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Intensive Multifactorial Intervention for Stable Coronary Artery Disease

Optimal Medical Therapy in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) Trial

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Objectives This paper describes the medical therapy used in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial and its effect on risk factors.

Background Most cardiovascular clinical trials test a single intervention. The COURAGE trial tested multiple lifestyle and pharmacologic interventions (optimal medical therapy) with or without percutaneous coronary intervention in patients with stable coronary disease.

Methods All patients, regardless of treatment assignment, received equivalent lifestyle and pharmacologic interventions for secondary prevention. Most medications were provided at no cost. Therapy was administered by nurse case managers according to protocols designed to achieve predefined lifestyle and risk factor goals.

Results The patients (n = 2,287) were followed for 4.6 years. There were no significant differences between treatment groups in proportion of patients achieving therapeutic goals. The proportion of smokers decreased from 23% to 19% ($p = 0.025$), those who reported <7% of calories from saturated fat increased from 46% to 80% ($p < 0.001$), and those who walked ≥150 min/week increased from 58% to 66% ($p < 0.001$). Body mass index increased from 28.8 ± 0.13 kg/m^2 to 29.3 ± 0.23 kg/m^2 ($p < 0.001$). Appropriate medication use increased from pre-randomization to 5 years as follows: antiplatelets 87% to 96%; beta-blockers 69% to 85%; renin-angiotensin-aldosterone system inhibitors 46% to 72%; and statins 64% to 93%. Systolic blood pressure decreased from a median of 131 ± 0.49 mm Hg to 123 ± 0.88 mm Hg. Low-density lipoprotein cholesterol decreased from a median of 101 ± 0.83 mg/dl to 72 ± 0.88 mg/dl.

Conclusions Secondary prevention was applied equally and intensively to both treatment groups in the COURAGE trial by nurse case managers with treatment protocols and resulted in significant improvement in risk factors. Optimal medical therapy in the COURAGE trial provides an effective model for secondary prevention among patients with chronic coronary disease. (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; NCT00007657)
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Numerous large randomized clinical trials have demonstrated the efficacy of secondary prevention of coronary artery disease (CAD). Effective lifestyle interventions include smoking cessation (1), dietary intervention (2,3), and exercise (4,5). Effective pharmacologic interventions include aspirin (6), clopidogrel (6), beta-blockers (7,8), angiotensin converting enzyme inhibitors (9,10), and statins (11). Studies of control of blood pressure (12), low-density lipoprotein (LDL) cholesterol (11,13–16), and—less consistently—blood glucose (17–19) serve as the basis for current secondary prevention guidelines. Although most secondary prevention trials have tested the impact of a single risk factor intervention, the American College of Cardiology (ACC), the American Heart Association (AHA), and the Canadian Cardiovascular Society recommend comprehensive lifestyle and pharmacologic interventions with specific risk factor targets (20–22). Few clinical trials have included multiple risk factor intervention with behavioral and pharmacologic therapy as recommended by practice guidelines (23,24).

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Previous randomized trials that compared percutaneous coronary intervention (PCI) with medical therapy in patients with stable CAD failed to apply medical therapy that was multifaceted, aggressive, and provided equally to both treatment arms (25). The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial tested the impact of comprehensive intensive lifestyle and pharmacologic interventions (optimal medical therapy [OMT]) with or without PCI in 2,287 patients with stable CAD. There was no difference in the primary outcome of death or myocardial infarction (MI) during 4.6 years of follow-up (26), and the PCI group had a small but significant incremental benefit in angina control that disappeared by 36 months (27). This report analyzes the completeness and success of medical therapy in the COURAGE trial.

Abbreviations and Acronyms

ACC = American College of Cardiology
AHA = American Heart Association
CAD = coronary artery disease
HbA1c = hemoglobin A1c
LDL = low-density lipoprotein
MI = myocardial infarction
OMT = optimal medical therapy
PCI = percutaneous coronary intervention

Methods

The methods, patient eligibility criteria, baseline characteristics, and main results of the COURAGE trial have been described previously (26,28). Data management and analyses were performed solely by the data coordinating center with oversight of the trial executive committee, which had full access to the data and analyses and vouches for their accuracy and completeness. Patients were enrolled from June 1999 to January 2004, and the study closed on June 30, 2006.

Treatment. RISK FACTOR GOALS. Risk factor goals were based on the 1995 ACC/AHA secondary prevention guidelines (Table 1) (29), although the blood pressure and LDL cholesterol goals were more aggressive in anticipation of what might become practice guidelines by the end of the trial. The LDL cholesterol goal—60 to 85 mg/dl—was established by the steering committee in 1997 when the National Cholesterol Education Program goal for CAD patients was <100 mg/dl. In July 2004, the National Cholesterol Education Program established an optional LDL cholesterol goal of <70 mg/dl for "very high risk patients" (30), and the COURAGE steering committee adopted that goal for the remainder of the trial.

Table 1 Risk Factor Goals in the COURAGE Trial

Risk Factor	Goal	
Smoking	Cessation	
Total dietary fat/saturated fat	<30%/<7% of calories	
Dietary cholesterol	<200 mg/day	
Physical activity	30–45 min, moderate intensity 5 times/week	
Body weight by BMI	Initial BMI	Weight Loss Goal
	25–27.5 kg/m^2	BMI <25 kg/m^2
	>27.5 kg/m^2	10% relative weight loss
Blood pressure	<130/85 mm Hg (<130/80 mm Hg if diabetes or renal disease present)	
LDL cholesterol (primary goal)	60–85 mg/dl; the goal became <70 mg/dl in July 2004	
HDL cholesterol (secondary goal)	>40 mg/dl	
Triglyceride (secondary goal)	<150 mg/dl	
Diabetes	HbA1c <7.0%	

BMI = body mass index; COURAGE = Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

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Table 2 Pharmacologic Therapy in the COURAGE Trial

Medication Class	Drug	Indications
Antiplatelet agents	Aspirin (clopidogrel if aspirin not tolerated)	Aspirin for all subjects; clopidogrel for at least 1 month after PCI with bare-metal stent
ACE inhibitors	Lisinopril	Hypertension, heart failure, LVEF <40%; encouraged for all patients
Angiotensin receptor blocker	Losartan	Consider in individuals with hypertension or clinical evidence of heart failure or LVEF <40% who are intolerant of ACE inhibitors
Beta-blocker	Long-acting metoprolol	Hypertension/angina/post-MI
Thiazide diuretic	Any	Hypertension
Statin	Simvastatin	All subjects
Calcium antagonist	Amlodipine	Hypertension/angina
Long-acting nitrate	Isosorbide mononitrate	Angina
Niacin	extended-release niacin	LDL >85 mg/dl, HDL <40 mg/dl, TG >150 mg/dl on statin
Cholesterol absorption inhibitor	Ezetimibe	LDL >85 mg/dl on statin
Fibrate	Fenofibrate	TG >150 mg/dl on statin
Omega-3 fatty acids	Various formulations	TG >150 mg/dl on statin

ACE = angiotensin converting enzyme; LVEF = left ventricular ejection fraction; MI = myocardial infarction; TG = triglycerides; other abbreviations as in Table 1.

CASE MANAGEMENT AND LIFESTYLE INTERVENTIONS. Each patient met with a nurse case manager at baseline and 1, 2, 3, and 6 months, then every 6 months until the study ended. At each visit lifestyle and medication adherence were assessed, and body weight, blood pressure, fasting glucose, and lipid values were measured. Lipids were analyzed in a core laboratory; glucose and hemoglobin A1c (HbA1c) were analyzed locally. Diabetes was defined as having a history of diabetes or taking hypoglycemic medication at baseline. The HbA1c was collected at baseline in most patients but during follow-up only in patients defined as having diabetes at baseline.

Lifestyle intervention was delivered equally to both treatment groups at each visit. Case managers were trained before trial launch and at annual meetings to assess patient behaviors and provide behavioral counseling focused on smoking cessation, nutrition, physical activity, and weight management. Each patient's readiness to change health-related behaviors was assessed with a system developed by the Patient-centered Assessment and Counseling for Exercise and nutrition (PACE) project (31). Lifestyle counseling was standardized across sites with written materials developed by the PACE project, including scripts to instruct patients regarding lifestyle change (32). These materials were designed for brief, practical, focused interventions by a physician or nurse in an outpatient setting. A more detailed description of the lifestyle intervention and training for nurse case managers is provided in the Online Appendix.

The behavioral counseling was based on Social Cognitive Theory (33) and the Transtheoretical Model (34). For each behavioral risk factor, patients were categorized into pre-contemplators (those who do not wish to change), contemplators (those who are willing to change), and actives (those who are already meeting the recommended goal). Nurse case managers were trained to provide messages tailored to the patient's stage of change for each behavioral risk factor. Each stage-based message focused on known mediators of behavior change (e.g., goal setting, increasing social support, and self-efficacy). Print-based patient materials were used to assess and counsel patients (see examples in the Online Appendix).

Smokers who were pre-contemplators were given advice and rationale to quit. Smokers who were contemplators were provided with stage-based counseling, pharmacologic therapy, and/or referral to a formal smoking cessation program.

Diet was assessed with MEDFICTS, a questionnaire recommended by the National Cholesterol Education Program to assess dietary fat (35,36). The questionnaire can be self-administered in 3 to 5 min and scored by a health care provider in 2 min. Nutritional counseling was designed to achieve the dietary guidelines of the National Cholesterol Education Program (35,37). With the same stage-based approach, patients were advised to reduce calories, total fat, and saturated fat and increase consumption of fruits and vegetables.

Subjects were counseled to gradually increase moderate-intensity physical activity to 30 to 45 min 5 times/week. Typically this was moderate-intensity walking. Counseling was tailored for weight loss if needed.

PHARMACOLOGIC THERAPY. Pharmacologic therapy conformed with ACC/AHA guidelines for secondary prevention and management of angina (20,21). All patients received the same medical therapy for secondary prevention, regardless of treatment assignment (Table 2). The intensity of anti-anginal therapy varied according to angina severity. Patients received medications at no cost except for aspirin, thiazide diuretics, fenofibrate, and omega-3 fatty acids.

Among patients randomized to PCI with no history of MI, an attempt was made to discontinue long-acting metoprolol, amlodipine, and/or isosorbide mononitrate if they had no angina 3 to 6 months after PCI. Patients undergoing PCI received aspirin and clopidogrel according to prevailing treatment guidelines (38). If a patient was not at blood pressure or lipid goals, pharmacologic therapy was adjusted according to study protocols (see treatment algorithms in the Online Appendix).

For LDL cholesterol control, all patients were prescribed simvastatin according to a dosing algorithm. If simvastatin was not tolerated or was not effective, patients were free to use other statins. Extended-release niacin or ezetimibe was added if needed to reach goal. After the LDL cholesterol goal was achieved, an attempt was made to raise high-density lipoprotein cholesterol above 40 mg/dl and lower triglycerides below 150 mg/dl with lifestyle change, extended-release niacin, fibrates, or omega-3 fatty acids.

ADHERENCE TO MEDICATIONS. Adherence to medical therapy was assessed by the 4-item self-report scale developed by Morisky et al. (39). Scores range from 0 to 4; higher scores indicate worse adherence. A score of 0 to 1 was defined as adherent.

PATIENT SATISFACTION. We assessed patient satisfaction at baseline and 1, 3, 6, and 12 months and annually thereafter with the Seattle Angina Questionnaire Treatment Satisfaction scale, which ranges from 0 to 100 (40). Higher scores indicate greater patient satisfaction with therapy.

Statistical analysis. The data are presented as percentage of individuals in each treatment group. Continuous variables are described as median ± standard error of the median (41). Missing data were not included in the calculation of medians or percentages. For comparisons between values at baseline and 5 years, McNemar's test was used for discrete variables, and Wilcoxon signed rank test was used for continuous variables (lifestyle changes, therapeutic targets). Proportions of patients taking various medications assigned to the PCI group compared with the OMT group are compared at each visit with the chi-square test (pharmacologic therapy). Comparisons of continuous variables between treatment groups at each visit were made with the median test (therapeutic targets). For over-time comparisons between treatments, sequential differences were modeled with baseline, interval, time, and (time)2 in addition to treatment (therapeutic targets, treatment satisfaction). The intention-to-treat principle was used in all analyses.

Results

Baseline characteristics. Baseline characteristics were similar between groups (Table 3).

Lifestyle change. In aggregate (both treatment groups combined), smoking decreased from 23% to 19% ($p = 0.025$). The proportion of subjects who reported the dietary goal of <7% of calories from saturated fat increased from 46% to 80% ($p < 0.001$). The proportion of subjects who achieved the physical activity goal in the form of walking ≥150 min/week increased from 58% to 66% ($p < 0.001$). When analyzed by treatment group, there were no significant differences between groups at any time for any lifestyle variables (Fig. 1). Body mass index increased from 28.8 ± 0.13 kg/m^2 at baseline to 29.3 ± 0.23 kg/m^2 at 5 years ($p \leq 0.001$).

Table 3 Baseline Clinical and Demographic Characteristics

Characteristic	PCI + OMT (n = 1,149)	OMT (n = 1,138)	p Value
Age, yrs (mean ± SD)*	61.5 ± 10.1	61.8 ± 9.7	0.54
Sex†			
Male	979 (85)	968 (85)	0.95
Female	169 (15)	169 (15)	
Race or ethnic group†			
White	988 (86)	975 (86)	0.64
Black	57 (5)	57 (5)	
Hispanic	68 (6)	58 (5)	
Other	35 (3)	47 (4)	
History†			
Diabetes	367 (32)	399 (35)	0.12
Hypertension	757 (66)	764 (67)	0.53
Congestive heart failure	57 (5)	51 (5)	0.59
Cerebrovascular disease	100 (9)	102 (9)	0.83
Myocardial infarction	437 (38)	439 (39)	0.80
Prior PCI	174 (15)	185 (16)	0.49
CABG	124 (11)	124 (11)	0.94
Risk factors‡			
Systolic blood pressure (mm Hg)	131 ± 0.77	130 ± 0.66	0.36
Diastolic blood pressure (mm Hg)	74 ± 0.33	74 ± 0.33	0.94
Total cholesterol (mg/dl)	172 ± 1.37	177 ± 1.41	0.01
HDL cholesterol (mg/dl)	39 ± 39	39 ± 0.37	0.97
LDL cholesterol (mg/dl)	100 ± 1.17	102 ± 1.22	0.18
TG (mg/dl)	143 ± 2.96	149 ± 3.03	0.12
BMI (kg/m^2)	28.7 ± 0.18	28.9 ± 0.17	0.51
HbAlc in diabetic subjects (%)‡	6.9 ± 0.1	7.1 ± 0.1	0.18
Current smoker†	260 (23)	259 (23)	0.89
AHA Step 2 diet†	626 (55)	613 (54)	0.54
Moderate activity†§	290 (25)	279 (25)	0.72

*Variables were compared with the *t* test. †Variables were compared with the chi-square or Wilcoxon rank sum test, n (%). ‡Variables were compared with the median test (median ± SE). §At least 30 to 45 min of moderate activity 5 times/week or vigorous activity 3 times/week.

AHA = American Heart Association; CABG = coronary artery bypass graft surgery; other abbreviations as in Tables 1 and 2.

Pharmacologic therapy, persistence, and adherence. Figure 2 shows medication use during the trial. In aggregate, medication use increased from baseline to 5 years as follows: antiplatelets 87% to 96%; beta-blockers 69% to 85%; and renin-angiotensin-aldosterone system inhibitors 46% to 72%. Before randomization, 31% of patients took calcium channel blockers. By 6 months, 40% of the PCI group and 50% of the OMT group took these agents ($p < 0.001$), and this difference persisted though 5 years of follow-up (42% vs. 52%, respectively, $p = 0.004$). Before randomization, 58% took long-acting nitrates. By 6 months, 55% of the PCI group and 71% of the OMT group took these agents ($p < 0.001$); at 5 years, the proportions were

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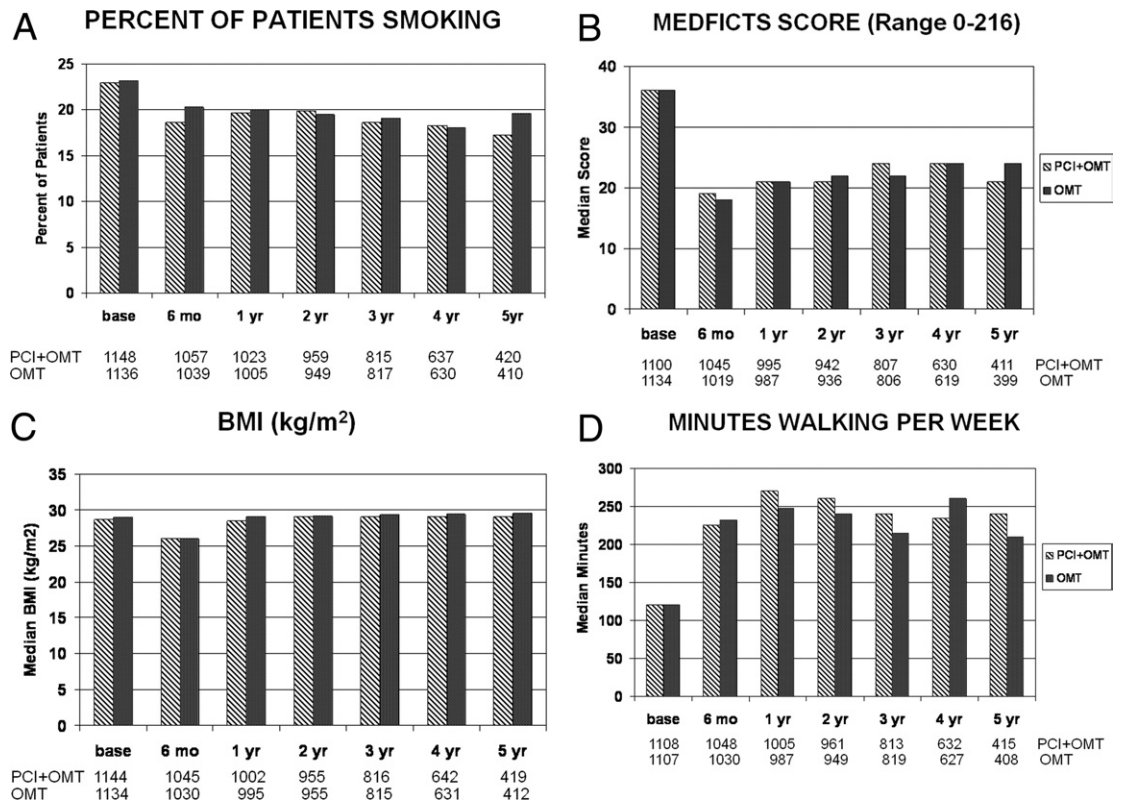

Figure 1 **Lifestyle and Weight Variables During the Trial**

A MEDFICTS score <40 indicates <7% of calories from saturated fat. There were no significant differences between treatment groups for any of the comparisons at any time. The chi-square test was used to compare smoking at each time point, and the median test was used for the other variables. BMI = body mass index; OMT = optimal medical therapy; PCI = percutaneous coronary intervention.

40% versus 57%, respectively ($p < 0.001$). Statin use rose from 64% to 93%, niacin use rose from <1% to 18%, and ezetimibe use rose from 0% to 33% (at the trial onset, ezetimibe was not approved for use). The use of any lipid medication rose from 67% to 97%.

At baseline, 51% of PCI group and 51% of OMT group patients took the combination of aspirin, beta-blocker, and lipid drug therapy. By 5 years, the proportions rose to 79% and 80%, respectively. At baseline, 27% of PCI group and 29% of OMT group patients took aspirin, beta-blocker, lipid lowering, and renin-angiotensin-aldosterone system inhibitor therapy. By 5 years, the proportions were 55% and 51%, respectively. No between-group differences were statistically significant.

At 6 months, average self-reported adherence to prescribed medications was 97% in both groups; adherence remained at 95% throughout the trial, with no significant difference between groups.

Diabetes and metabolic syndrome. At baseline, 845 patients (37%) without the diagnosis of diabetes had fasting glucose <100 mg/dl, 635 (28%) had impaired fasting glucose (fasting glucose 100 to 125 mg/dl), and 766 (34%) had diabetes. During the study, 191 patients developed diabetes, 97 in the PCI group and 94 in the OMT group. At baseline, 59% of patients had metabolic syndrome.

Therapeutic targets achieved. Figure 3 presents the changes in blood pressure, lipids, and HbA1c. Median systolic blood pressure was 131 ± 0.49 mm Hg at study entry and 123 ± 0.88 mm Hg at 5 years ($p < 0.001$). Before randomization, median LDL cholesterol was 101 ± 0.83 mg/dl. At 6 months the median LDL cholesterol was 82 ± 0.62 mg/dl and declined to 72 ± 0.88 mg/dl at 5 years ($p < 0.001$). There were no significant intergroup differences in LDL cholesterol levels at any visit during the study. During the trial high-density lipoprotein cholesterol rose from 39 ± 0.3 mg/dl to 41 ± 0.5 mg/dl ($p < 0.001$) and triglycerides fell from 146 ± 2 mg/dl to 126 ± 3 mg/dl ($p < 0.001$). Among patients with diabetes, HbA1c was 7.0 ± 0.1% at baseline and 7.1 ± 0.01% at 5 years ($p = 1.0$).

Figure 4 shows the percentage of subjects who achieved blood pressure, lipid, and HbA1c goals. At randomization, 43% of patients were at the systolic blood pressure goal of <130 mm Hg; this increased to approximately 60% by 3 years and remained unchanged through the rest of the trial in both groups. At randomization, 28% of patients had

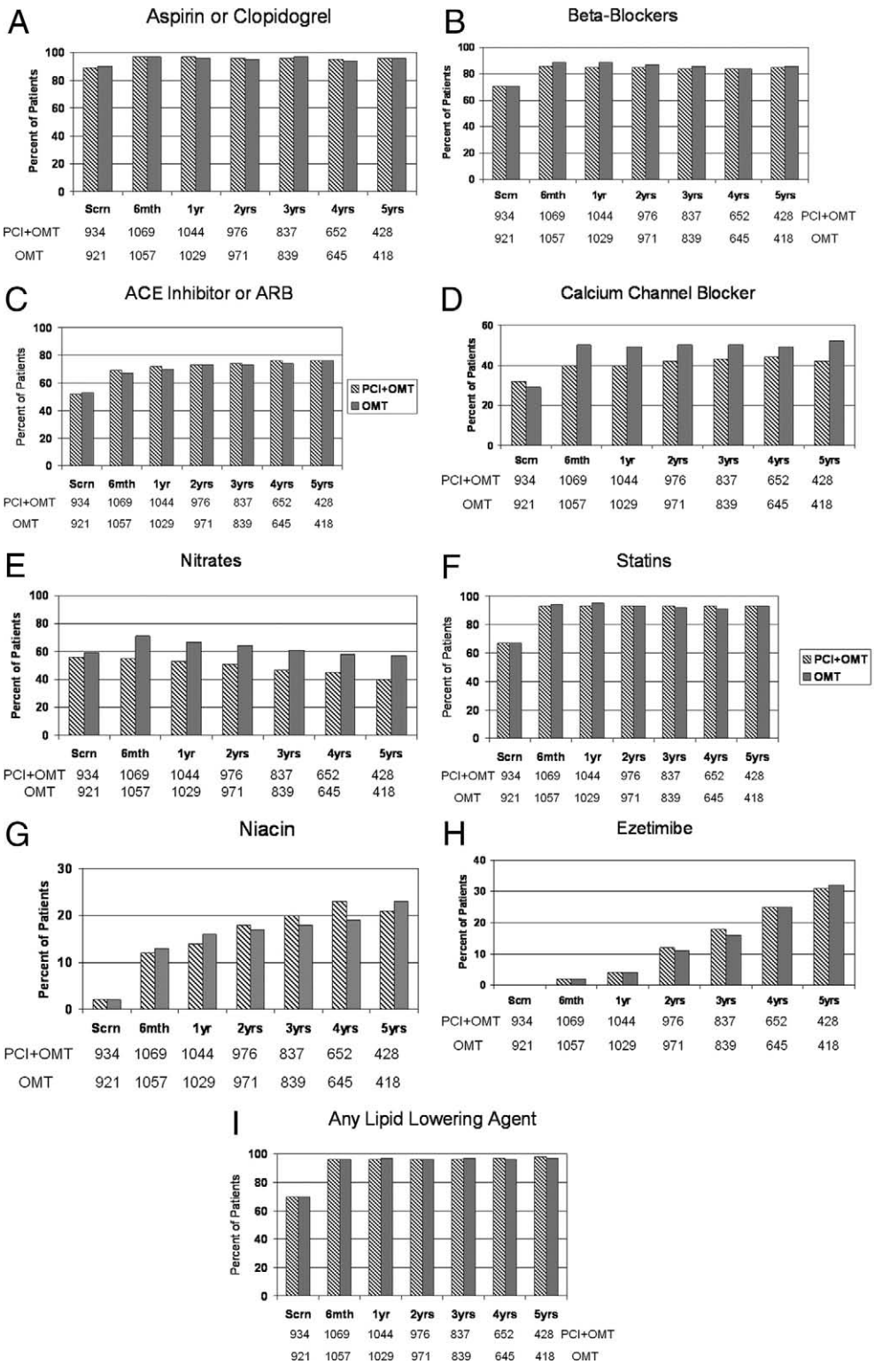

Figure 2 **Percent of Patients Taking Medications During the Trial**

Before randomization medications were not collected on the first 432 patients who enrolled. With McNemar's test, $p < 0.001$ for all drug classes comparing baseline and 5 years except calcium channel blockers ($p = 0.01$). With the chi-square test there is no difference between treatment groups at any follow-up visit for any drug classes except nitrates ($p < 0.001$ for all visits) and calcium channel blockers ($p < 0.001$ until 3 years when $p = 0.005$, 4 years $p = 0.06$, and 5 years $p = 0.004$). ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; other abbreviations as in Figure 1.

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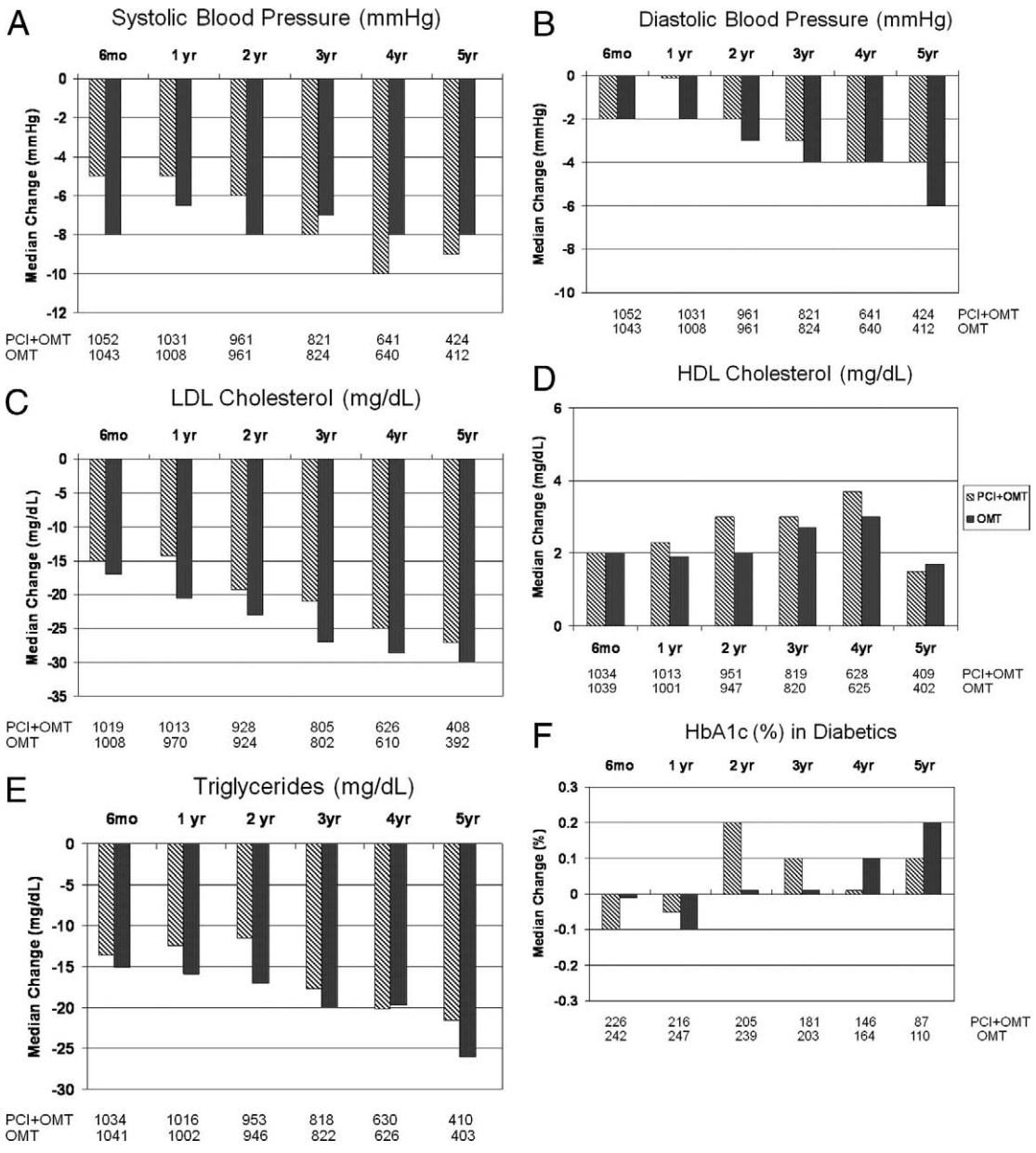

Figure 3 **Changes in Risk Factors During the Trial**

There was no significant treatment effect for any of the variables over the course of the trial with the modeling procedure described in the statistical methods. Hemoglobin A1c (HbA1c; glycated hemoglobin) is reported only for those patients with diabetes at baseline. HDL = high-density lipoprotein; LDL = low-density lipoprotein; other abbreviations as in Figure 1.

LDL cholesterol levels at study goal (≤85 mg/dl); by 5 years, this proportion had increased to 70%. With the more aggressive LDL cholesterol target of <70 mg/dl proposed in 2004 (30), 14% of patients were below this target at randomization, and 46% achieved this target by 5 years.

Patient adherence and risk factor control. During the first year, 4% of patients in each treatment group missed follow-up visits; during subsequent years, the proportion of patients who missed clinic visits gradually increased. By year 5, 12% of the PCI group and 10% of the OMT group had missed at least 1 visit during the trial (see the Online Appendix). Patients who attended every visit had better systolic blood pressure and LDL cholesterol-lowering than patients who missed visits (see Figs. A and B in the Online Appendix). There were no significant differences between treatment groups. Medication-adherent patients had lower systolic blood pressure and LDL cholesterol than patients who were not adherent (see Figs. C and D in the Online Appendix).

Treatment satisfaction score. The Seattle Angina Questionnaire Treatment Satisfaction score was 88 for the PCI

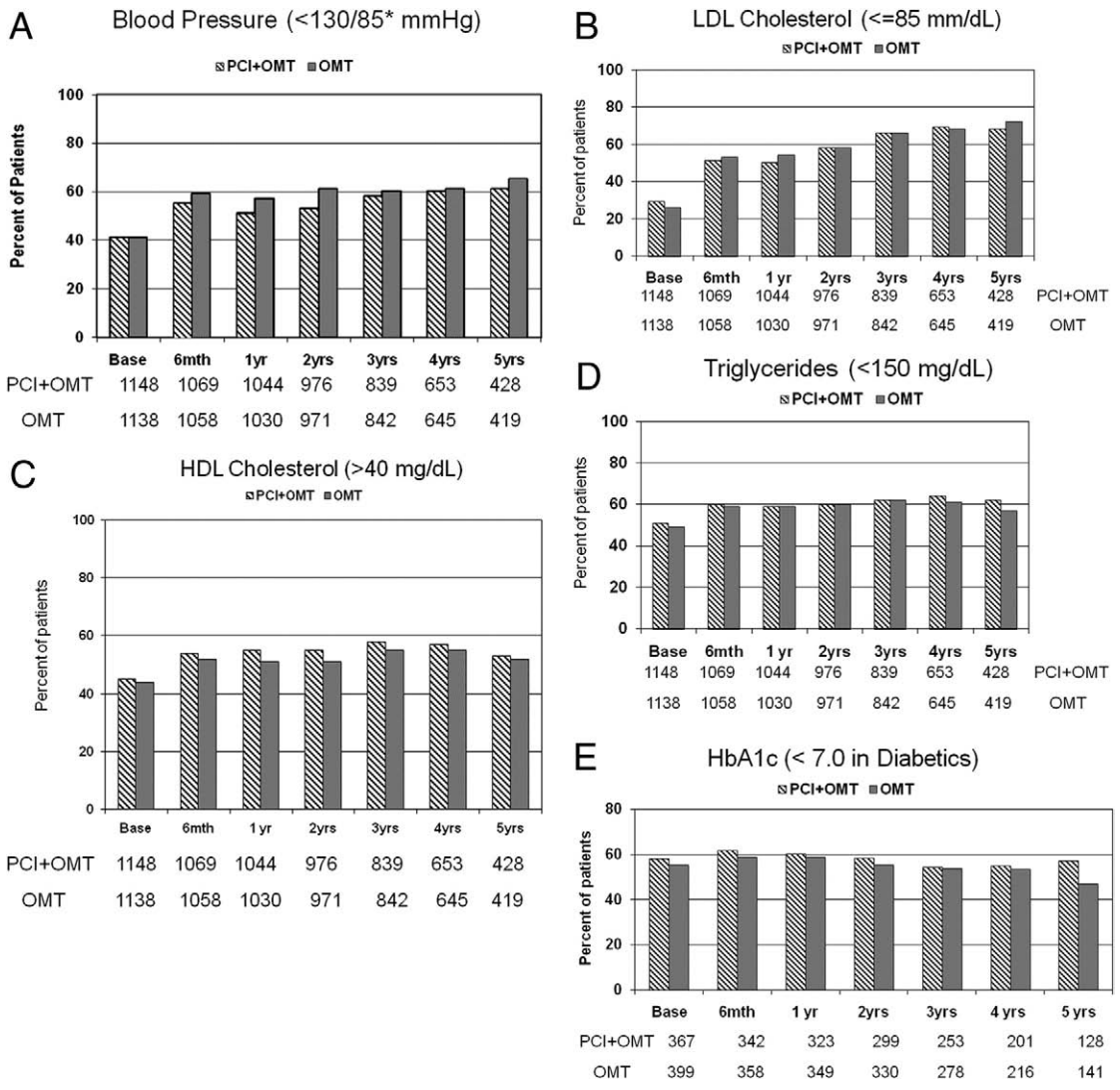

Figure 4 **Percent of Patients at Target During the Trial**

The HbA1c is reported only for those patients with diabetes at baseline. With the chi-square test, significantly more OMT patients were at blood pressure goal at 6 months ($p = 0.03$), 1 year ($p = 0.01$), and 2 years ($p = 0.003$) and at LDL goal at 1 year ($p = 0.04$). There were no significant differences between treatment groups for any other comparisons at any time. *Blood pressure target was <130/80 mm Hg if diabetes or renal disease was present. Abbreviations as in Figures 1 and 3.

group and 86 for the OMT group at randomization. The scores gradually increased during the study, and at 5 years, they were 92 ($p = 0.08$) and 94 ($p = 0.001$), respectively, indicating that patients were satisfied with their treatment and their satisfaction increased during the trial. There were no differences between treatment groups over time ($p = 0.91$).

Discussion

Unlike previous trials of revascularization versus medical therapy, the COURAGE trial applied a multifaceted strategy of intensive secondary prevention to both treatment arms. We succeeded in achieving multiple therapeutic targets and in applying OMT equally to both treatment groups. Moreover, this aggressive treatment strategy was associated with improved treatment satisfaction. Smoking, dietary fat intake, and physical activity improved. Although some behavioral improvements were modest, they were observed over several years and achieved with simple counseling techniques that can be replicated. We were not successful in assisting people with weight loss.

Self-reported long-term adherence to drug therapy and risk factor control in the COURAGE trial far exceeded what has been reported in surveys of CAD outpatients. The EUROASPIRE II (European Action on Secondary and Primary Prevention by Intervention to Reduce Events) trial, a European survey of CAD patients, found use of aspirin to

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be 86%, use of beta-blockers to be 63%, and use of lipid-lowering therapy to be 61% (42). Newby et al. (43) reported consistent use of aspirin to be 71%, use of beta-blockers to be 46%, use of lipid-lowering therapy to be 44%, and use of the combination of aspirin, beta-blockers, and lipid-lowering therapy to be 21%. The corresponding numbers at the end of the COURAGE trial were substantially higher: aspirin, 96%; beta-blockers, 85%; lipid-lowering therapy, 97%; and all 3 drug classes, 80%. Our success might be attributable to several factors. First, clinical trial volunteers are more likely to adhere to drug regimens. Second, drugs were provided free of charge. Third, treatment protocols were used to provide standardized care. Fourth, nurses who delivered the intervention were trained to improve lifestyle and medication adherence, shown previously to improve success in risk-factor control (23,44,45).

In the EUROASPIRE III trial, 18% of CAD patients smoked, 39% achieved blood pressure <140/90 mm Hg in nondiabetic patients or <130/80 mm Hg in diabetic patients, and 54% attained total cholesterol <175 mg/dl (46). By the end of the COURAGE trial, 19% of patients smoked, 61% achieved our more stringent blood pressure goals, and 70% achieved our more aggressive lipid goal (LDL cholesterol ≤85 mg/dl). Hence, with the exceptions of smoking (where our positive effect was modest) and weight loss, we were quite successful in achieving and maintaining ambitious risk-factor goals in high proportions of patients. This endorses a secondary prevention model with nurse case managers with simple behavior assessment and counseling tools and treatment algorithms to effect positive lifestyle change, appropriate use of medications, and titration of medications to achieve treatment targets. This method is consistent with guidelines from the ACC, AHA, and the Canadian Cardiovascular Society (20,21) and is responsive to what EUROASPIRE investigators describe as "a compelling need for more effective lifestyle management of patients with coronary heart disease" (46).

Study limitations. The design of the COURAGE trial precludes the opportunity to measure the impact of OMT on death, MI, or other major cardiovascular events, because OMT was provided equally to both treatment arms. With evidence from prior clinical trials, before the initiation of the COURAGE trial we projected a 3-year primary event rate of 16.4% in the PCI group and 21.0% in the OMT group (relative difference of 22%, absolute difference of 4.6%). We observed a 4.6-year primary event rate of 19.0% in the PCI group and 18.5% in the OMT group (26). Hence, we overestimated the event rate by a substantial margin. In part, this might have been due to the impact of OMT. The medical therapy delivered in the COURAGE trial has been criticized as not achievable in the real world (47). We cannot assess to what extent free medication influenced behavior, but we acknowledge that medication adherence and persistence would probably have declined if patients had been required to share the cost of medications (48–50). However, the key medications used in the COURAGE trial are all available in more affordable generic forms. Furthermore, OMT was delivered by nurses who were provided with simple protocols and a modest amount of training to deliver behavioral counseling. The frequency of patient contact mandated by the protocol was within the norms of conventional practice in the U.S. and Canada. Hence, this quality of care is feasible in typical outpatient practice.

Conclusions

Medical therapy in the COURAGE trial was protocol-driven, delivered by nurse case managers, comprehensive in scope, intensive in its application, and provided equally to patients whether or not they received PCI. Significant behavior change was achieved, self-reported medication adherence and persistence was high, and therapeutic targets were reached in large proportions of patients. The delivery of OMT in the COURAGE trial is a model for secondary prevention in practice, with potential policy implications regarding the use of nurse case managers and free medications to optimally manage patients with chronic CAD.

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Key Words: coronary disease ■ medical therapy ■ risk factors ■ secondary prevention.

APPENDIX

For a detailed description of training for nurse case managers to perform lifestyle assessment and behavioral counseling; samples of PACE materials; COURAGE treatment algorithms; and an analysis of clinic visit attendance, medication adherence, and risk factor control, please see the online version of this article.