Annals of Internal Medicine | Review

Meta-Analysis: Secondary Prevention Programs for Patients with Coronary Artery Disease

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Background: **Although supervised exercise programs reduce mortality in survivors of myocardial infarction, the effects of other types of cardiac secondary prevention programs are unknown.**

Purpose: **To determine the effectiveness of secondary cardiac prevention programs with and without exercise components.**

Data Sources: **The authors searched MEDLINE (1966–2004), the Cochrane Central Register of Controlled Trials, EMBASE, CINAHL, SIGLE, and the Cochrane Effective Practice and Organization of Care Study Registry. They also contacted primary study authors and hand-searched bibliographies provided by the Centers for Medicare & Medicaid Services.**

Study Selection: **Randomized clinical trials.**

Data Extraction: **Two reviewers chose studies and extracted data independently; random-effects summary risk ratios were calculated.**

Data Synthesis: **The authors identified 63 randomized trials (21 295 patients with coronary disease). The summary risk ratio was 0.85 (95% CI, 0.77 to 0.94) for all-cause mortality, but this result differed over time with a risk ratio of 0.97 (CI, 0.82 to 1.14) at 12 months and 0.53 (CI, 0.35 to 0.81) at 24 months. The summary risk ratio was 0.83 (CI, 0.74 to 0.94) for recurrent myocardial infarction over a median follow-up of 12 months. Effects were similar for programs that included risk factor education or counseling with a structured exercise component (risk ratio, 0.88 [CI, 0.74 to 1.04] for mortality and 0.62 [CI, 0.44 to 0.87] for myocardial infarction), for programs that included risk factor education or counseling without an exercise component (risk ratio, 0.87 [CI, 0.76 to 0.99] for mortality and 0.86 [CI, 0.72 to 1.03] for myocardial infarction), and for programs that were solely exercise-based (risk ratio, 0.72 [CI, 0.54 to 0.95] for mortality and 0.76 [CI, 0.57 to 1.01] for myocardial infarction). Most of these programs improved quality of life or functional status, but effect sizes were small.**

Limitations: **Although these programs may reduce total health care costs, published data on the costs of the programs are inadequate to conclusively comment on their cost-effectiveness.**

Conclusions: **A wide variety of secondary prevention programs improve health outcomes in patients with coronary disease.**

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Cardiovascular disease remains the most common cause of office visits, hospitalizations, and death in the United States: More than 13 million Americans have documented coronary artery disease (CAD), and costs for CAD are expected to exceed $393 billion in 2005 (1). Control of the CAD epidemic requires a multifaceted strategy targeting the currently recognized modifiable risk factors for CAD that account for more than 90% of risk, regardless of sex, age, or region (2). This strategy should include primary prevention maneuvers (for the general population and high-risk individuals) and secondary prevention programs (for patients with established CAD). Despite the abundant evidence base for CAD prevention (3), health outcomes studies consistently demonstrate gaps in applying this evidence to clinical practice; these gaps contribute to suboptimal patient outcomes (4).

Secondary prevention programs are often proposed as a way to improve management and outcomes. Although several reviews have shown that cardiac rehabilitation reduces mortality in survivors of myocardial infarction (MI) (5–8), these conclusions are informed largely by trials that tested supervised exercise programs versus no exercise postinfarction. Since exercise training confers substantial physiologic and clinical benefits and activity levels are inversely proportional to cardiovascular mortality (9), it is not surprising that trials of exercise programs found positive effects on survival.

However, few trials included in these reviews evaluated secondary prevention programs that were not primarily exercise-based. In an earlier review (10), we identified 12 randomized trials (9803 patients) of non–exercise-based secondary prevention programs in patients with established CAD. We demonstrated improvements in risk factor profiles and processes of care (particularly the prescription of proven efficacious therapies) but indeterminate effect on rates of death or recurrent MIs (10).

Because current guidelines recommend that secondary prevention programs should not be restricted to supervised exercise programs but should address the full range of modifiable risk factors (11), we conducted a systematic review to update earlier work and to determine the effects of different types of secondary prevention programs (particularly those with a structured exercise component versus those without).

See also:

Print
Summary for Patients I-87

Web-Only
Conversion of figures and tables into slides

METHODS

Data Sources

We searched MEDLINE (1966–2004); the Cochrane Central Register of Controlled Trials, Issue 4, 2004; EMBASE (1980–2004); CINAHL (1982–2004); SIGLE (1980–2004); and PubMed (January 2004–December 2004). We also conducted a cited reference search for our previous review (10) in Web of Science (1999–2004). We based the searches 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*. We handsearched reference lists of all identified studies, review articles, and references provided by the Centers for Medicare & Medicaid Services and content experts (search strategy available upon request). We limited our search to English-language publications (no abstracts), and the search extends from 1966 to 2004 (we completed the search on 16 December 2004).

Study Selection

Two investigators independently reviewed the titles and abstracts of all citations to identify studies reporting the effect of secondary prevention programs on mortality, MI, or hospitalization rates in patients with CAD. Both investigators obtained the full text of potentially relevant articles and reviewed them by using prestandardized data abstraction forms and eligibility criteria defined a priori. Any discrepancies were resolved by consensus.

We excluded studies if they were not randomized, if they did not include a "usual care" group, if the outcomes for CAD patients were not reported or were not obtainable from the study investigators, if they evaluated single-modality interventions except exercise (such as telephone follow-up), if they tested interventions delivered to inpatients, or if the interventions were not provided by health professionals (for example, mailed reminders, self-help groups, or self-directed interventions).

Data Extraction and Quality Assessment

Two investigators extracted all outcome data independently, and a third investigator checked the data. We assigned outcomes according to the intention-to-treat principle and by using the definitions from the primary studies. When necessary, we contacted original investigators to clarify the data for any trial published in the past decade. Authors for 10 of these 21 studies provided further data.

Two investigators independently assigned each intervention to 1 of 3 groups: 1) programs that incorporated education and counseling about coronary risk factors with a supervised exercise program (either in a group setting, per traditional comprehensive cardiac rehabilitation programs, or individually delivered), 2) programs that included education and counseling about coronary risk factors but had no exercise component (either delivered in a group setting or individually), and 3) supervised exercise programs only.

Data Synthesis and Analysis

We performed analyses by using RevMan 4.2 (Update Software, Oxford, United Kingdom). Our outcomes of interest were all-cause mortality and recurrent MIs. Because the outcomes were relatively common, we calculated risk ratios and used the I^2 statistic to assess for heterogeneity in each outcome of interest. We combined studies by using the DerSimonian and Laird random-effects model. For the primary analysis, we used data from the longest follow-up period reported in each trial. In a priori sensitivity analyses, we pooled data for 3 follow-up periods (12, 24, and 60 months). To evaluate whether different types of secondary prevention programs had different effects, we calculated the summary risk ratio for each program type and used adjusted indirect comparisons to compare different types of interventions, according to the method of Song and colleagues (12).

Role of the Funding Source

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RESULTS

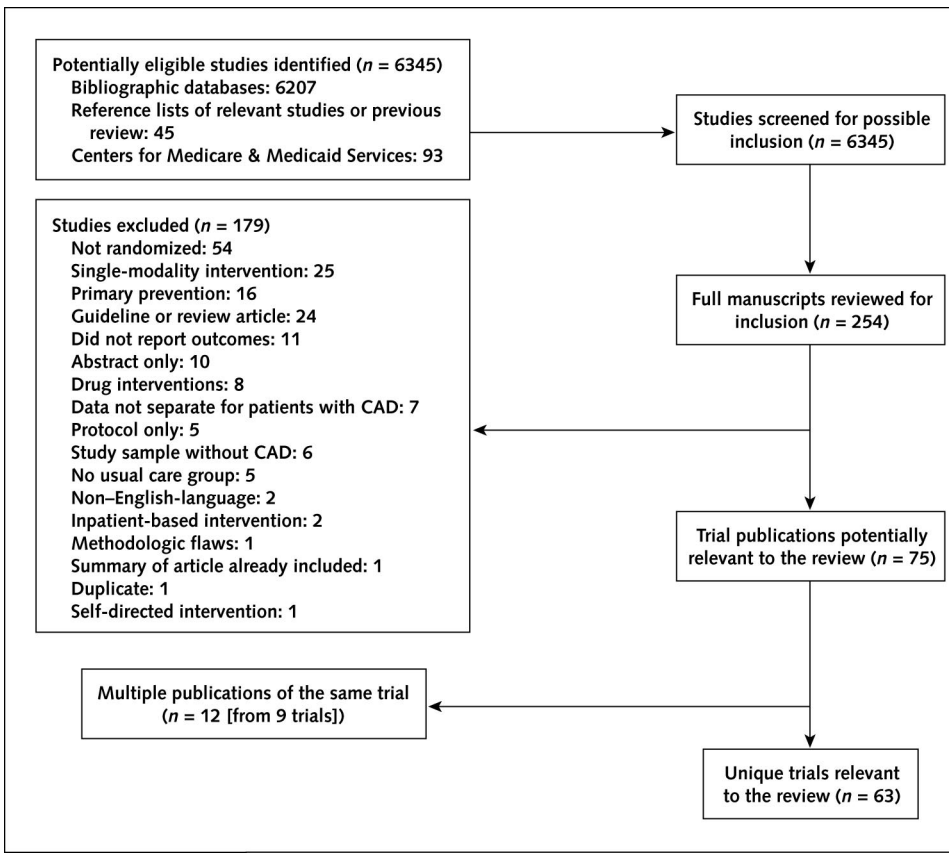
Study Selection and Evaluation

We identified 6345 citations from electronic databases ($n = 6207$), reference lists ($n = 45$), and the Centers for Medicare & Medicaid Services ($n = 93$). After the initial screening, we reviewed 254 full manuscripts and excluded 179 of these studies after detailed evaluation (**Figure 1**).

Sixteen disagreements among the reviewers about eligibility of the studies occurred for a κ value of 0.81. All disagreements were resolved by consensus.

Of the randomized trials that were eligible for inclusion (13–87), 9 were reported in more than 1 publication. The second publication reported different end points in 2 cases (13–16), results from different follow-up periods in 5 cases (13, 17–26), and results from the subgroup of patients with cardiac disease in 1 case (27, 28). The ninth trial (the World Health Organization [WHO] trial) (29) included 24 collaborating centers; however, the original investigators excluded 7 sites because of poor participant follow-up and 4 sites because of statistically significant differences between the intervention and control groups at baseline. We included the outcome data from the remaining 13 sites as 1 trial for our analysis, an approach validated by the nonsignificant test results for statistical heterogeneity for all-cause mortality and MI. While the 2 Finnish centers in the WHO trial published their results separately (and for several follow-up periods), we included only their 3-year outcome data with the other 11 WHO sites for consistency of data presentation (30–32).

Figure 1. **Flow of trials through the selection process.**



CAD = coronary artery disease.

Studies Included in the Systematic Review

Table 1 presents summary data from the 63 unique randomized trials that were eligible for our systematic review (13–87). Our search retrieved 51 trials that were not included in our previous systematic review (which was limited to literature published before 1999 and excluded any studies with exercise components) (10) and 26 trials that were not included in a more recent systematic review of cardiac rehabilitation (which was limited to literature published before 2003 and included few "individual counseling" programs) (8).

Qualitative Data Synthesis

In all trials, patients who were randomly assigned to the control groups received usual care (this was generally undefined). **Table 1** describes the types of secondary prevention programs; few trials described the intensity of the interventions. Almost all trials enrolled highly selected study samples: Forty-five trials recruited patients after acute MI or a coronary revascularization procedure. Thirty-five trials excluded elderly patients, and 19 trials excluded women (**Table 1**). Indeed, women constituted fewer than 50% of study participants in all but 2 trials.

No trial was double-blind (which is not surprising, considering the nature of the intervention), and very few trials described randomization procedures or accounted for discrepancies between sample sizes at recruitment and follow-up. As a result, Jadad quality scores clustered around 2 (**Table 2**). Furthermore, only 15 (24%) trial reports described adequate allocation concealment.

No trial reported side effects with the secondary prevention programs beyond the adverse clinical outcomes described later.

Quantitative Data Synthesis

All-Cause Mortality

Only 1 of the 40 trials reporting this outcome found a statistically significant survival benefit with the intervention (**Figure 2**). The summary risk ratio for all 40 trials reporting all-cause mortality (16 142 patients) was 0.85 (95% CI, 0.77 to 0.94; P for heterogeneity = 0.96; I^2 = 0%). The treatment effects did not statistically significantly differ among the 3 types of secondary prevention programs (**Figure 2**), even if all exercise-based programs were combined (27 trials, 6940 patients) (summary risk ratio, 0.83 [CI, 0.72 to 0.96]) and compared with non–exercise-based programs (14 trials, 9202 patients) (summary risk ratio, 0.87 [CI, 0.76 to 0.99]; P = 0.64).

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Table 1. **Description of Included Studies***

Study, Year (Reference)	Sample Size, *n*	Study Sample (Location)	Mean Age, *y*	Men, %	Key Components of Intervention	Duration of Intervention, *mo*	Length of Follow-up, *mo*
Programs that included risk factor education or counseling with a structured exercise component							
Comprehensive cardiac rehabilitation in a group setting (19 trials, 4208 patients)							
Sivarajan et al., 1982 (33)	258 (170 in control and comprehensive secondary prevention groups)	Patients age < 70 y, discharged after acute MI (U.S.)	57	>80	Group education or counseling sessions about risk factor management plus exercise program	3	6
Vermeulen et al., 1983 (34)	98	Men age 40–55 y, discharged after acute MI (the Netherlands)	49	100	Multidisciplinary team (details not given) involved in exercise rehabilitation and social and psychological support for patients	1.5–2.0	60
Bengtsson, 1983 (35)	87	Patients age < 65 y, 1 y after acute MI (Sweden)	56	85	Rehabilitation program involving counseling and exercise training	3	12
WHO trial, 1983 (29)†	1735	Men age < 65 y, discharged after acute MI (Europe)	53	100	Multidisciplinary team (components differed at each center) involved in patient health education and supervised exercise program	36	36
Ornish et al., 1990 (25) and 1998 (26)	48	Patients age 35–75 y with angiography-proven coronary disease (U.S.)	58	88	Group education or counseling sessions about lifestyle modification (low-fat, vegetarian diet; stress management; smoking cessation) plus exercise program	12	60
Oldridge et al., 1991 (36)	201	Patients discharged with diagnosis of acute MI and evidence of anxiety or depression (Canada)	52	89	Behavioral counseling and supervised exercise training	2	12
P.RE.COR., 1991 (37)	182	Men age < 65 y, discharged after acute MI (France)	51	100	Two intervention groups, 1 of which was comprehensive cardiac rehabilitation (supervised exercise program, relaxation training, risk factor management, education)	1.5	24
Fridlund et al., 1991 (38)	178	Patients age < 65 y, discharged after acute MI (Sweden)	56	87	Nurse-led rehabilitation program addressing lifestyle, stress, and social support	6	12
Engblom et al., 1992 (15) and 1997 (16)	228	Patients age < 65 y, discharged after CABG (Finland)	54	88	Group education, individual counseling (with physician and dietitian) about diet and physical activity, supervised exercise training	0.75	12
Heidelberg Trial, 1992 (21) and 1997 (22)	113	Men with CAD on angiography (Germany)	54	100	Education about diet and exercise, exercise program with individual and group training sessions	12	12 and 72
Bell, 1998 (39)	353 (201 in control and comprehensive secondary prevention groups)	Patients age ≤ 75 y, discharged after acute MI (UK)	60	78	Comprehensive cardiac rehabilitation (supervised exercise program, group education sessions on risk factor management)	3	12
Johnston et al., 1999 (40)	100	Patients age ≤ 70 y, discharged after acute MI (UK)	56	65	Nurse-led inpatient and outpatient cardiac rehabilitation program consisting of education, support for risk factor change, and psychological counseling	1.5	12
Lisspers et al., 1999 (41)	93	Patients age < 65 y after PCI (Sweden)	53	37	Comprehensive residential program (health education, behavioral change) consisting of skills training, habit rehearsal on stress management, diet, exercise, and smoking; followed by outpatient program of self observation and reporting of risk factors with follow-up support	12	12
Toobert et al., 2000 (42)	25	Postmenopausal women with CAD (U.S.)	63	0	1-wk residential program, including dietary support, stress management, and physical activity, followed by subsequent weekly meetings	24	24
Sundin et al., 2003 (43)	132	Men age < 70 y after PCI, acute MI, or CABG (Sweden)	59	100	Group-based multidisciplinary program addressing stress management, diet, and exercise by using lectures and skills training	12	12
Seki et al., 2003 (44)	38	Men age > 65 y after MI, CABG, or PTCA (Japan)	70	100	Comprehensive outpatient cardiac rehabilitation program including exercise, diet advice, and education	6	6
Yu et al., 2003 (45)	112	Obese patients attending cardiac rehabilitation after acute MI or PCI (China)	62	79	Exercise program with group education classes about risk factor modification	2.5	2.5
Vestfold Heartcare Study, 2003 (46)	197	Patients discharged after acute coronary syndrome, CABG, or 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, dietitian, and physiotherapist)	24	24
Marchionni et al., 2003 (47)	270	Patients age > 45 y, discharged after acute MI (Italy)	69	71	Supervised exercise training and education or counseling about risk factor management, with optional monthly support groups	2	12
Individual counseling with exercise component (5 trials, 1446 patients)							
SCRIP, 1994 (67)	300	Patients age < 75 y, referred for angiography for known or suspected CAD (U.S.)	56	86	Nurse-managed patient education and algorithm-driven management of risk factors, exercise program, and frequent telephone and clinic visits with nurse	48	12, 24, 36, and 48
DeBusk et al., 1994 (17); Taylor et al., 1997 (18)	585	Patients age ≤ 70 y, discharged after acute MI (U.S.)	57	79	Nurse-managed patient education and counseling, exercise program, frequent telephone contact, and algorithm-based lipid therapy	12	12

Table 1—**Continued**

Study, Year (Reference)	Sample Size, *n*	Study Sample (Location)	Mean Age, *y*	Men, %	Key Components of Intervention	Duration of Intervention, *mo*	Length of Follow-up, *mo*
Carlsson et al., 1997 (68)	168	Patients age 50–70 y, discharged after acute MI (Sweden)	62	75	Nurse-run education program (individual and group), exercise training program, nurse clinic visits	12	12
Allison et al., 1999 (69)	152	Patients not treated with lipid-lowering medication who completed cardiac rehabilitation after an acute coronary event (U.S.)	64	82	Nurse-led follow-up program every 6 wk after start or change in lipid-lowering therapy, including diet and exercise advice and lipid-lowering medications	6	6
Stagmo et al., 2001 (70)	241	Patients age 50–69 y, hospitalized in a coronary care unit for MI or previous CABG (Sweden)	62	78	Hospital-based secondary prevention program	12	12
Programs that included risk factor education or counseling without a structured exercise component							
Group cardiac rehabilitation without exercise component (4 trials, 2671 patients)							
Stern et al., 1983 (48)	106 (64 in control and group counseling groups)	Patients age 30–69 y with recent MI (U.S.)	54	83	Group education and counseling sessions (12 sessions) led by nurse and psychiatrists or social workers	3	12
P.RE.COR., 1991 (37)	182	Men age < 65 y, discharged after acute MI (France)	51	100	Two intervention groups, 1 of which was group counseling program (group education and counseling led by physician, psychiatrist, and nutritionist)	1.5	24
Jones and West, 1996 (49)	2328	Patients discharged home within 28 d of acute MI (UK)	62	73	Nurse and psychologist regularly saw participants for education, counseling, and relaxation or stress management training	1.75	12
D.I.E.T., 2001 (50)	97	Patients with known CAD and hyperlipidemia in specialty clinics (U.S.)	65	70	Nurse-led education (group) and provision of written materials about diet and physical activity	12	12
Individual counseling without exercise component (19 trials, 10 496 patients)							
Ornish et al., 1983 (51)	46	Men and women age ≤ 75 y with CAD (U.S.)	59	78	Residential stress management and vegan dietary program without exercise program	0.75	0.75
Fitzgerald et al., 1994 (52)	668	Patients age > 45 y who were discharged from a general medicine inpatient service (two thirds with heart disease) and being followed at the general medicine clinic of a Veterans Affairs hospital (U.S.)	65	100	Nurse-managed patient education, coordination of care, frequent telephone contact, and protocol-driven systematic assessments for unmet sociomedical needs	12	12
Naylor et al., 1994 (53)	276 (142 with cardiac disease)	Patients age > 70 y who were discharged from a tertiary care hospital with CAD or heart failure (U.S.)	76	49	Comprehensive discharge planning protocol with gerontologic nurse providing education, coordinating care, and maintaining telephone contact for 2 wk	0.5	3
Cupples and McKnight, 1994 (23) and 1999 (24)	688	Patients age < 75 y with angina for ≥6 mo who were identified from general practice records (UK)	63	59	Individual, nurse-led personalized health promotion program every 4 mo	24	24 and 60
M-HART, 1997 (54)	1376	Patients discharged after acute MI (Canada)	59	66	Nurse contacted patients monthly by telephone, providing education and advice, screening patients for psychological distress, and referring patients to other health care resources as needed	12	12
Carlsson, 1998 (55)	530	Patients age 50–70 y who were discharged after acute MI, CABG, or PCI (Sweden)	62	79	Individualized assessment and nurse counseling on risk factors and diet	12	12
Campbell et al., 1998 (13) and 1998 (14); Murchie et al., 2003 (19) and 2004 (20)	1343	Patients age < 80 y with documented CAD who were recruited from general practice records (UK)	66	58	Regular follow-up at secondary prevention clinics run by nurses, promoting medical and lifestyle approaches to prevention	12	12 and 56
Jolly et al., 1999 (56)	597	Patients with acute MI or recent-onset angina, discharged from hospital or seen in a chest pain clinic (UK)	64	71	Cardiac liaison nurse coordinated care between discharging service and family physician, patients given personal health record and prompts for follow-up	12	12
Naylor et al., 1999 (27); Naylor and McCauley, 1999 (28)	363 (202 with cardiac disease)	Patients age ≥ 65 y, discharged from a tertiary care hospital with CAD or heart failure or after CABG or heart surgery (U.S.)	75	50	Nurse-led patient education, coordination of home care, at least 2 home visits, use of a standardized protocol to optimize medications, and weekly telephone contact for 1 mo	1	6
Allison et al., 2000 (57)	326	Patients attending ED with confirmed unstable angina (U.S.)	58	56	Nurse-led intervention including lipid management, referral to support services, counseling on risk factors and physician collaboration on abnormal results, and two 1-h sessions at least 6 and 25 d after discharge	1	6
Moher et al., 2001 (58)	1906	Patients age 55–75 y who were identified in family practices with established CAD (UK)	66	68	Nurse-led clinic providing support for risk factor change by using electronic disease register and recall system	1	18
McHugh et al., 2001 (59)	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	7
Higgins et al., 2001 (60)	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	12

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Table 1—**Continued**

Study, Year (Reference)	Sample Size, *n*	Study Sample (Location)	Mean Age, *y*	Men, %	Key Components of Intervention	Duration of Intervention, *mo*	Length of Follow-up, *mo*
Allen et al., 2002 (61)	228	Patients age ≤ 75 y, discharged after CABG or PCI, who had hypercholesterolemia (U.S.)	60	63	Nurse practitioner case management in partnership with patients' primary care provider (nurse-directed education and lifestyle modification advice; nurse clinic visits; nurse prescribed medications, if necessary; follow-up telephone calls)	12	12
COACH pilot, 2002 (62)	245	Patients age ≤ 75 y, discharged after coronary revascularization procedure (Australia)	61	75	Personal coaching by dietitian through 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	6
COACH trial, 2003 (63)	792	Patients discharged from 6 hospitals after CABG, PCI, acute MI, or coronary angiography (Australia)	59	77	Personal coaching (delivered by nurses or dietitians) through 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	6 and 48
ELMI trial, 2003 (64)	302	Patients discharged from 2 tertiary care cardiac rehabilitation programs (Canada)	64	83	Personal coaching by case manager delivered through telephone and in-person counseling sessions; if suboptimal coronary risk factors at 6 mo, treatment algorithms with cover letter from cardiologist mailed to primary care physicians	12	12
Young et al., 2003 (65)	146	Patients discharged after acute MI (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	14
REACH trial, 2004 (66)	756	Patients age 30–80 y, discharged from tertiary care hospital with documented coronary disease (U.S.)	64	71	Nurse-based education and counseling about cholesterol and target levels delivered through telephone (4 calls in 9 mo) and mailed educational materials about various secondary prevention maneuvers	12	12
Supervised exercise program only (17 trials, 2566 patients)							
Wilhelmsen et al., 1975 (71)	315	Men and women age > 55 y after acute MI (Sweden)	51	89	Exercise program 3 mo after diagnosis	NR	48
NEHDP, 1981 (72)	651	Men age ≤ 64 y after acute MI (U.S.)	52	100	Supervised exercise initially in exercise laboratory (8 wk) then gymnasium	42	36
Carson et al., 1982 (73)	303	Men after acute MI (UK)	51	100	Supervised exercise program	3	25
Ballantyne et al., 1982 (74)	42	Men age < 65 y after acute MI (UK)		100	Supervised exercise program	6	6
Miller et al., 1984 (75)	198	Men age ≤ 70 y with acute MI (U.S.)	52	100	Home or hospital-based exercise training	6	6
Roviaro et al., 1984 (76)	48	Men age < 70 y after MI or CABG (U.S.)	56	100	Exercise program containing supervised exercise sessions and related education	3	7
Erdman et al., 1986 (77)	80	Men age < 65 y after acute MI (the Netherlands)	51	100	Supervised exercise program	6	60
Agren et al., 1989 (78)	37	Men age < 65 y after CABG (Sweden)	55	100	Supervised exercise program	3	12
Bethell and Mullee, 1990 (79)	229	Men age < 65 y after acute MI (UK)	54	100	Supervised exercise program	3	3
Bertie et al., 1992 (80)	103	Patients after acute MI (UK)	52	NR	Supervised exercise in gymnasium	1	24
Fletcher et al., 1994 (81)	88	Men < 73 y with documented coronary disease and a concurrent physical disability (U.S.)	63	100	Home exercise program	6	6
Holmbäck et al., 1994 (82)	69	Patients age < 70 y after acute MI (Sweden)	55	97	In-hospital exercise training program provided by physiotherapist	3	12
Wosornu et al., 1996 (83)	81	Men referred for CABG (UK)	57	100	6 mo of graduated exercise training with aerobic or strength training	6	6
Dugmore et al., 1999 (84)	124	Patients after acute MI (UK)	55	98	Supervised weekly aerobic training program	12	60
Heldal et al., 2000 (85)	37	Men age ≤ 65 y after acute MI (Norway)	53	100	Supervised exercise training provided by specialist physiotherapist	1	6
Ståhle et al., 2000 (86)	43	Men age > 65 y with acute MI or unstable angina (Sweden)	71	77	Supervised outpatient exercise program 3 times per wk	3	12
ETICA trial, 2001 (87)	118	Patients after PCI (Italy)	57	84	Supervised exercise program	6	6

* CABG = coronary artery bypass grafting; CAD = coronary artery disease; COACH = Coaching patients On Achieving Cardiovascular Health; D.I.E.T. = Dietary Intervention and Evaluation Trial; ED = emergency department; 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; PTCA = percutaneous transluminal coronary angioplasty; REACH= Reinforcing Education About Cholesterol; SCRIP = Stanford Coronary Risk Intervention Project; UK = United Kingdom; U.S. = United States; WHO = World Health Organization.
† The results for 13 of the 24 collaborating centers in the WHO trial are included in the table. Reasons for the exclusion of the other 11 centers are given in the text.

However, the effects of secondary prevention programs differed over time, while the risk ratio for all-cause mortality was 0.97 (CI, 0.82 to 1.14) in the 20 trials (9462 patients) reporting 12-month outcome data (P for heterogeneity = 0.97; I^2 = 0%) and 0.53 (CI, 0.35 to 0.81) in the 6 trials (1780 patients) reporting 24-month outcome data (P for heterogeneity = 0.58; I^2 = 0%). Furthermore, pooling the data from the 7 trials (2477 patients) reporting follow-up data from at least 5 years after initiation of the intervention program demonstrated that these programs had a sustained beneficial effect: The risk ratio for all-cause mortality at 5 years was 0.77 (CI, 0.63 to 0.93; P for heterogeneity = 0.72; I^2 = 0%).

Table 2. **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
Programs that included risk factor education or counseling with a structured exercise component					
Comprehensive cardiac rehabilitation in a group setting					
Sivarajan et al., 1982 (33)	Yes	No	Yes	2	Unclear
Vermeulen et al., 1983 (34)	Yes	No	Yes	2	Unclear
Bengtsson, 1983 (35)	Yes	No	Yes	2	Unclear
WHO trial, 1983 (29)	Yes	Yes	No	2	Unclear
Ornish et al., 1990 (25)	Yes	No	Yes	2	Unclear
Oldridge et al., 1991 (36)	Yes	No	No	1	Unclear
P.RE.COR., 1991 (37)	Yes	No	Yes	2	Unclear
Fridlund et al., 1991 (38)	Yes	No	Yes	2	Unclear
Engblom et al., 1992 (15) and 1997 (16)	Yes	No	No	1	Unclear
Heidelberg Trial, 1992 (21)	Yes	No	Yes	2	Adequate
Bell, 1998 (39)	Yes	No	Yes	2	Unclear
Johnston et al., 1999 (40)	Yes	No	Yes	2	Unclear
Lisspers et al., 1999 (41)	Yes	No	Yes	2	Unclear
Toobert et al., 2000 (42)	Yes	No	Yes	2	Unclear
Sundin et al., 2003 (43)	Yes	No	No	1	Unclear
Seki et al., 2003 (44)	Yes	No	Yes	2	Adequate
Yu et al., 2003 (45)	Yes	No	No	1	Unclear
Vestfold Heartcare Study, 2003 (46)	Yes	No	No	1	Adequate
Marchionni et al., 2003 (47)	Yes	No	Yes	2	Unclear
Individual counseling with exercise component					
SCRIP, 1994 (67)	Yes	Yes	Yes	3	Adequate
DeBusk et al., 1994 (17); Taylor et al., 1997 (18)	Yes	Yes	Yes	3	Adequate
Carlsson et al., 1997 (68)	Yes	No	Yes	2	Unclear
Allison et al., 1999 (69)	Yes	No	Yes	2	Unclear
Stagmo et al., 2001 (70)	Yes	No	Yes	2	Unclear
Programs that included risk factor education or counseling without a structured exercise component					
Group cardiac rehabilitation without exercise component					
Stern et al., 1983 (48)	Yes	No	No	1	Unclear
P.RE.COR., 1991 (37)	Yes	No	Yes	2	Unclear
Jones and West, 1996 (49)	Yes	No	Yes	2	Adequate
D.I.E.T., 2001 (50)	Yes	No	No	1	Unclear
Individual counseling without exercise component					
Ornish et al., 1983 (51)	Yes	Yes	No	2	Unclear
Fitzgerald et al., 1994 (52)	Yes	No	Yes	2	Unclear
Naylor et al., 1994 (53)	Yes	No	Yes	2	Unclear
Cupples and McKnight, 1994 (23) and 1999 (24)	Yes	Yes	Yes	3	Adequate
M-HART, 1997 (54)	Yes	No	Yes	2	Adequate
Carlsson et al., 1998 (55)	Yes	No	Yes	2	Unclear
Campbell et al., 1998 (13)	Yes	Yes	Yes	3	Adequate
Jolly et al., 1999 (56)	Yes	No	Yes	2	Adequate
Naylor et al., 1999 (27); Naylor and McCauley, 1999 (28)	Yes	Yes	Yes	3	Adequate
Allison et al., 2000 (57)	Yes	Yes	No	2	Unclear
Moher et al., 2001 (58)	Yes	Yes	Yes	3	Unclear
McHugh et al., 2001 (59)	Yes	No	Yes	2	Unclear
Higgins et al., 2001 (60)	Yes	No	Yes	2	Unclear
Allen et al., 2002 (61)	Yes	Yes	Yes	3	Unclear
COACH pilot, 2002 (62)	Yes	No	Yes	2	Unclear
COACH trial, 2003 (63)	Yes	Yes	Yes	3	Unclear
ELMI trial, 2003 (64)	Yes	Yes	Yes	3	Unclear
Young et al., 2003 (65)	Yes	Yes	Yes	3	Adequate
REACH trial, 2004 (66)	Yes	Yes	Yes	3	Unclear
Supervised exercise program only					
Wilhelmsen et al., 1975 (71)	Yes	Yes	Yes	3	Unclear
NEHDP, 1981 (72)	Yes	No	Yes	2	Unclear
Carson et al., 1982 (73)	Yes	No	Yes	2	Unclear
Ballantyne et al., 1982 (74)	Yes	No	Yes	2	Unclear
Miller et al., 1984 (75)	Yes	No	Yes	2	Unclear
Roviaro et al., 1984 (76)	Yes	No	No	1	Unclear
Erdman et al., 1986 (77)	Yes	Yes	Yes	3	Unclear
Agren et al., 1989 (78)	Yes	No	Yes	2	Unclear
Bethell and Mullee, 1990 (79)	Yes	No	Yes	2	Unclear

Continued on following page

Table 2—**Continued**

Study	Described as Randomized	Method of Randomization Described and Appropriate	Description of Withdrawals or Losses to Follow-up	Jadad Score	Allocation Concealment
Bertie et al., 1992 (80)	Yes	No	Yes	2	Unclear
Fletcher et al., 1994 (81)	Yes	No	Yes	2	Unclear
Holmbäck et al., 1994 (82)	Yes	No	No	1	Adequate
Wosornu et al., 1996 (83)	Yes	No	Yes	2	Adequate
Dugmore et al., 1999 (84)	Yes	No	No	1	Unclear
Heldal et al., 2000 (85)	Yes	No	Yes	2	Adequate
Ståhle et al., 2000 (86)	Yes	No	Yes	2	Unclear
ETICA trial, 2001 (87)	Yes	No	Yes	2	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; D.I.E.T. = 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; WHO = World Health Organization.

Recurrent MI Rate

Two of the 27 trials reporting this end point (**Figure 3**) detected a statistically significant difference between intervention and control patients, and the summary risk ratio for reinfarction for all 11 723 patients over a median follow-up of 12 months was 0.83 (CI, 0.74 to 0.94; P for heterogeneity = 0.55; $I^2 = 0\%$). The treatment effects did not appreciably differ over various follow-up periods among the 3 types of programs (**Figure 3**), among all programs that incorporated exercise (22 trials, 6194 patients) (summary risk ratio, 0.73 [CI, 0.60 to 0.89]), and among non–exercise-based programs (6 trials, 5529 patients) (summary risk ratio, 0.86 [CI, 0.72 to 1.03]; $P = 0.23$).

Processes of Care

Details on these outcomes in each trial are available at www.cms.hhs.gov/mcac/id144a.pdf. In brief, 35 trials reported effects on cardiovascular risk factors, with 26 trials demonstrating better cholesterol profiles in patients who were randomly assigned to the intervention programs, although the differences were statistically significant in only 17 trials and the effect sizes were generally small to moderate. Of the 22 trials that assessed the use of proven efficacious medications, 8 trials demonstrated statistically significantly better application of at least 1 therapy in the intervention patients, 3 trials demonstrated better prescribing in intervention patients but did not achieve statistical significance, and 11 trials did not demonstrate any appreciable difference between intervention and control patients. In many cases, improved processes of care were not seen with the intervention because of improved risk factor management in control patients. For example, 55% of control patients in 1 study were exposed to comprehensive secondary prevention clinics by the end of follow-up (19).

Other End Points

Twenty-four of the 42 trials evaluating quality of life or functional status reported statistically significantly better scores in patients exposed to the intervention programs, although the effect sizes were generally small. Only 7 of these trials (17, 27, 47, 50, 52, 53, 88) described the costs of the intervention. Of these, 2 trials (27, 53) reported that their intervention was cost-saving and only 1 trial (88) performed formal cost-effectiveness analyses (demonstrating incremental cost per quality-adjusted life-year of £1097). Another 2 trials did not report costs but did report fewer physician visits, fewer emergency department visits, less laboratory testing, and fewer total hospital days in intervention patients than control patients (Vale M. Personal communication; 63, 65).

Publication Bias

There was no evidence of publication bias (Egger test; $P = 0.51$).

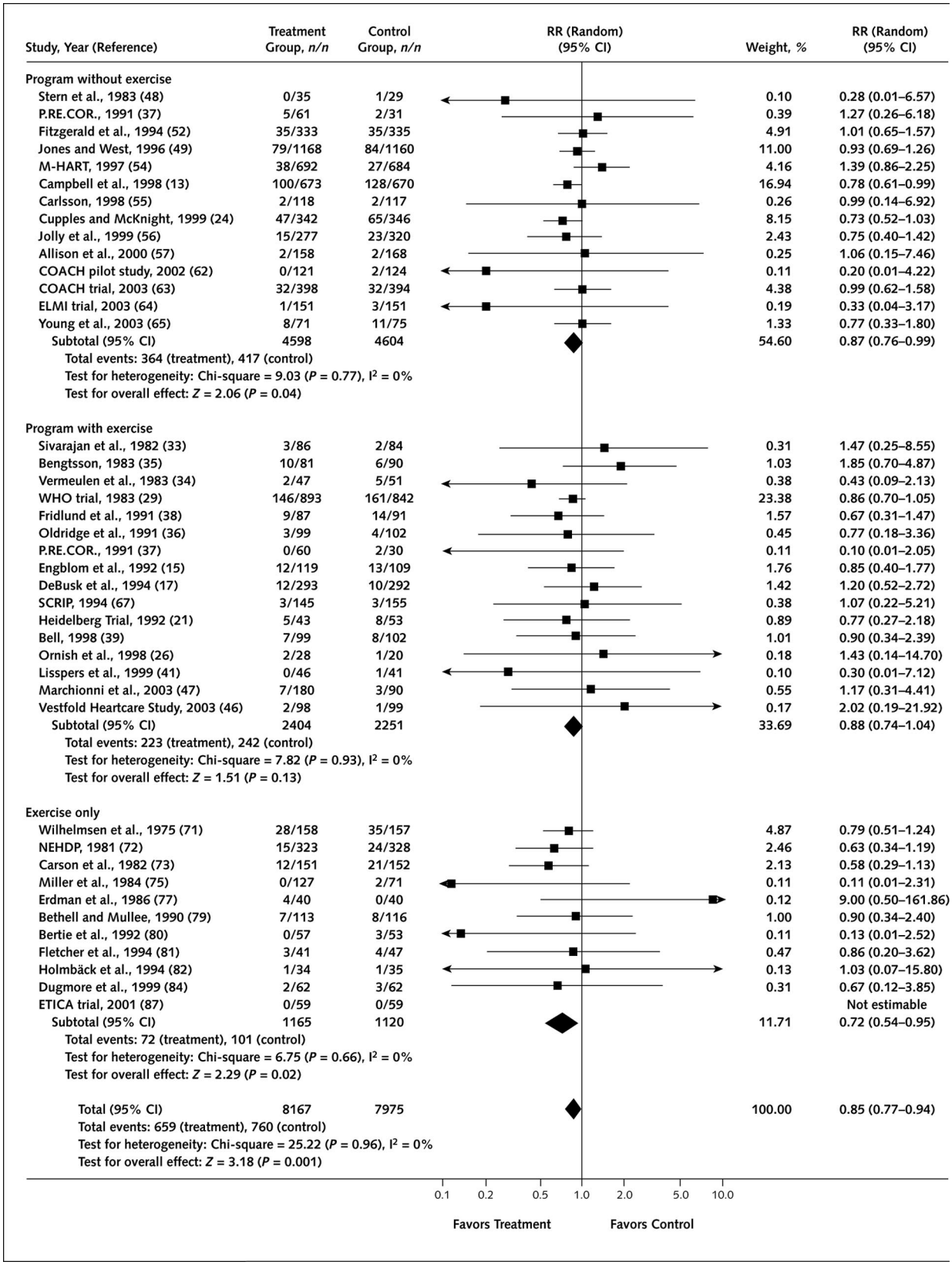
DISCUSSION

Secondary prevention programs positively affect processes of care (risk factor profiles and use of proven efficacious therapies) and functional status or quality of life for participants and reduce MIs by 17% over a median follow-up of 12 months. The mortality benefit derived from participation in secondary prevention programs (15% overall and 47% at 2 years) became apparent with longer follow-up and was of similar magnitude in recently published trials and in trials published more than 2 decades ago (before the widespread use of contemporary medical therapies). Benefits did not differ among the 3 types of programs: those that incorporated education and counseling about coronary risk factors with a supervised exercise program, those that included risk factor education or counseling but no exercise component, and those that consisted of only a structured exercise program.

Many reasons may explain why the mortality benefit was not evident at 12 months despite a rapid effect on processes of care linked to CAD outcomes (89). First, 12 months is probably too short to show a clear effect on

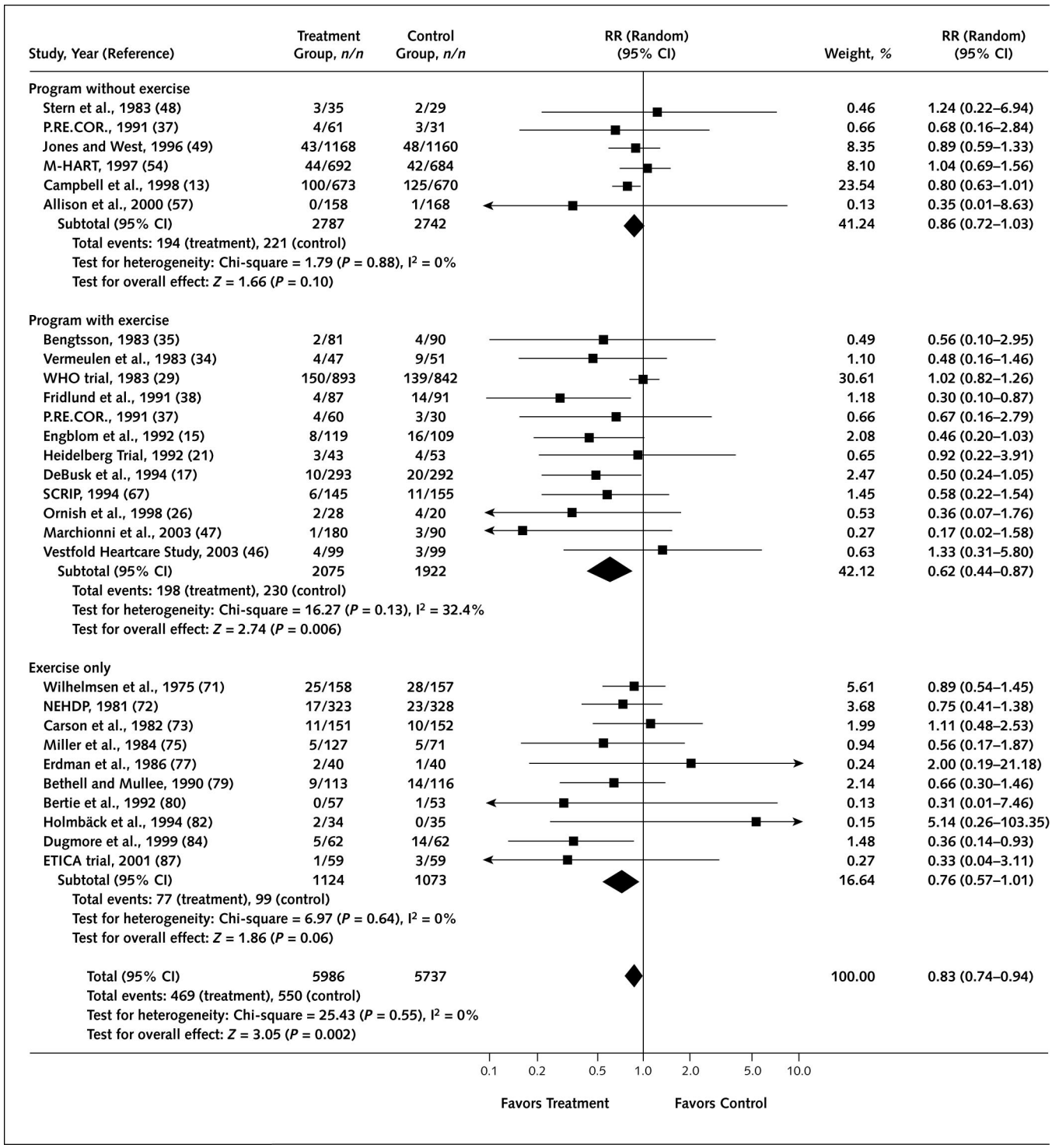
Text continued on page 669

Figure 2. **All-cause mortality in trials evaluating secondary prevention programs.**



Note that P.RE.COR. had 2 intervention groups and 1 control group. The control group data have been included only once in the total pooled estimate. COACH = Coaching patients On Achieving Cardiovascular Health; 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; RR = risk ratio; SCRIP = Stanford Coronary Risk Intervention Project; WHO = World Health Organization.

Figure 3. **Recurrent myocardial infarctions in trials evaluating secondary prevention programs.**



Note that P.RE.COR. had 2 intervention groups and 1 control group. The control group data have been included only once in the total pooled estimate. Data for all trials are for the combined end point of nonfatal and fatal myocardial infarction, except for data from Campbell et al., 1998 (13); DeBusk et al., 1994 (17); Allison et al., 2000 (57); Bertie et al., 1992 (80); Carson et al., 1982 (73); Dugmore et al., 1999 (84); Erdman et al., 1986 (77); and Holmbäck et al., 1994 (82). These 8 trials collected data on nonfatal reinfarction rate. ETICA = Exercise Training Intervention after Coronary Angioplasty; M-HART = Montreal Heart Attack Readjustment Trial; NEHDP = National Exercise and Heart Disease Project; RR = risk ratio; SCRIP = Stanford Coronary Risk Intervention Project; WHO = World Health Organization.

mortality given the natural history of atherosclerotic CAD (that is, changes in coronary risk factors would not be expected to produce immediate improvements in atherosclerotic plaque stability or coronary artery diameter). The 2 trials that evaluated coronary angiographic lesions reported statistically significant regression rates in patients who adhered to comprehensive lifestyle modifications within 12 months even without statistically significant changes in metabolic profiles or medication use (22, 25). 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. Third, the incremental benefit of secondary prevention programs over usual care may be very small in the settings in which the trials were performed (where management in the "usual care" group was probably close to optimal already—as witnessed by the low control event rates). Secondary prevention programs are likely to be most beneficial in settings where usual care is less optimal.

Limitations

As with all systematic reviews, our study has some potential limitations. There was a lack of blinding in outcome ascertainment and insufficient detail on whether randomization was conducted properly or whether allocation concealment was achieved in most trials. These weaknesses arise from the primary data and, because all tend to result in overestimation of any treatment effect, these factors should be considered when interpreting our summary estimates. Our interpretations of programs were hampered by imprecise descriptions of the interventions and the lack of data to "open the black box" and determine the incremental benefits of the various components of each intervention. Finally, we could not make a definitive comment on the cost-effectiveness and economic effect of the programs tested in these trials because of the paucity of long-term data in all but 1 trial (88). Although some trials reported costs and outcomes after 1 year, this time horizon is undoubtedly too short to fully evaluate the cost-effectiveness of secondary prevention programs, and studies with 5- and 10-year time horizons are clearly needed.

Generalizability of Findings

Translation of the benefits demonstrated in these trials into clinical practice depends on suitable patients being referred to, accessing, and completing the secondary prevention programs. However, studies have consistently demonstrated that, even in publicly funded health care systems (where access is free), fewer than 50% of patients with CAD access rehabilitation programs (90–92). Moreover, those groups that are less likely to be referred, to attend, and to complete these programs are often those in greatest need (such as women, elderly people, low-income groups, and ethnic minorities) (90). Indeed, these groups were underrepresented in the trials published thus far (**Table 1**). While selection bias in trial enrollment always raises concerns about generalizability, elderly patients and women have been shown to derive similar benefits after secondary prevention programs as younger men (93–96).

Furthermore, as with any intervention proven efficacious in trial settings, applying this evidence to clinical practice, where adherence is often lower than that observed in trial participants, is a potential concern. While some people may conclude that our results should be viewed as a "best-case scenario" for the effect of secondary prevention programs, we disagree because trial participants assigned to the control groups also received better care than usual care. Indeed, while the incremental benefit of secondary prevention programs over usual care may be very small in the settings in which these trials were performed (where management in the "usual care" group was often close to optimal), secondary prevention programs will probably be more beneficial in other settings (perhaps more akin to the "real world" of current clinical practice) where usual care is less optimal.

Conclusion

In summary, although the interventions tested in these trials varied substantially and the trials enrolled highly selected study samples, secondary prevention programs improve processes of care, coronary risk factor profiles, and functional status or quality of life. Although the optimal mix of interventions, including frequency and duration, is unclear, secondary prevention programs also reduce subsequent MI and mortality in patients with coronary disease. While these programs reduce health care resource use and thus will probably reduce total health care expenditures, the costs of the program components and their cost-effectiveness have been inadequately evaluated thus far in the literature. Thus, while the implementation of secondary prevention programs on a wide scale for patients with coronary disease is justified, it should be accompanied by plans to rigorously evaluate long-term clinical and economic outcomes in participants and nonparticipants.

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