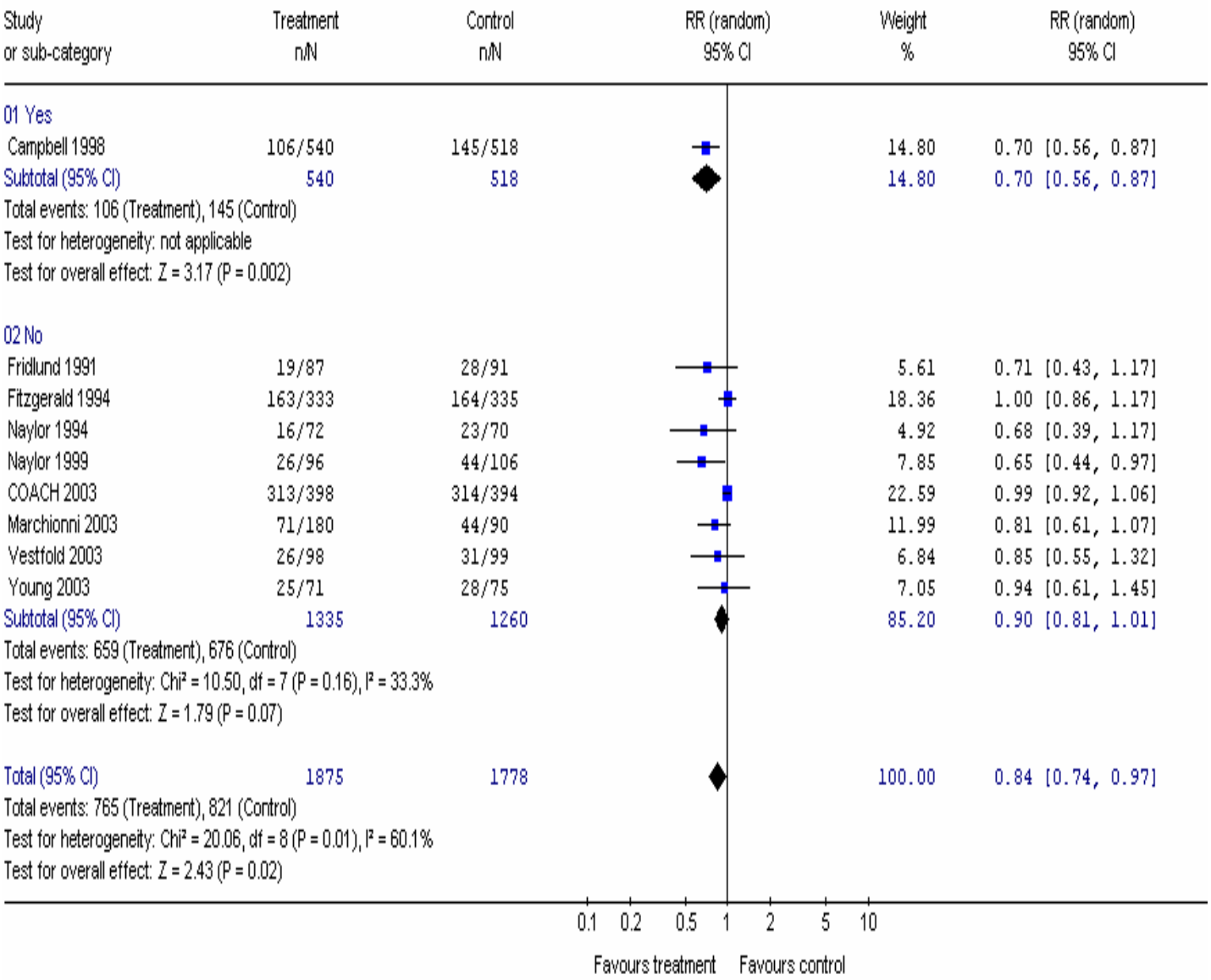


Figure 14: All-cause hospitalizations stratified by nurse prescribing



Appendix A. Search Strategies

MEDLINE - Ovid Version: rel9.1.0
Searched December 16, 2004
Results: 2527 unique records

1. exp "Case Management"/
2. exp "Comprehensive Health Care"/
3. exp "Disease Management"/
4. exp "Health Services Research"/
5. exp "Home Care Services"/
6. exp "Clinical Protocols"/
7. exp "Patient Care Planning"/
8. exp "Quality of Health Care"/
9. exp REHABILITATION/
10. (nurse adj led adj1 clinic$).ti,ab.
11. (special$ adj1 clinic$).ti,ab.
12. or/1-11
13. exp "Myocardial Ischemia"/ or "Myocardial Ischemia$".ti,ab.
14. RANDOMIZED CONTROLLED TRIAL.pt.
15. ANIMAL/ not HUMAN/
16. 14 not 15
17. 12 and 13 and 16
18. limit 17 to (english language and yr=1999 - 2005)
19. remove duplicates from 18

- The same search was conducted in **EBM Reviews - Cochrane Central Register of Controlled Trials - Ovid Version: rel9.1.0** (4th Quarter 2004) on December 16, 2004.
- There were 141 unique results.

PubMed
Searched December 16, 2004
Results: 50 unique records

The following search was conducted:

("Case Management"[MeSH] OR "Comprehensive Health Care"[MeSH] OR "Disease Management"[MeSH] OR "Health Services Research"[MeSH] OR "Home Care Services"[MeSH] OR "Clinical Protocols"[MeSH] OR "Clinical Protocols"[MeSH] OR "Patient Care Planning"[MeSH] OR "Quality of Health Care"[MeSH] OR "Rehabilitation"[MeSH]) AND ("Myocardial Ischemia"[MeSH] OR Myocardial Ischemia Field: Title/Abstract)

Limits: Publication Date from 2004/01/01 to 2004/12/17, Randomized Controlled Trial

Web of Science
Searched December 17, 2004
Results: 606 unique records

The **Cited Reference Search** feature was used to search for studies that cited the included studies from the original article.

EMBASE - Ovid Version: rel9.1.0
1988 to 2004 Week 51
Searched December 20, 2004
Results: 1313 unique records

1. exp "Patient Care"/
2. exp "Health Care"/
3. exp "Disease Management"/
4. exp "Health Services Research"/
5. exp "Home Care"/
6. exp "Clinical Protocol"/
7. exp "Health Care Quality"/
8. exp REHABILITATION/
9. (nurse adj led adj1 clinic$).ti,ab.
10. (special$ adj1 clinic$).ti,ab.
11. or/1-10
12. exp "Heart Muscle Ischemia"/ or exp "Ischemic Heart Disease"/ or exp "Coronary Heart Disease"/ or "Myocardial Ischemia$".ti,ab.
13. RANDOMIZED CONTROLLED TRIAL/
14. 11 and 12 and 13
15. limit 14 to english
16. limit 15 to human
17. remove duplicates from 16
18. limit 17 to yr=1999 - 2005

CINAHL (Cumulative Index to Nursing & Allied Health Literature) - Ovid Version: rel9.1.0
1982 to December Week 2 2004
Searched December 21, 2004
Results: 9 unique records

1. exp "Case Management"/
2. *Health Care Delivery/

3. exp "Disease Management"/
4. exp "Health Services Research"/
5. exp Home Health Care/
6. exp Protocols/
7. exp "Quality of Health Care"/
8. exp REHABILITATION/
9. (nurse adj led adj1 clinic$).ti,ab.
10. (special$ adj1 clinic$).ti,ab.
11. or/1-10
12. exp "Myocardial Ischemia"/ or "Myocardial Ischemia$".ti,ab.
13. clinical trial.pt.
14. animals/
15. 13 not 14
16. and/11-12,15
17. limit 16 to yr=1999-2005

SIGLE - FIZ Karlsruhe – Version Interhost 3000
Searched December 21, 2004
Results: 53

CORONARY OR MYOCARDIAL

AND

Health services, health administration, community care services

Appendix B: List of Excluded Studies and Reasons for Exclusion (full references at end of table)

Author year	Source	Reason for exclusion
Ades and Coello 2000	Database (WOS)	Guideline / review article
Akosah, Schaper, Havlik et al 2002	Database	Not randomized
Aldana, Whitmer, Greenlaw et al 2003	CMS	Not randomized
Ammerman, Keyserling, Atwood et al 2003	Database (Medline)	Primary prevention
Angerer, Siebert, Kothny et al 2000	CMS	Not randomized
Anonymous 1982	Database	Primary prevention
Ariyo, Haan, Tangen et al 2000	CMS	Not randomized
Arthur, Daniels, McKelvie 2000	Database (Medline)	Did not report primary outcomes
Barnard, Massey, Cherny et al 1983	CMS	Evaluated interventions which were not comprehensive disease management systems
Barnes, Trieber, Turner et al 1999	CMS	Population not CHD
Bartels, Gerdes, Babin-Ebell et al 2002	CMS	Guideline / review article
Beckie 1989	Database	Did not report primary outcomes
Bennett, Blackall, Clapham et al 1989	Database	Not randomized
Bentsson 1983	Database	Methodological flaw (patients excluded after randomization)
Berglund, Nilsson, Ericksson et al 2000	Database	Primary prevention
Berkman, Blumenthal, Burg et al 2003	Database (Medline)	Evaluated interventions which were not comprehensive disease management systems
Bethell and Mullee 1990	Reference list	Evaluated interventions which were not comprehensive disease management systems
Billings, Scherwitz, Sullivan et al 1996	CMS	Guideline / review article
Bjarnason-Wehrens, Benesch, Bischoff et al 2003	Database (WOS)	Non-English
Blair, Bryant, Bocuzzi 1988	Database	Not randomized
Blumenthal, Jiang, Babyak et al 1997	CMS	Not randomized
Bogden, Koontz, Williamson et	Database	Did not report primary outcomes

al 1997		
Boulay and Prud'homme 2004	Database (WOS)	Not randomized
Bramlet, King, Young et al 1997	Database	Not randomized
Brown, Zhao, Chait et al 2001	CMS	Drug interventions
Burell 1996	CMS	Guideline / review article
Cambien, Richard, Ducimetiere et al 1981	Database	Primary prevention
Campbell, Ritchie, Thain et al 1998	Database (Embase)	Protocol only
Cannon, Braunwald, McCabe et al 2004	CMS	Evaluated interventions which were not comprehensive disease management systems
Caracciolo, Davis, Sopko et al 1995	CMS	Not randomized
Carlson, Johnson, Franklin et al 2000	Database (WOS)	No usual care arm
Carney, Blumenthal, Stein et al 2001	CMS	Not randomized
Castillo-Richmond, Schneider, Alexander et al 2000	CMS	Evaluated interventions which were not comprehensive disease management systems
Chinaglia, Gaschino, Asteggiano et al 2002	Database	Not randomized
Clark, Bakhai, Lacey et al 2004	CMS	Not randomized
Coleman, Grothaus, Sandhu et al 1999	Database	Did not report the outcomes for patients with CHD separately
Corti, Fuster, Fayad et al 2002	CMS	Drug interventions
Coull, Taylor, Elton et al 2004	Database (Medline)	Evaluated interventions which were not comprehensive disease management systems
Council on Clinical Cardiology and Council on Nutrition, Physical Activity and Metabolism 2003	CMS	Guideline / review article
Cummings, Hughes, Weaver et al 1990	Database	Did not report the outcomes for patients with CHD separately
Cundiff 2002	CMS	Guideline / review article
DeBusk, Haskell, Miller et al 1985	Database	Evaluated interventions which were not comprehensive disease management systems
DeBusk, Miller, Parker et al 2004	Database (WOS)	Population not CHD
De Lorgeril, Salen, Martin et al 1999	CMS	Evaluated interventions which were not comprehensive disease management systems

Denollet and Brutsaert 2001	CMS	Not randomized
Detry, Vierendel, Vanbutsele et al 2001	Database (WOS)	Not randomized
DeVries, Palmer, Scheib et al 2002	CMS	Not randomized
DeVries, Day, Scott 2003	CMS	Not randomized
Diehl 1998	CMS	Not randomized
Dugan, Cohen 1998	CMS	Guideline / review article
Dugmore, Tipson, Phillips et al 1999	Database (Medline)	Evaluated interventions which were not comprehensive disease management systems
Eaker, Sullivan, Kelly-Hayes et al 2004	CMS	Not randomized
Eddy 2000	CMS	Guideline / review article
Ellingsen, Hjermann, Abdelnoor et al 2003	Database (Medline)	Primary prevention
Elliott-Eller, Weidner, Pischke 2003	CMS	Abstract
Engblom, Korpilahti, Hamalainen et al 1997	Database	Did not report primary outcomes
Esposito, Giugliano, Nappo et al 2004	CMS	Drug interventions
Esselstyn 1999	CMS	Guideline / review article
Family Heart Study Group 1994	Database	Primary prevention
Fields, Walton, Schneider et al 2002	CMS	Protocol only
Flanagan, Cox, Paine et al 1999	Database	Not randomized
Frasure-Smith and Prince 1985	Database	Not randomized
Frasure-Smith, Lesperance, Gravel et al 2000	CMS	Not randomized
Friedman, Thoreson, Gill et al 1984	Database	Not randomized
Galatius, Gustafsson, Kistorp et al 2003	Database	Not randomized
Geil, Anderson, Gustafson 1995	CMS	Evaluated interventions which were not comprehensive disease management systems
George and Goldberg 2001	CMS	Guideline / review article
Ghoncheh and Smith 2004	CMS	Population not CHD
Gielen, Schuler, Hambrecht 2001	CMS	Guideline / review article
Gleason, Bourdet, Koehn et al 2002	CMS	Not randomized
Gould, Ornish, Scherwitz et al 1995	CMS	Duplicate publication (same study population and follow-up period

		as Ornish 1998)
Gould, Ornish, Kirkeeide et al 1992	CMS	Protocol only
Grimm for the MRFIT 1983	Database	Primary prevention
Grundy, Cleeman, Merz et al 2004	CMS	Guideline / review article
Gulati, Pandey, Arnsdorf et al 2003	CMS	Not randomized
Hakim, Curb, Petrovitch et al 1999	CMS	Evaluated interventions which were not comprehensive disease management systems
Hambrecht, Walther, Mobius-Winkler 2004	CMS	Evaluated interventions which were not comprehensive disease management systems
Harris, Record, Gipson et al 1998	Database	Not randomized
Hedback and Perk 1987	Database	Not randomized
Imperial Cancer Research Fund OXCHECK Study Group 1995	Database	Primary prevention
Jain, Uppal, Bhatnagar et al 1993	CMS	Evaluated interventions which were not comprehensive disease management systems
Jukema, Bruschke, van Boven et al 1995	CMS	Drug interventions
Kawachi, Sparrow, Vokonas et al 1994	CMS	Not randomized
Ketola, Makela, Klockars 2001	Database (WOS)	Primary prevention
Koertge, Weidner, Billings et al 2002	CMS	Abstract
Koertge, Weidner, Elliott-Eller et al 2003	CMS	Not randomized
Kornitzer, De Backer, Dramaix et al 1980	Database	Primary prevention
Krachler 1997	Reference list	Did not report primary outcomes
Kris-Etherton, Harris, Appel et al 2002	CMS	Guideline / review article
Lampert, Joska, Burg et al 2002	CMS	Not randomized
Lear, Ignaszewski, Linden et al 2002	Database (WOS)	Protocol only
Lesperance, Frasure-Smith, Talajic et al 2002	CMS	Not randomized
Lewin, Furze, Robinson et al 2002	Database (Medline)	No usual care arm
Lewis and Resnik 1967	Database	Did not report the outcomes for

		patients with CHD separately
Liao, Ma, Dong et al 2003	Database (Embase)	Non-English
Lichtenstein and Van Horn 1998	CMS	Guideline / review article
Lindholm, Ekbom, Dash et al 1995	Database	Primary prevention
Maggioni 2000	Database (Embase)	Guideline / review article
Malach and Imperato 2004	CMS	Not randomized
Marra, Paolillo, Spadaccini et al 1985	Database	Evaluated interventions which were not comprehensive disease management systems
Marshall, Penckofer, Llewellyn 1986	Database	Not randomized
Matthews, Gump, Harris et al 2004	CMS	Not randomized
Meer 1999	Database (SIGLE)	Not randomized
Meland, Laerum, Ulvik 1997	Database	Primary prevention
Merritt, Scherwitz, Brown et al 1990	CMS	Abstract
Merritt, Ornish, Scherwitz et al 1995a	CMS	Abstract
Merritt, Ornish, Scherwitz et al 1995b	CMS	Abstract
Merritt-Worden, Pettengill, Ornish 2003	CMS	Abstract
Miettinen, Pyorala, Olsson et al 1997	CMS	Drug interventions
Miller, Erlinger, Young et al 2002	CMS	Non-CHD population
Mittleman, Maclure, Sherwood et al 1995	CMS	Not randomized
National Cholesterol Education Program, National Institutes of Health 2002	CMS	Guidelines / review article
Ness, Hughes, Elwood et al 2002	Database (Medline)	Evaluated interventions which were not comprehensive disease management systems
Nicholson, Sklar, Barnard et al 1999	CMS	Evaluated interventions which were not comprehensive disease management systems
Oldenburg, Martin, Greenwood 1995	Database	Did not report primary outcomes
Ornish 1998	CMS	Not randomized
Ornish 2002	CMS	Guideline / review article

Ornish and Pettengill 2003	CMS	Abstract
Ornish 2004	CMS	Guideline / review article
Ornish (chapter 8)	CMS	Guideline / review article
Ornish and Hart (chapter 34)	CMS	Guideline / review article
Pater, Ditlef Jacobsen, Rollag et al 2000	Database (Embase)	Protocol only (no data presented)
Peiss, Kurleto, Rubenfire 1995	Database	Not randomized
Pettengill, Pearson, Pifalo et al 2002	CMS	Abstract
Pfisterer, Buser, Osswald et al 2003	CMS	Not randomized
Picard, Schwartz, Ahn et al 1989	Database	Evaluated interventions which were not comprehensive disease management systems
Pischke, Weidner, Billings J et al 2002	CMS	Abstract
Pitt, Waters, Brown et al 1999	CMS	Drug interventions
Pollock, Franklin, Balady et al 2000	CMS	Guideline / review article
Pozen, Stechmiller, Harris et al 1977	Database	Inpatient-based intervention
Prochaska, Johnson, Lee	CMS	Guideline / review article
Pyke, Wood, Kinmonth et al 1997	Database	Primary prevention
Rahe, Ward, Hayes 1979	Database	Did not report primary outcomes
Rihal, Raco, Gersh et al 2003	CMS	Guideline / review article
Roderick, Ruddock, Hunt et al 1997	Database	Primary prevention
Roman, Gutierrez, Luksic et al 1983	Database	Evaluated interventions which were not comprehensive disease management systems
Rose, Heller, Pedoe et al 1980	Database	Primary prevention
Rubenstein, Kahn, Reinisch et al 1990	Database	Not randomized
Ruo, Rumsfeld, Hlatky et al 2003	CMS	Not randomized
Scandinavian Simvastatin Survival Study 1994	CMS	Drug interventions
Schectman, Wolff, Byrd et al 1996	Database	Did not report the outcomes for patients with CHD separately
Schneider, Staggers, Alexander et al 1995	CMS	Evaluated interventions which were not comprehensive disease management systems
Sdringola, Nakagawa, Nakagawa et al 2003	CMS	Not randomized

Shaffer and Wexler 1995	Database	Not randomized
Shintani, Beckham, Brown et al 2001	CMS	Population not CHD
Simpson, Dixon, Bolli 2004	Database (WOS)	Not randomized
Sivarajan, Newton, Almes et al 1983	Database	Did not report primary outcomes
The South East London Screening Study Group 1977	Database	Primary prevention
Specchia, De Servi, Scire et al 1996	Reference list	No usual care arm
Stahle, Mattsson, Ryden et al 1999	Database (Medline)	Evaluated interventions which were not comprehensive disease management systems
Starkey, Michaelis, Lusignan 2000	Database	Not randomized
Stern and Cleary 1982	Database	Evaluated interventions which were not comprehensive disease management systems
Strandberg, Pitkala, Berglind et al 2001	Database (Embase)	Protocol only (no data presented)
Taddei, Galetta, Virdis et al 2000	CMS	Evaluated interventions which were not comprehensive disease management systems
Thoresen, Friedman, Gill et al 1982	Database	Not randomized
Townsend, Piper, Frank et al 1988	Database	Evaluated interventions which were not comprehensive disease management systems
Tu, Pashos, Naylor et al 1997	CMS	Not randomized
Vale, Jelinek, Best et al 2003	Database (Medline)	Summary of trial already included
Van Drenth, Hulscher, Mokkink et al 1997	Database	Not randomized
Vedin, Wilhelmsson, Tibblin et al 1976	Database	Not randomized
Von Birgelen, Hartmann, Mintz et al 2003	CMS	Not randomized
Wallner, Watzinger, Lindschinger et al 1999	Database (Medline)	No usual care arm
Wasson, Gaudette, Whaley et al 1992	Database	Evaluated interventions which were not comprehensive disease management systems
Waters, Higginson, Gladstone et al 1994	CMS	Drug interventions

Weber, Barnard, Roy 1983	CMS	Population not CHD
Weidner, Pischke, Eller 2003	CMS	Abstract
Weinberger, Smith, Katz et al 1988	Database	Did not report the outcomes for patients with CHD separately
Weingarten, Reidinger, Conner et al 1994	Database	Inpatient-based intervention
Weintraub, Clements, Crisco et al 2003	CMS	Not randomized
Williams, Paton, Siegler et al 2000	CMS	Not randomized
Woollard, Burke, Beilin et al (Journal of Cardiovascular Risk) 2003	Database (Medline)	Did not report the outcomes for patients with CHD separately
Woollard, Burke, Beilin (Journal of Human Hypertension) 2003	Database (WOS)	Did not report the outcomes for patients with CHD separately
Yu-Poth, Zhao, Etherton et al 1999	CMS	Guideline / review article

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Appendix C: Copy of questions sent to primary study authors

Secondary Prevention Review:
Paper Title:
Year:
First author:

1. Program type CCR □ CR □ IC □

2. Location Res □ Hospital □ GP □ Comm □ Home □ Comb. □
Author query: Where was the main location of the program?

3. Commencement after index event _____ weeks
Author query: What was the mean time between index clinical event and program commencement?

4.. Mean Length _____weeks
Author query: What was the mean length of the program?

5. Number sessions per pt _____ sessions □ Unclear
Author query: What was the total number of hours patients should participate in the program?

6. Physician involvement Unclear □ None □ Yes □ specify: _____
Author query: How were physicians involved in the program?

7. Theoretical basis Unclear □ None □ Yes □ specify: _____
Author query: Was the program based on any stated behavioural change theory? If so, what type?

8. Individualization
□ Unclear
□ Standardized components and content
□ Individualization as *per usual care*
□ Individualized components and standardized content
□ Individualized components and individualized content

Author query : How was the program individualized for each patient (if at all)?

9. Miscellaneous facets & features

		Unclear	No	Yes
1)	Nurse prescribing	□	□	□
2)	Supplementary pt telephone support	□	□	□
3)	Specialist CR/cardiac profs	□	□	□
4)	Based on stated guidelines	□	□	□

Author queries:
Did the program involve any nurse or pharmacist prescribing / telephone support?
Did the program involve specialists in cardiology or rehabilitation?
Was the program based on any stated clinical guidelines?

Appendix D: Missing fields prior to and after author survey

Unclear variables	Prior to survey	After survey
Location of program	3	3
Commencement	10	3
Program length	5	1
Session total	17	8
Physician Involvement	6	0
Theoretical Basis	2	0
Individualization	2	1
Nurse / Pharm Prescribing	2	0
Telephone Support	1	1
Specialist input	7	2
Guidelines	2	2
Total missing fields	57	21

Appendix E: Results of descriptive survey

Physician Involvement	Number of Studies (%)
None	8 (17%)
ETT / Exercise Supervision	24 (52%)
Follow up	5 (11%)
Coordination	4 (9%)
Lipid Management	1 (2%)
Screening for Inclusion	2 (4%)
Teaching	2 (4%)

Theoretical Basis	Number of Studies n=46 (%)
None	39 (85%)
Social Cognitive / Learning	2 (4%)
Cognitive Behavioral / Motivation	3 (7%)
Behavioral	2 (4%)

Individualization	Number of Studies n=46 (%)
Unclear	1 (2%)
Standardized components and contents	14 (30%)
Individualized as per usual care	20 (43%)
Individualized components or individualized contents	6 (13%)
Individualized components and individualized contents	5 (10%)

Nurse Prescribing	Number of Studies n=46 (%)
No	40 (87%)
Yes	6 (13%)

Phone Support	Number of Studies n=46 (%)
0. Unclear	1 (2%)
1. No	27 (59%)
2. Yes	18 (39%)

Specialist CR / Cardiac Professionals	Number of Studies n=46 (%)
Unclear	2 (4%)
No	7 (17%)
Yes	37 (79%)

Based on Stated Guidelines	Number of Studies n=46 (%)
Unclear	2 (4%)
No	34 (72%)
Yes	10 (23%)