

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

APRIL 12, 2007

VOL. 356 NO. 15

Optimal Medical Therapy with or without PCI for Stable Coronary Disease

William E. Boden, M.D., Robert A. O'Rourke, M.D., Koon K. Teo, M.B., B.Ch., Ph.D., Pamela M. Hartigan, Ph.D., David J. Maron, M.D., William J. Kostuk, M.D., Merrill Knudtson, M.D., Marcin Dada, M.D., Paul Casperson, Ph.D., Crystal L. Harris, Pharm.D., Bernard R. Chaitman, M.D., Leslee Shaw, Ph.D., Gilbert Gosselin, M.D., Shah Nawaz, M.D., Lawrence M. Title, M.D., Gerald Gau, M.D., Alvin S. Blaustein, M.D., David C. Booth, M.D., Eric R. Bates, M.D., John A. Spertus, M.D., M.P.H., Daniel S. Berman, M.D., G.B. John Mancini, M.D., and William S. Weintraub, M.D., for the COURAGE Trial Research Group*

ABSTRACT

BACKGROUND

In patients with stable coronary artery disease, it remains unclear whether an initial management strategy of percutaneous coronary intervention (PCI) with intensive pharmacologic therapy and lifestyle intervention (optimal medical therapy) is superior to optimal medical therapy alone in reducing the risk of cardiovascular events.

METHODS

We conducted a randomized trial involving 2287 patients who had objective evidence of myocardial ischemia and significant coronary artery disease at 50 U.S. and Canadian centers. Between 1999 and 2004, we assigned 1149 patients to undergo PCI with optimal medical therapy (PCI group) and 1138 to receive optimal medical therapy alone (medical-therapy group). The primary outcome was death from any cause and nonfatal myocardial infarction during a follow-up period of 2.5 to 7.0 years (median, 4.6).

RESULTS

There were 211 primary events in the PCI group and 202 events in the medical-therapy group. The 4.6-year cumulative primary-event rates were 19.0% in the PCI group and 18.5% in the medical-therapy group (hazard ratio for the PCI group, 1.05; 95% confidence interval [CI], 0.87 to 1.27; $P=0.62$). There were no significant differences between the PCI group and the medical-therapy group in the composite of death, myocardial infarction, and stroke (20.0% vs. 19.5%; hazard ratio, 1.05; 95% CI, 0.87 to 1.27; $P=0.62$); hospitalization for acute coronary syndrome (12.4% vs. 11.8%; hazard ratio, 1.07; 95% CI, 0.84 to 1.37; $P=0.56$); or myocardial infarction (13.2% vs. 12.3%; hazard ratio, 1.13; 95% CI, 0.89 to 1.43; $P=0.33$).

CONCLUSIONS

As an initial management strategy in patients with stable coronary artery disease, PCI did not reduce the risk of death, myocardial infarction, or other major cardiovascular events when added to optimal medical therapy. (ClinicalTrials.gov number, NCT00007657.)

Affiliations for all authors are listed in the Appendix. Address reprint requests to Dr. Boden at the Division of Cardiology, Buffalo General Hospital, 100 High St., Buffalo, NY 14203, or at wboden@kaleidahealth.org.

*Members of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial are listed in the Appendix and in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

This article (10.1056/NEJMoa070829) was published at www.nejm.org on March 26, 2007.

N Engl J Med 2007;356:1503-16.
Copyright © 2007 Massachusetts Medical Society.

DURING THE PAST 30 YEARS, THE USE OF percutaneous coronary intervention (PCI) has become common in the initial management strategy for patients with stable coronary artery disease in North America, even though treatment guidelines advocate an initial approach with intensive medical therapy, a reduction of risk factors, and lifestyle intervention (known as optimal medical therapy).^{1,2} In 2004, more than 1 million coronary stent procedures were performed in the United States,³ and recent registry data indicate that approximately 85% of all PCI procedures are undertaken electively in patients with stable coronary artery disease.⁴ PCI reduces the incidence of death and myocardial infarction in patients who present with acute coronary syndromes,⁵⁻¹⁰ but similar benefit has not been shown in patients with stable coronary artery disease.¹¹⁻¹⁵ This issue has been studied in fewer than 3000 patients,¹⁶ many of whom were treated before the widespread use of intracoronary stents and current standards of medical management.¹⁷⁻²⁸

Although successful PCI of flow-limiting stenoses might be expected to reduce the rate of death, myocardial infarction, and hospitalization for acute coronary syndromes, previous studies have shown only that PCI decreases the frequency of angina and improves short-term exercise performance.^{11,12,15} Thus, the long-term prognostic effect of PCI on cardiovascular events in patients with stable coronary artery disease remains uncertain. Our study, the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, was designed to determine whether PCI coupled with optimal medical therapy reduces the risk of death and nonfatal myocardial infarction in patients with stable coronary artery disease, as compared with optimal medical therapy alone.

METHODS

STUDY DESIGN

The methods we used in the trial have been described previously.^{29,30} Sponsorship and oversight of the trial were provided by the Department of Veterans Affairs Cooperative Studies Program. Additional funding was provided by the Canadian Institutes of Health Research. Supplemental corporate support from several pharmaceutical companies included funding and in-kind support. All

support from the pharmaceutical industry consisted of unrestricted research grants payable to the Department of Veterans Affairs.

The study protocol was approved by the human rights committee at the coordinating center and by the local institutional review board at each participating center. An independent data and safety monitoring board oversaw the conduct, safety, and efficacy of the trial. Data management and statistical analyses were performed solely by the data coordinating center with oversight by the trial executive committee, whose members, after unblinding, had full access to the data and vouch for the accuracy and completeness of the data and the analyses. The companies that provided financial support, products, or both had no role in the design, analysis, or interpretation of the study.

STUDY POPULATION

Patients with stable coronary artery disease and those in whom initial Canadian Cardiovascular Society (CCS) class IV angina subsequently stabilized medically were included in the study. Entry criteria included stenosis of at least 70% in at least one proximal epicardial coronary artery and objective evidence of myocardial ischemia (substantial changes in ST-segment depression or T-wave inversion on the resting electrocardiogram or inducible ischemia with either exercise or pharmacologic vasodilator stress) or at least one coronary stenosis of at least 80% and classic angina without provocative testing. Exclusion criteria included persistent CCS class IV angina, a markedly positive stress test (substantial ST-segment depression or hypotensive response during stage 1 of the Bruce protocol), refractory heart failure or cardiogenic shock, an ejection fraction of less than 30%, revascularization within the previous 6 months, and coronary anatomy not suitable for PCI. A detailed description of the inclusion and exclusion criteria is included in the Supplementary Appendix (available with the full text of this article at www.nejm.org). Patients who were eligible for the study underwent randomization after providing written informed consent.

TREATMENT

Patients were randomly assigned to undergo PCI and optimal medical therapy (PCI group) or optimal medical therapy alone (medical-therapy group). A permuted-block design was used to generate

random assignments within each study site along with previous coronary-artery bypass grafting (CABG) as a stratifying variable. All patients received antiplatelet therapy with aspirin at a dose of 81 to 325 mg per day or 75 mg of clopidogrel per day, if aspirin intolerance was present. Patients undergoing PCI received aspirin and clopidogrel, in accordance with accepted treatment guidelines and established practice standards. Medical anti-ischemic therapy in both groups included long-acting metoprolol, amlodipine, and isosorbide mononitrate, alone or in combination, along with either lisinopril or losartan as standard secondary prevention. All patients received aggressive therapy to lower low-density lipoprotein (LDL) cholesterol levels (simvastatin alone or in combination with ezetimibe) with a target level of 60 to 85 mg per deciliter (1.55 to 2.20 mmol per liter). After the LDL cholesterol target was achieved, an attempt was made to raise the level of high-density lipoprotein (HDL) cholesterol to a level above 40 mg per deciliter (1.03 mmol per liter) and lower triglyceride to a level below 150 mg per deciliter (1.69 mmol per liter) with exercise, extended-release niacin, or fibrates, alone or in combination.

In patients undergoing PCI, target-lesion revascularization was always attempted, and complete revascularization was performed as clinically appropriate. Success after PCI as seen on angiography was defined as normal coronary-artery flow and less than 50% stenosis in the luminal diameter after balloon angioplasty and less than 20% after coronary stent implantation, as assessed by visual estimation of the angiograms before and after the procedure. Clinical success was defined as angiographic success plus the absence of in-hospital myocardial infarction, emergency CABG, or death. Drug-eluting stents were not approved for clinical use until the final 6 months of the study, so few patients received these intracoronary devices.

CLINICAL OUTCOME

Clinical outcome was adjudicated by an independent committee whose members were unaware of treatment assignments. The primary outcome measure was a composite of death from any cause and nonfatal myocardial infarction. Secondary outcomes included a composite of death, myocardial infarction, and stroke and hospitalization for unstable angina with negative biomarkers. The an-

gina status of patients was assessed according to the CCS classification during each visit. Further analyses of other secondary outcomes — including quality of life, the use of resources, and cost-effectiveness — are being conducted but have not yet been completed.

The prespecified definition of myocardial infarction (whether periprocedural or spontaneous) required a clinical presentation consistent with an acute coronary syndrome and either new abnormal Q waves in two or more electrocardiographic leads or positive results in cardiac biomarkers. Silent myocardial infarction, as detected by abnormal Q waves, was confirmed by a core laboratory and was also included as an outcome of myocardial infarction.

STATISTICAL ANALYSIS

We projected composite 3-year event rates of 21.0% in the medical-therapy group and 16.4% in the PCI group (relative difference, 22%) during a follow-up period of 2.5 to 7.0 years. We also incorporated assumptions about crossover between study groups and loss to follow-up.³¹ We estimated that the enrollment of 2270 patients would provide a power of 85% to detect the anticipated difference in the primary outcome at the 5% two-sided level of significance. A detailed description of the sample-size calculation is included in the Supplementary Appendix.

Estimates of the cumulative event rate were calculated by the Kaplan–Meier method,³² and the primary efficacy of PCI, as compared with optimal medical therapy, was assessed by the stratified log-rank statistic.³³ The treatment effect, as measured by the hazard ratio and its associated 95% confidence interval (CI), was estimated with the use of the Cox proportional-hazards model.³⁴ Data for patients who were lost to follow-up were censored at the time of the last contact. Analyses were performed according to the intention-to-treat principle. Categorical variables were compared by use of the chi-square test or the Wilcoxon rank-sum test, and continuous variables were compared by use of the Student t-test. Adjusted analysis of the primary outcome was performed with the use of a Cox proportional-hazards regression model with eight preidentified covariates of interest — age, sex, race, previous myocardial infarction, extent or distribution of angiographic coronary artery disease, ejection frac-

tion, presence or absence of diabetes, and health care system (Veterans Affairs or non-Veterans Affairs facility in the United States, or a Canadian facility) — as well as the stratifying variable of previous CABG. All other comparisons were unadjusted. A level of significance of less than 0.01 was used for all subgroup analyses and interactions.

RESULTS

BASELINE CHARACTERISTICS AND ANGIOGRAPHIC DATA

Between June 1999 and January 2004, a total of 2287 patients were enrolled in the trial at 50 U.S. and Canadian centers (Fig. 1). Of these patients, 1149 were randomly assigned to the PCI group and 1138 to the medical-therapy group. The baseline characteristics of the patients were recently published³⁵ and were similar in the two groups (Table 1). The median time from the first episode of angina before randomization was 5 months (median, three episodes per week, with exertion or at rest), and 58% of patients had CCS class II or III angina. A total of 2168 patients (95%) had objective evidence of myocardial ischemia, whereas the remaining 119 patients with classic angina (CCS class III) and severe coronary stenoses did not undergo ischemia testing (56 in the PCI group and 63 in the medical-therapy group). Among patients who underwent myocardial perfusion imaging at baseline, 90% had either single (23%) or multiple (67%) reversible defects for inducible ischemia. Two thirds of the patients had multivessel coronary artery disease.

Of the 1149 patients in the PCI group, 46 never underwent a procedure because the patient either declined treatment or had coronary anatomy unsuitable for PCI, as determined on clinical reassessment. In 27 patients (2%), the operator was unable to cross any lesions. PCI was attempted for 1688 lesions in 1077 patients, of whom 1006 (94%) received at least one stent. In the stent group, 590 patients (59%) received one stent and 416 (41%) more than one stent. Drug-eluting stents were used in 31 patients. On average, stenosis in the luminal diameter, as evaluated on visual assessment of angiograms, was reduced from a mean (\pm SD) of $83\pm 14\%$ to $31\pm 34\%$ in the 244 lesions not treated with stents and from $82\pm 12\%$ to $1.9\pm 8\%$ in the 1444 lesions treated with stents.

After PCI, successful treatment as seen on angiography was achieved in 1576 of 1688 lesions (93%), and clinical success (i.e., all lesions successfully dilated and no in-hospital complications) was achieved in 958 of 1077 patients (89%).

MEDICATION AND TREATMENT TARGETS

Patients had a high rate of receiving multiple, evidence-based therapies after randomization and during follow-up, with similar rates in both study groups (Table 2). At the 5-year follow-up visit, 70% of subjects had an LDL cholesterol level of less than 85 mg per deciliter (2.20 mmol per liter) (median, 71 ± 1.3 mg per deciliter [1.84 ± 0.03 mmol per liter]); 65% and 94% had systolic and diastolic blood pressure targets of less than 130 mm Hg and 85 mm Hg, respectively; and 45% of patients with diabetes had a glycosylated hemoglobin level of no more than 7.0% (Table 2). Patients had high rates of adherence to the regimen of diet, regular exercise, and smoking cessation as recommended by clinical practice guidelines,^{1,2} although the mean body-mass index did not decrease.

FOLLOW-UP PERIOD

The median follow-up period was 4.6 years (interquartile range, 3.3 to 5.7) and was similar in the two study groups, with a total of 120,895 patient-months at risk. Only 9% of patients were lost to follow-up in the two groups (107 in the PCI group and 97 in the medical-therapy group, $P=0.51$) before the occurrence of a primary outcome or the end of follow-up. Vital status was not ascertained in 194 patients (99 in the PCI group and 95 in the medical-therapy group, $P=0.81$).

PRIMARY OUTCOME

The primary outcome (a composite of death from any cause and nonfatal myocardial infarction) occurred in 211 patients in the PCI group and 202 patients in the medical-therapy group (Table 3). The estimated 4.6-year cumulative primary event rates were 19.0% in the PCI group and 18.5% in the medical-therapy group (unadjusted hazard ratio for the PCI group, 1.05; 95% CI, 0.87 to 1.27; $P=0.62$) (Fig. 2).

SECONDARY OUTCOMES

For the prespecified composite outcome of death, nonfatal myocardial infarction, and stroke, the event rate was 20.0% in the PCI group and 19.5%

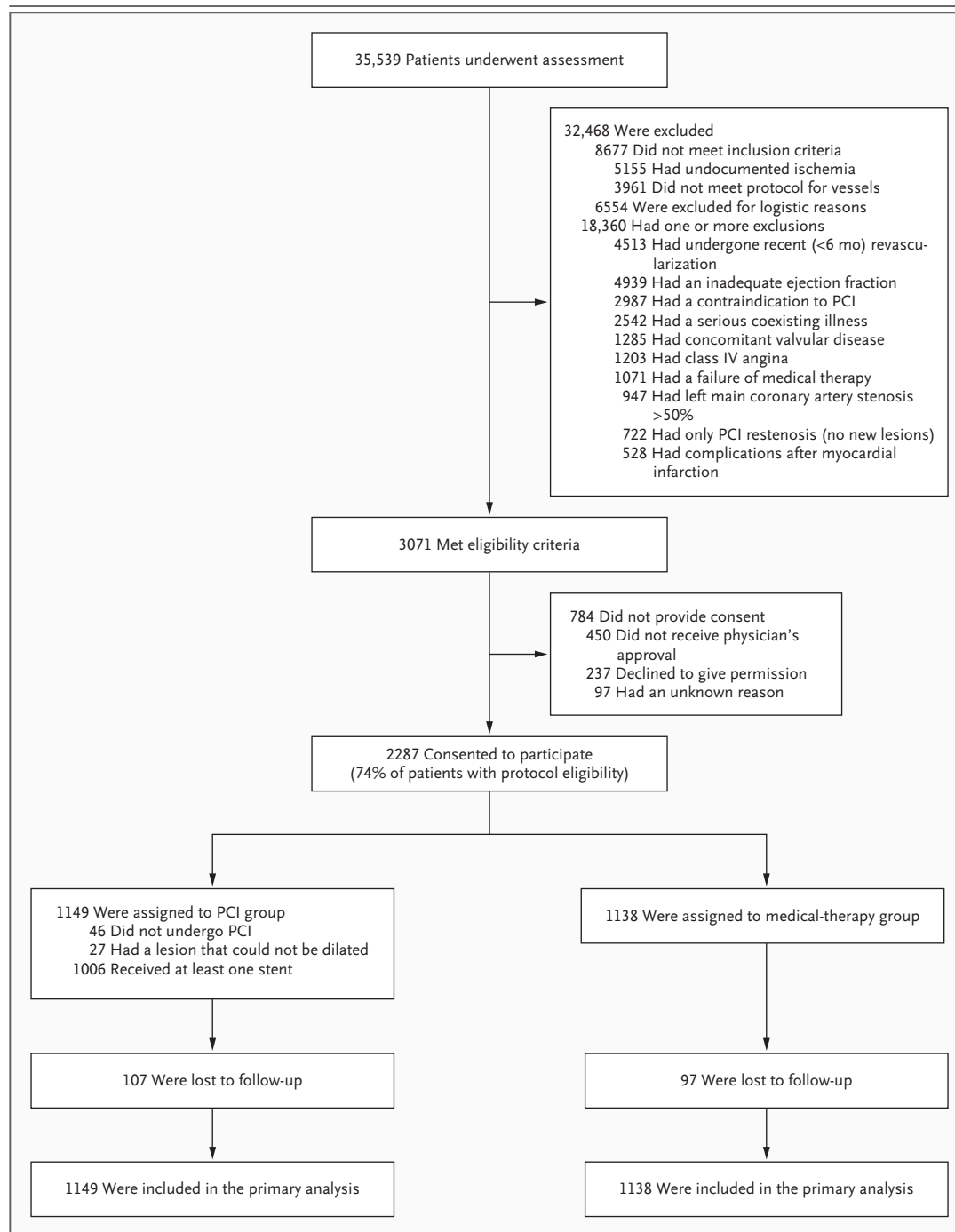


Figure 1. Enrollment and Outcomes.

Of 35,539 patients who were assessed for eligibility in the trial, 32,468 were excluded for a variety of reasons (patients could have more than one reason for exclusion). A total of 3071 patients met all inclusion criteria. Of these, 2287 (74%) consented to participate in the study (932 in Canada, 968 in U.S. Veterans Affairs facilities, and 387 in U.S. facilities other than Veterans Affairs hospitals). Of these patients, 1149 were randomly assigned to the PCI group and 1138 to the medical-therapy group. The median follow-up was 4.6 years for both study groups.

Table 1. Baseline Clinical and Angiographic Characteristics.*			
Characteristic	PCI Group (N = 1149)	Medical-Therapy Group (N = 1138)	P Value
Demographic			
Age — yr	61.5±10.1	61.8±9.7	0.54
Sex — no. (%)			0.95
Male	979 (85)	968 (85)	
Female	169 (15)	169 (15)	
Race or ethnic group — no. (%)†			0.64
White	988 (86)	975 (86)	
Black	57 (5)	57 (5)	
Hispanic	68 (6)	58 (5)	
Other	35 (3)	47 (4)	
Clinical			
Angina (CCS class) — no. (%)			0.24
0	135 (12)	148 (13)	
I	340 (30)	341 (30)	
II	409 (36)	425 (37)	
III	261 (23)	221 (19)	
Missing data	3 (<1)	2 (<1)	
Duration of angina — mo			0.53
Median	5	5	
Interquartile range	1–15	1–15	
Episodes/wk with exertion or at rest within last mo			0.83
Median	3	3	
Interquartile range	1–6	1–6	
History — no. (%)			
Diabetes	367 (32)	399 (35)	0.12
Hypertension	757 (66)	764 (67)	0.53
Congestive heart failure	57 (5)	51 (4)	0.59
Cerebrovascular disease	100 (9)	102 (9)	0.83
Myocardial infarction	437 (38)	439 (39)	0.80
Previous PCI	174 (15)	185 (16)	0.49
CABG	124 (11)	124 (11)	0.94
Stress test‡			
Total patients — no. (%)	972 (85)	977 (86)	0.84
Treadmill test — no. (%)	555 (57)	553 (57)	
Duration of treadmill test — min	7.0±2.7	6.9±2.3	0.43
Pharmacologic stress — no. (%)	417 (43)	424 (43)	
Echocardiography — no. (%)	63 (6)	54 (6)	
Nuclear imaging — no. (%)	685 (70)	708 (72)	0.59
Single reversible defect§	154 (22)	161 (23)	0.09
Multiple reversible defects¶	444 (65)	483 (68)	0.09

Table 1. (Continued.)

Characteristic	PCI Group (N=1149)	Medical-Therapy Group (N=1138)	P Value
Angiographic			
Vessels with disease — no. (%)			0.72
1	361 (31)	343 (30)	
2	446 (39)	439 (39)	
3	341 (30)	355 (31)	
Disease in graft¶	77 (62)	85 (69)	0.36
Proximal LAD disease	360 (31)	417 (37)	0.01
Ejection fraction	60.8±11.2	60.9±10.3	0.86

* Plus–minus values are means ±SD. Baseline data were missing for one patient in each study group. CCS denotes Canadian Cardiovascular Society, CABG coronary-artery bypass grafting, and LAD left anterior descending artery.

† Race or ethnicity was reported by the patient at enrollment.

‡ Nuclear imaging could have been performed after either an exercise treadmill test or pharmacologic stress.

§ The percentage in this category is the proportion of patients who underwent imaging.

¶ The percentage in this category is the proportion of patients who had undergone previous CABG.

in the medical-therapy group (hazard ratio, 1.05; 95% CI, 0.87 to 1.27; $P=0.62$) (Table 3 and Fig. 2). The rates of hospitalization for acute coronary syndromes were 12.4% in the PCI group and 11.8% in the medical-therapy group (hazard ratio, 1.07; 95% CI, 0.84 to 1.37; $P=0.56$), and adjudicated rates of myocardial infarction were 13.2% and 12.3%, respectively (hazard ratio, 1.13; 95% CI, 0.89 to 1.43; $P=0.33$). For death alone, the rates were 7.6% and 8.3%, respectively (hazard ratio, 0.87; 95% CI, 0.65 to 1.16); the mortality curves for the two groups were virtually identical during the initial 4.6 years of the study. For stroke alone, the rate was 2.1% in the PCI group and 1.8% in the medical-therapy group (hazard ratio, 1.56; 95% CI, 0.80 to 3.04; $P=0.19$). When the primary end point was calculated with the exclusion of periprocedural myocardial infarction, the event rates were 16.2% and 17.9% (hazard ratio, 0.90; 95% CI, 0.73 to 1.10; $P=0.29$).

At a median follow-up of 4.6 years, 21.1% of patients in the PCI group had additional revascularization, as compared with 32.6% of those in the medical-therapy group (hazard ratio, 0.60; 95% CI, 0.51 to 0.71; $P<0.001$). In the PCI group, 77 patients subsequently underwent CABG, as compared with 81 patients in the medical-therapy group. Revascularization was performed for angina that was unresponsive to maximal medical therapy or when there was objective evidence of worsening ischemia on noninvasive testing, at the

discretion of the patient's physician. The median time to subsequent revascularization was 10.0 months (interquartile range, 4.5 to 28.0) in the PCI group and 10.8 months (interquartile range, 3.2 to 30.7) in the medical-therapy group.

There was a substantial reduction in the prevalence of angina in both groups during follow-up. There was a statistically significant difference in the rates of freedom from angina throughout most of the follow-up period, in favor of the PCI group (Table 2). At 5 years, 74% of patients in the PCI group and 72% of those in the medical-therapy group were free of angina ($P=0.35$).

SUBGROUP ANALYSES

There was no significant interaction ($P<0.01$) between treatment effect and any predefined subgroup variable (Fig. 3). Of note, among patients with multivessel coronary artery disease, previous myocardial infarction, and diabetes, the rate of the primary end point was similar for both groups. When subgroup variables were included in a multivariate analysis, the hazard ratio for treatment was essentially unchanged (1.09; 95% CI, 0.90 to 1.33; $P=0.77$).

DISCUSSION

As an initial management strategy, PCI added to optimal medical therapy did not reduce the primary composite end point of death and nonfatal

Table 2. Clinical Status, Risk and Lifestyle Factors, and Use of Medication.*

Variable	PCI Group (N=1149)				Medical-Therapy Group (N=1138)			
	Baseline	1 Yr	3 Yr	5 Yr	Baseline	1 Yr	3 Yr	5 Yr
	<i>median ±SE</i>							
Clinical status								
No. evaluated	1148	1031	820	423	1137	1010	824	406
Blood pressure — mm Hg								
Systolic	131±0.77	126±0.64	125±0.68	124±0.81	130±0.66	124±0.73	123±0.78	122±0.92
Diastolic	74±0.33	72±0.35	70±0.52	70±0.81	74±0.33	70±0.43	70±0.52	70±0.65
Cholesterol — mg/dl								
Total	172±1.37	156±1.17	148±1.13	143±1.74	177±1.41	150±1.10	145±1.30	140±1.64
HDL	39±0.39	42±0.39	43±0.47	41±0.67	39±0.37	41±0.42	42±0.49	41±0.75
LDL	100±1.17	84±0.97	76±0.85	71±1.33	102±1.22	81±0.86	74±0.92	72±1.21
Triglycerides — mg/dl	143±2.96	129±2.74	124±2.79	123±4.13	149±3.03	133±2.90	126±2.84	131±4.70
Body-mass index	28.7±0.18	28.5±0.19	29.0±0.21	29.0±0.34	28.9±0.17	29.0±0.19	29.3±0.21	29.5±0.31
Angina-free — no. (%)†	135 (12)	680 (66)	602 (72)	316 (74)	148 (13)	595 (58)	558 (67)	296 (72)
Risk or lifestyle factor								
Current smoker — no. (%)	260 (23)	206 (20)	156 (19)	74 (17)	259 (23)	206 (20)	160 (19)	80 (20)
AHA Step 2 diet — no. (%)	626 (55)	803 (78)	631 (77)	326 (77)	613 (54)	800 (79)	660 (80)	312 (77)
Moderate activity — no. (%)‡	290 (25)	473 (46)	351 (42)	179 (42)	279 (25)	433 (43)	330 (40)	146 (36)
Glycated hemoglobin in patients with diabetes								
No. evaluated	319	239	197	97	336	286	233	123
Level — %	6.9±0.1	7.1±0.1	7.1±0.1	7.1±0.1	7.1±0.1	7.0±0.1	7.1±0.1	7.1±0.1
Medication								
No. evaluated	1147	1044	837	428	1138	1028	838	417
ACE inhibitor — no. (%)	669 (58)	668 (64)	536 (64)	284 (66)	680 (60)	633 (62)	522 (62)	260 (62)
ARB — no. (%)	48 (4)	93 (9)	104 (12)	49 (11)	54 (5)	99 (10)	108 (13)	67 (16)
Statin — no. (%)	992 (86)	972 (93)	780 (93)	398 (93)	1014 (89)	972 (95)	769 (92)	386 (93)
Other antilipid — no. (%)	89 (8)	236 (23)	324 (39)	211 (49)	94 (8)	253 (25)	321 (38)	224 (54)
Aspirin — no. (%)	1097 (96)	995 (95)	792 (95)	408 (95)	1077 (95)	977 (95)	796 (95)	391 (94)
Beta-blocker — no. (%)	975 (85)	887 (85)	705 (84)	363 (85)	1008 (89)	916 (89)	724 (86)	357 (86)
Calcium-channel blocker — no. (%)§	459 (40)	415 (40)	360 (43)	180 (42)	488 (43)	501 (49)	418 (50)	217 (52)
Nitrates — no. (%)¶	714 (62)	553 (53)	396 (47)	173 (40)	825 (72)	690 (67)	511 (61)	237 (57)

* Plus-minus values are medians ±SE, with the SE calculated with the use of the interquartile range. To convert cholesterol values to millimoles per liter, multiply by 0.02586. To convert triglyceride values to millimoles per liter, multiply by 0.01129. ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.

† The comparison between the PCI group and the medical-therapy group was significant at 1 year ($P<0.001$) and 3 years ($P=0.02$) but not at baseline or at 5 years.

‡ This category includes at least 30 to 45 minutes of moderate activity five times per week or vigorous activity three times per week.

§ The comparison between the PCI group and the medical-therapy group was significant at 1 year ($P<0.001$), 3 years ($P=0.005$), and 5 years ($P=0.003$).

¶ The comparison between the PCI group and the medical-therapy group was significant at all time points ($P<0.001$).

Table 3. Primary and Secondary Outcomes.*

Outcome	Number of Events		Hazard Ratio (95% CI)†	P Value‡	Cumulative Rate at 4.6 Years	
	PCI Group	Medical-Therapy Group			PCI Group	Medical-Therapy Group %
Death and nonfatal myocardial infarction‡	211	202	1.05 (0.87–1.27)	0.62	19.0	18.5
Death§	68	74				
Periprocedural myocardial infarction	35	9				
Spontaneous myocardial infarction	108	119				
Death, myocardial infarction, and stroke	222	213	1.05 (0.87–1.27)	0.62	20.0	19.5
Hospitalization for ACS	135	125	1.07 (0.84–1.37)	0.56	12.4	11.8
Death§	85	95	0.87 (0.65–1.16)	0.38	7.6	8.3
Cardiac	23	25				
Other	45	51				
Unknown	17	19				
Total nonfatal myocardial infarction	143	128	1.13 (0.89–1.43)	0.33	13.2	12.3
Periprocedural myocardial infarction	35	9				
Spontaneous myocardial infarction	108	119				
Death, myocardial infarction, and ACS	294	288	1.05 (0.90–1.24)	0.52	27.6	27.0
Stroke	22	14	1.56 (0.80–3.04)	0.19	2.1	1.8
Revascularization (PCI or CABG)¶	228	348	0.60 (0.51–0.71)	<0.001	21.1	32.6

* ACS denotes acute coronary syndrome, PCI percutaneous coronary intervention, and CABG coronary-artery bypass grafting.

† The hazard ratio is for the PCI group as compared with the medical-therapy group, and P values were calculated by the log-rank test and are unadjusted for multiple variables.

‡ The definition of myocardial infarction was the finding of new Q waves at any time; a spontaneous creatine kinase MB fraction of at least 1.5 times the upper limit of normal or a troponin T or I level of at least 2.0 times the upper limit of normal; during a PCI procedure, a creatine kinase MB fraction of at least 3 times the upper limit of normal or a troponin T or I level of at least 5.0 times the upper limit of normal, associated with new ischemic symptoms; and after CABG, a creatine kinase MB fraction or a troponin T or I level of at least 10.0 times the upper limit of normal. If periprocedural myocardial infarction is excluded from the primary outcome, the hazard ratio is 0.90 (95% CI, 0.73 to 1.10; P=0.29).

§ Some patients had a nonfatal myocardial infarction before their subsequent death so that the number of deaths overall is greater than the number of deaths in the primary outcome analysis, which includes the time until the first event.

¶ Values exclude the initial PCI procedure in patients who were originally assigned to the PCI group.

myocardial infarction or reduce major cardiovascular events, as compared with optimal medical therapy alone, during follow-up of 2.5 to 7.0 years, despite a high baseline prevalence of clinical coexisting illnesses, objective evidence of ischemia, and extensive coronary artery disease as seen on angiography. Although the degree of angina relief was significantly higher in the PCI group than in the medical-therapy group, there was also substantial improvement in the medical-therapy

group. All secondary outcomes and individual components of the primary outcome showed no significant differences between the study groups, nor was there a significant interaction between treatment effect and any prespecified subgroup variable. For the primary outcome, the 95% CI excludes a relative benefit of more than 13% in the PCI group. Thus, it is highly unlikely that we missed a prognostically important treatment benefit in favor of the initial PCI strategy.

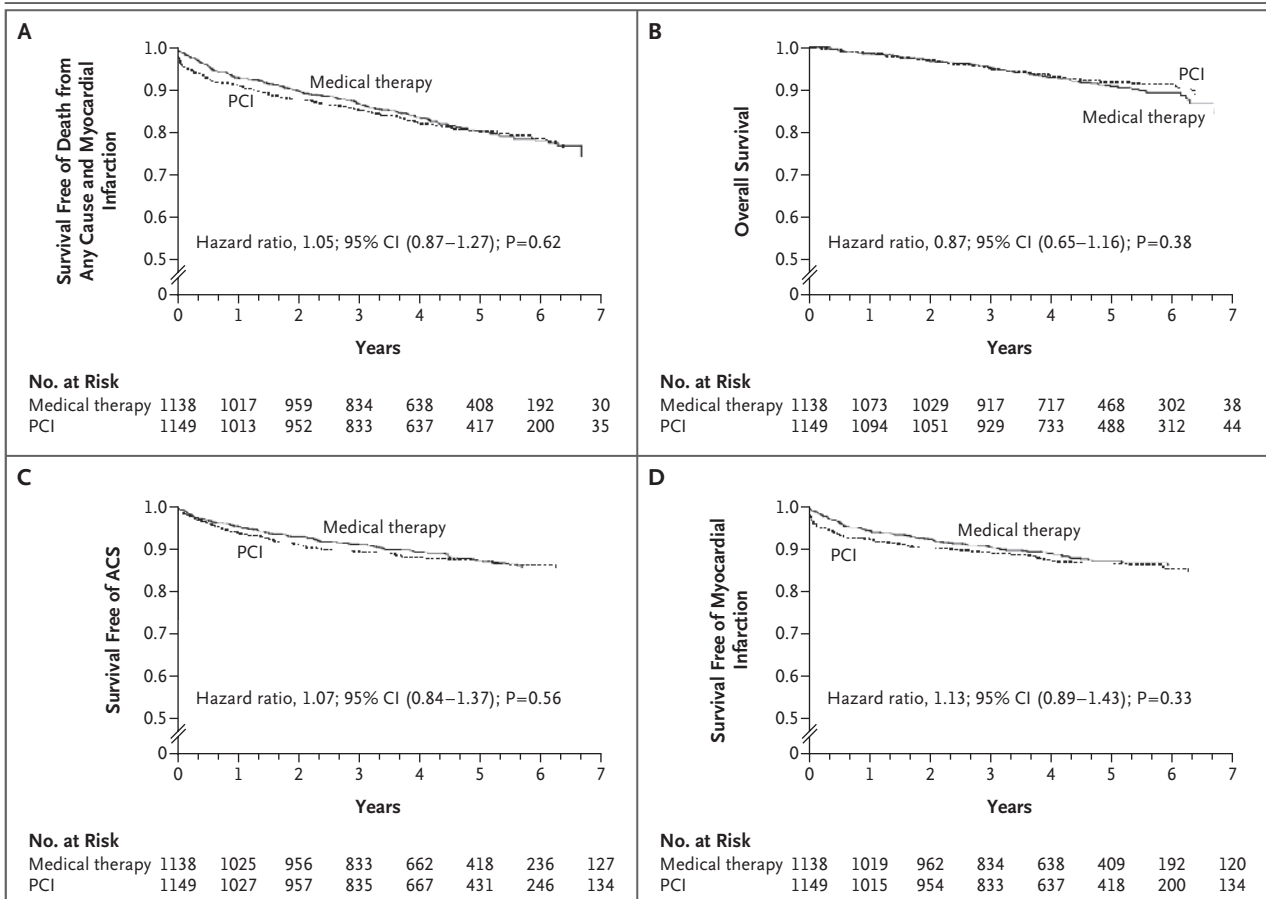


Figure 2. Kaplan–Meier Survival Curves.

In Panel A, the estimated 4.6-year rate of the composite primary outcome of death from any cause and nonfatal myocardial infarction was 19.0% in the PCI group and 18.5% in the medical-therapy group. In Panel B, the estimated 4.6-year rate of death from any cause was 7.6% in the PCI group and 8.3% in the medical-therapy group. In Panel C, the estimated 4.6-year rate of hospitalization for acute coronary syndrome (ACS) was 12.4% in the PCI group and 11.8% in the medical-therapy group. In Panel D, the estimated 4.6-year rate of acute myocardial infarction was 13.2% in the PCI group and 12.3% in the medical-therapy group.

Our findings may be explained, in part, by differences in atherosclerotic plaque morphology and vascular remodeling associated with acute coronary syndromes, as compared with stable coronary artery disease. Vulnerable plaques (precursors of acute coronary syndromes) tend to have thin fibrous caps, large lipid cores, fewer smooth-muscle cells, more macrophages, and less collagen, as compared with stable plaques, and are associated with outward (expansive) remodeling of the coronary-artery wall, causing less stenosis of the coronary lumen.³⁶ As a result, vulnerable plaques do not usually cause significant stenosis before rupture and the precipitation of an acute coronary syndrome.³⁶ By contrast, stable plaques tend to have thick fibrous caps, small lipid cores,

more smooth-muscle cells, fewer macrophages, and more collagen and are ultimately associated with inward (constrictive) remodeling that narrows the coronary lumen. These lesions produce ischemia and anginal symptoms and are easily detected by coronary angiography but are less likely to result in an acute coronary syndrome.^{37,38}

Thus, unstable coronary lesions that lead to myocardial infarction are not necessarily severely stenotic, and severely stenotic lesions are not necessarily unstable. Focal management of even severely stenotic coronary lesions with PCI in our study did not reduce the rate of death and myocardial infarction, presumably because the treated stenoses were not likely to trigger an acute coronary event. Furthermore, our lower-than-projected

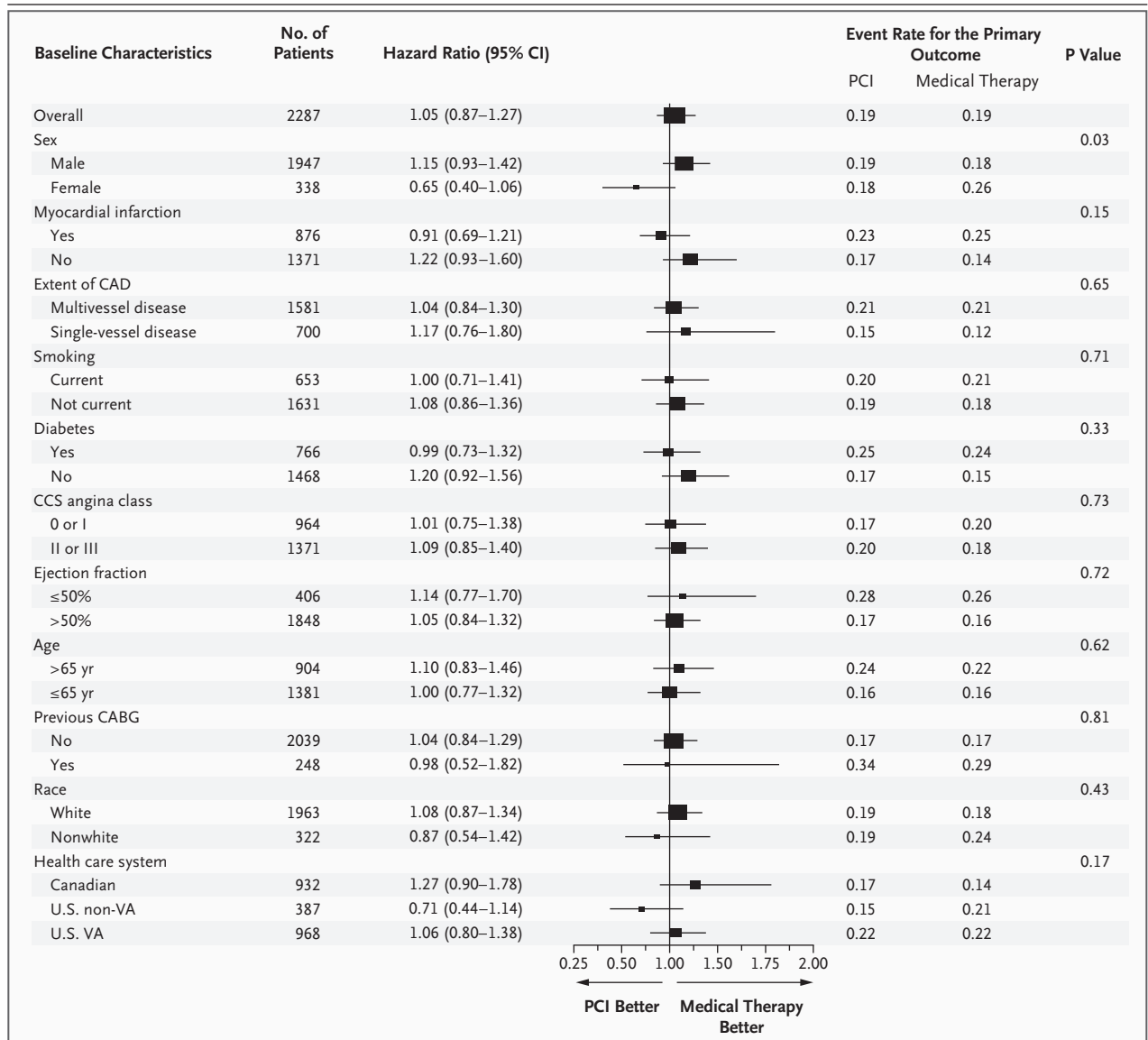


Figure 3. Subgroup Analyses.

The chart shows hazard ratios (black squares, sized in proportion to the number of subjects in a group), 95% CIs (horizontal lines), cumulative 4.6-year event rates for the composite primary outcome (death from any cause and nonfatal myocardial infarction) for the PCI group versus the medical-therapy group for the specified subgroups, and P values for the interaction between the treatment effects and subgroup variables. P values were calculated with the use of the Wald statistic. There was no significant interaction between treatment and subgroup variables as defined according to the prespecified value for interaction ($P < 0.01$), although there was a trend for interaction with respect to sex ($P = 0.03$). PCI denotes percutaneous coronary intervention, CAD coronary artery disease, CCS Canadian Cardiovascular Society, CABG coronary-artery bypass grafting, and VA Veterans Affairs.

event rate in the medical-therapy group may be explained by systemic therapy that reduced plaque vulnerability through aggressive intervention for multiple risk factors and evidence-based use of medication.

Rates of angina were consistently lower in the PCI group than in the medical-therapy group dur-

ing follow-up, and rates of subsequent revascularization were likewise lower. However, there was a substantial increase in freedom from angina in patients in the medical-therapy group as well, most of which had taken place at 1 year but with a further improvement at 5 years. To what extent this finding reflects a benefit of specific

antianginal medications (e.g., nitrates and beta-blockers) or a favorable effect of therapies such as statins on endothelial function and atherosclerosis is unclear.

Our findings parallel those reported in recent trials,^{39,40} in which observed clinical-event rates that were associated with optimal medical therapy were lower than projected in the trial design. These results are also concordant with a meta-analysis of all previous trials involving PCI versus medical management.¹⁶ In the aggregate, these studies, including our own, include outcome data on more than 5000 patients and show that PCI has no effect in reducing major cardiovascular events.

The preponderance of male patients (85%) is a limitation of our study, as is the lack of ethnic diversity (14% of the patients were nonwhite). We used bare-metal stents, since drug-eluting stents were not available until late during accrual. Although the latter factor may be perceived as a limitation, published data indicate no benefit (either short-term or long-term) with respect to death and myocardial infarction in patients with stable coronary artery disease who receive drug-eluting stents, as compared with those who receive bare-metal stents.⁴¹⁻⁴⁶

Our findings reinforce existing clinical practice guidelines, which state that PCI can be safely deferred in patients with stable coronary artery disease, even in those with extensive, multivessel involvement and inducible ischemia, provided that intensive, multifaceted medical therapy is instituted and maintained.^{1,2} As an initial management approach, optimal medical therapy without routine PCI can be implemented safely in the majority of patients with stable coronary artery disease. However, approximately one third of these patients may subsequently require revascularization

for symptom control or for subsequent development of an acute coronary syndrome.

In summary, our trial compared optimal medical therapy alone or in combination with PCI as an initial management strategy in patients with stable coronary artery disease. Although the addition of PCI to optimal medical therapy reduced the prevalence of angina, it did not reduce long-term rates of death, nonfatal myocardial infarction, and hospitalization for acute coronary syndromes.

Supported by the Cooperative Studies Program of the U.S. Department of Veterans Affairs Office of Research and Development, in collaboration with the Canadian Institutes of Health Research; and by unrestricted research grants from Merck, Pfizer, Bristol-Myers Squibb, Fujisawa, Kos Pharmaceuticals, Datascope, AstraZeneca, Key Pharmaceutical, Sanofi-Aventis, First Horizon, and GE Healthcare. All industrial funding in support of the trial was directed through the U.S. Department of Veterans Affairs.

Dr. Boden reports receiving consulting fees and lecture fees from Kos Pharmaceuticals, PDL BioPharma, Pfizer, CV Therapeutics, and Sanofi-Aventis, and grant support from Merck and Abbott Laboratories; Dr. O'Rourke, consulting fees from King Pharmaceuticals, Lilly, and CV Therapeutics; Dr. Teo, grant support from Boehringer Ingelheim; Dr. Knudtson, lecture fees from Medtronic and Lilly; Dr. Harris, having equity ownership in Amgen; Dr. Chaitman, receiving consulting fees from CV Therapeutics, Merck, and Bayer, lecture fees from Pfizer, AstraZeneca, and CV Therapeutics, and grant support from Pfizer, CV Therapeutics, and Sanofi-Aventis; Dr. Shaw, grant support from Bristol-Myers Squibb and Astellas Healthcare; Dr. Booth, grant support from Actelion; Dr. Bates, consulting fees from Sanofi-Aventis and AstraZeneca and lecture fees from Sanofi-Aventis; Dr. Sertus, consulting fees from Amgen and United Healthcare and grant support from Amgen, Roche Diagnostics, and Lilly (and in the past, consulting fees and grant support from CV Therapeutics and owning the copyright for the Seattle Angina Questionnaire, the Peripheral Artery Questionnaire, and the Kansas City Cardiomyopathy Questionnaire); Dr. Berman, consulting fees and lecture fees from Bristol-Myers Squibb, Astellas, Tyco, and Siemens and grant support from Bristol-Myers Squibb and Astellas; Dr. Mancini, consulting and lecture fees from Pfizer, Abbott, and GlaxoSmithKline, lecture fees from Merck and Sanofi-Aventis, and grant support from Cordis and GlaxoSmithKline; and Dr. Weintraub, consulting fees from Sanofi-Aventis and Bristol-Myers Squibb and grant support from Sanofi-Aventis. No other potential conflict of interest relevant to this article was reported.

APPENDIX

The authors' affiliations are as follows: Western New York Veterans Affairs (VA) Healthcare Network and Buffalo General Hospital—SUNY, Buffalo, NY (W.E.B.); South Texas Veterans Health Care System—Audie Murphy Campus, San Antonio, TX (R.A.O., P.C.); McMaster University Medical Center, Hamilton, ON, Canada (K.K.T.); VA Cooperative Studies Program Coordinating Center, VA Connecticut Healthcare System, West Haven, CT (P.M.H.); Vanderbilt University Medical Center, Nashville (D.J.M.); London Health Sciences Centre, London, ON, Canada (W.J.K.); Foothills Hospital, Calgary, AB, Canada (M.K.); Hartford Hospital, Hartford, CT (M.D.); VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque, NM (C.L.H.); Saint Louis University, St. Louis (B.R.C.); Cedars-Sinai Medical Center, Los Angeles (L.S., D.S.B.); Montreal Heart Institute, Montreal (G. Gosselin); Sudbury Regional Hospital, Sudbury, ON, Canada (S.N.); Queen Elizabeth Health Sciences Centre, Halifax, NS, Canada (L.M.T.); Mayo Clinic, Rochester, MN (G. Gau); Houston VA Medical Center, Houston (A.S.B.); Lexington VA Medical Center, Lexington, KY (D.C.B.); University of Michigan Medical Center, Ann Arbor (E.R.B.); Mid America Heart Institute, Kansas City, MO (J.A.S.); Vancouver Hospital and Health Sciences Centre, Vancouver, BC, Canada (G.B.J.M.); and Christiana Care Health System, Newark, DE (W.S.W.).

The members of the COURAGE trial were as follows: **Writing Committee:** W. Boden (study cochair), R. O'Rourke (study cochair), K. Teo (study cochair), P. Hartigan, W. Weintraub, D. Maron, J. Mancini; **Executive Committee:** W. Weintraub (chair), W. Boden, R. O'Rourke, K. Teo, P. Hartigan, M. Knudtson, D. Maron, E. Bates, A. Blaustein, D. Booth, R. Carere, S. Ellis, G. Gosselin, G. Gau, A. Jacobs,

S. King, III, W. Kostuk, C. Harris, J. Spertus, P. Peduzzi (ex officio); **Data and Safety Monitoring Board:** T. Ryan (chair), B. Turnbull, T. Feldman, R. Bonow, W. Haskell, P. Diehr, P. Lachenbruch, D. Waters, D. Johnstone; **Adjudication Committee:** L. Cohen (chair), B. Cantin, W. Hager, F. Samaha, J. Januzzi, J. Arrighi, B. Chaitman; **Economics Committee:** W. Weintraub (chair), P. Hartigan, R. O'Rourke, W. Boden, P. Barnett, J. Spertus, R. Goeree; **Optimal Medical Therapy Committee:** D. Maron (chair), W. Boden, R. O'Rourke, K. Teo, W. Weintraub.

The following members assisted in coordination of the study: VA Cooperative Studies Program Coordinating Center, VA Connecticut Healthcare System, West Haven, CT — P. Peduzzi (director); M. Antonelli, (associate director of operations); J. Smith (project manager); R. Kilstrom, B. Hunter (coordinators); L. Durant (quality assurance officer); S. O'Neil (end points coordinator); T. Economou, J. Nabors (programmers); A. Kossack (data clerk); VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque, NM — M. Sather (director), C. Harris (assistant director), W. Gagne (project manager), C. Fye (pharmacist); VA Cooperative Studies Human Rights Committee, West Haven, CT — R. Marottoli (chair), H. Allore, D. Beckwith, W. Farrell, R. Feldman, R. Mehta, J. Neiderman, E. Perry, S. Kasl, M. Zeman; VA Office of Research and Development, Clinical Science Research and Development, Washington, DC — T. O'Leary (acting director), G. Huang (deputy director, Cooperative Studies Program); Study Chairs Offices — Western New York VA Healthcare Network and Buffalo General Hospital—SUNY, Buffalo, NY — W. Boden (study cochair), M. Dada, K. Potter (national coordinators), T. Rivera (program assistant); South Texas Veterans Health Care System, San Antonio, TX — R. O'Rourke (study cochair), P. Casperson (national coordinator), A. O'Shea (program assistant); McMaster University Medical Center, Hamilton, ON, Canada — K. Teo (study cochair), G. Woodcock (coordinator); Laboratories: Christiana Care Center for Outcomes Research, Newark, DE, and Emory University, Atlanta — W. Weintraub; Health Economics Research Center, Menlo Park, CA — P. Barnett; Program for Assessment of Technology in Health, Hamilton, ON, Canada — R. Goeree, B. O'Brien; Vancouver Hospital, Cardiovascular Imaging Research Core Laboratory, Vancouver, BC, Canada — G.B.J. Mancini, E. Yeoh; Washington University Central Lipid Core Laboratory, St. Louis — J. Ladenson, V. Thompson; Saint Louis University ECG Core Laboratory, St. Louis — B. Chaitman, T. Bertran; Cedars-Sinai Medical Center Nuclear Core Laboratory, Los Angeles — D. Berman, J. Gerlach, R. Littman, L. Shaw; San Diego State University PACE Program, San Diego, CA — K. Calfas, J. Sallis.

The following investigators are listed according to their clinical study sites: **VA:** *South Texas Veterans Health Care System, San Antonio, TX* — R. O'Rourke, P. Baker, J. Bolton; *VA Medical Center, Houston* — A. Blaustein, C. Rowe; *VA Medical Center, Durham, NC* — K. Morris, S. Hoffman; *VA Health Care System, New York* — S. Sedlis, M. Keary; *VA Health Care System, Ann Arbor, MI* — C. Duvernoy, C. Majors; *VA Medical Center, Lexington, KY* — Booth, M. Shockey; *James A. Haley Veterans Hospital, Tampa, FL* — R. Zoble, I. Fernandez; *VA Health Care System, Puget Sound, WA* — K. Lehmann, A. Sorley, M. Abel; *VA Health Care System, Albuquerque, NM* — M. Sheldon, K. Wagoner; *Portland VA Medical Center, Portland, OR* — E. Murphy, K. Avalos; *Iowa City VA Medical Center, Iowa City* — J. Rossen, K. Schneider; *Central Arkansas Veterans Health Care System, Little Rock, AR* — B. Molavi, L. Garza, P. Barton; *VA Medical Center, Atlanta* — K. Mavromatis, Z. Forghani; *Tennessee Valley Health Care System, Nashville* — R. Smith, C. Mitchell; *VA Medical Center, Memphis, TN* — K. Ramanathan, T. Touchstone. **Canada:** *London Health Sciences Centre, London, ON* — W. Kostuk, K. Sridhar, S. Carr, D. Wiseman; *Sudbury Regional Hospital, Sudbury, ON* — S. Nawaz, C. Dion; *Montreal Heart Institute, Montreal* — G. Gosselin, J. Theberge, M. Cuso; *Queen Elizabeth II Health Care Center, Halifax, NS* — L. Title, P. Simon, L. Carroll, K. Courtney-Cox; *Sunnybrook Health Care Centre, Toronto* — E. Cohen, E. Hsu; *University Health Network—Toronto Hospital, Toronto* — V. Dzavik, J. Lan; *Foothills Hospital, Calgary, AB* — M. Knudson, D. Lundberg; *Hamilton General Hospital—McMaster Clinic, Hamilton, ON* — M. Natarajan, G. Cappelli; *St. Michael's Hospital, Toronto* — M. Kutryk, A. DiMarco, B. Strauss; *Vancouver Hospital, Vancouver, BC* — A. Fung, J. Chow; *Saint John Regional Hospital, Saint John, NB* — D. Marr, F. Fitzgerald; *St. Paul's Hospital, Vancouver, BC* — R. Carere, T. Nacario; *University of Alberta Hospital, Edmonton* — W. Tymchak, L. Harris; *Trillium Health Care, Newmarket, ON* — C. Lazzam, A. Carter; *Hôpital du Sacre Coeur de Montreal, Montreal* — D. Palisaitis, C. Mercure. **U.S. Non-VA:** *Mayo Clinic, Rochester, MN* — M. Bell, M. Peterson; *MIMA Century Research Associates, Melbourne, FL* — R. Vicari, M. Carroll; *University of Michigan Medical Center, Ann Arbor* — E. Bates, A. Luciano; *Southern California Kaiser Permanente Medical Group, CA* — P. Mahrer, S. Reyes; *University of Oklahoma, Oklahoma City* — J. Saucedo, D. vanWieren; *Mid America Heart Institute, St. Louis* — J. O'Keefe, P. Kennedy; *Boston Medical Center, Boston* — A. Jacobs, C. Berger, S. Mayo; *Emory University Hospital, Atlanta* — J. Miller, T. Arnold; *Hartford Hospital, Hartford, CT* — F. Kiernan, D. Murphy; *Henry Ford Health System, Detroit* — A. Kugelmass, R. Pangilinan; *University of Rochester Medical Center, Rochester, NY* — R. Schwartz, L. Caufield; *Vanderbilt University Hospital, Nashville* — D. Hansen, C. Mitchell; *SUNY University Hospital, Syracuse, NY* — R. Carhart, A. Pennella; *Cleveland Clinic, Cleveland* — S. Ellis, C. Stevenson; *Barnes-Jewish Hospital, St. Louis* — R. Krone, J. Humphrey; *Mayo Clinic, Scottsdale, AZ* — C. Appleton, J. Wisbey; *Christiana Care Health Systems, Wilmington, DE* — M. Stillabower, A. DiSabatino; *Rush—Presbyterian—St. Luke's Medical Center, Chicago* — M. Davidson, J. Mathien.

REFERENCES

- Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina — summary article: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on the Management of Patients with Chronic Stable Angina). *J Am Coll Cardiol* 2003;41:159-68.
- Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention — summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation* 2006;113:156-75.
- Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics — 2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2007;115(5):e69-e171.
- Feldman DN, Gade CL, Slotwiner AJ, et al. Comparison of outcomes of percutaneous coronary interventions in patients of three age groups (<60, 60 to 80, and >80 years) (from the New York State Angioplasty Registry). *Am J Cardiol* 2006;98:1334-9.
- Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction — executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation* 2004;110:588-636. [Erratum, *Circulation* 2005;111:2013.]
- Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;361:13-20.
- Fragmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. Invasive compared with non-invasive treatment in unstable coro-

- nary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999; 354:708-15.
8. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;344:1879-87.
 9. Fox KA, Poole-Wilson PA, Henderson RA, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial: Randomized Intervention Trial of unstable Angina. *Lancet* 2002;360:743-51.
 10. Mehta SR, Cannon CP, Fox KA, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *JAMA* 2005;293:2908-17.
 11. Parisi AF, Folland ED, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. *N Engl J Med* 1992;326:10-6.
 12. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. *Lancet* 1997;350:461-8.
 13. Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. *N Engl J Med* 1999;341:70-6.
 14. Hueb W, Soares PR, Gersh BJ, et al. The Medicine, Angioplasty, or Surgery Study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease: one-year results. *J Am Coll Cardiol* 2004;43:1743-51.
 15. Henderson RA, Pocock SJ, Clayton TC, et al. Seven-year outcome in the RITA-2 trial: coronary angioplasty versus medical therapy. *J Am Coll Cardiol* 2003;42:1161-70.
 16. Katritsis DG, Ioannidis JP. Percutaneous coronary intervention versus conservative therapy in nonacute coronary artery disease: a meta-analysis. *Circulation* 2005; 111:2906-12.
 17. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. I. Treatments following myocardial infarction. *JAMA* 1988;260:2088-93.
 18. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA* 1982;247:1707-14.
 19. Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement trial. *N Engl J Med* 1992;327: 669-77.
 20. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293-302.
 21. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342:145-53. [Errata, *N Engl J Med* 2000;342:748, 1376.]
 22. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;362:782-8.
 23. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-9.
 24. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
 25. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;352:1425-35.
 26. The Clopidogrel in Unstable Angina to Prevent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502. [Errata, *N Engl J Med* 2001;345:1506, 1716.]
 27. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation* 1999;99:779-85.
 28. O'Connor GT, Buring JE, Yusuf S, et al. An overview of randomized trials of rehabilitation with exercise after myocardial infarction. *Circulation* 1989;80:234-44.
 29. Boden WE, O'Rourke RA, Teo KK, et al. Design and rationale of the Clinical Outcomes Utilizing Revascularization and Aggressive DruG Evaluation (COURAGE) trial Veterans Affairs Cooperative Studies Program no. 424. *Am Heart J* 2006;151:1173-9.
 30. Weintraub WS, Barnett P, Chen S, et al. Economics methods in the Clinical Outcomes Utilizing percutaneous coronary Revascularization and Aggressive Guideline-driven drug Evaluation (COURAGE) trial. *Am Heart J* 2006;151:1180-5.
 31. Shih JH. Sample size calculation for complex clinical trials with survival endpoints. *Control Clin Trials* 1995;16:395-407.
 32. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
 33. Schoenfeld DA, Tsatis AA. A modified log rank test for highly stratified data. *Biometrika* 1987;74:167-75.
 34. Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
 35. Boden WE, O'Rourke RA, Teo KK, et al. The evolving pattern of symptomatic coronary artery disease in the United States and Canada: baseline characteristics of the Clinical Outcomes Utilizing Revascularization and Aggressive DruG Evaluation (COURAGE) trial. *Am J Cardiol* 2007;99: 208-12.
 36. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment-strategies. *Circulation* 2003;108:1664-72.
 37. Ambrose JA, Tannenbaum MA, Alexopoulos D, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. *J Am Coll Cardiol* 1988;12:56-62.
 38. Little WC, Constantinescu M, Applegate RJ, et al. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? *Circulation* 1988;78:1157-66.
 39. Hochman JS, Lamas GA, Buller CE, et al. Coronary intervention for persistent occlusion after myocardial infarction. *N Engl J Med* 2006;355:2395-407.
 40. de Winter RJ, Windhausen F, Cornel JH, et al. Early invasive versus selectively invasive management for acute coronary syndromes. *N Engl J Med* 2005;353:1095-104.
 41. Curfman GD, Morrissey S, Jarcho JA, Drazen JM. Drug-eluting coronary stents: promise and uncertainty. *N Engl J Med* 2007;356:1059-60.
 42. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007; 356:989-97.
 43. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 2007;356:998-1008.
 44. Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007;356:1030-9.
 45. Lagerqvist B, James SK, Stenestrand U, Lindbäck J, Nilsson T, Wallentin L. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. *N Engl J Med* 2007;356:1009-19.
 46. Mauri L, Hsieh W, Massaro JM, Ho KKL, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007;356:1020-9.

Copyright © 2007 Massachusetts Medical Society.