ORIGINAL ARTICLE

Effect of PCI on Long-Term Survival in Patients with Stable Ischemic Heart Disease

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ABSTRACT

BACKGROUND

Percutaneous coronary intervention (PCI) relieves angina in patients with stable ischemic heart disease, but clinical trials have not shown that it improves survival. Between June 1999 and January 2004, we randomly assigned 2287 patients with stable ischemic heart disease to an initial management strategy of optimal medical therapy alone (medical-therapy group) or optimal medical therapy plus PCI (PCI group) and did not find a significant difference in the rate of survival during a median follow-up of 4.6 years. We now report the rate of survival among the patients who were followed for up to 15 years.

METHODS

We obtained permission from the patients at the Department of Veterans Affairs (VA) sites and some non-VA sites in the United States to use their Social Security numbers to track their survival after the original trial period ended. We searched the VA national Corporate Data Warehouse and the National Death Index for survival information and the dates of death from any cause. We calculated survival according to the Kaplan–Meier method and used a Cox proportional-hazards model to adjust for significant between-group differences in baseline characteristics.

RESULTS

Extended survival information was available for 1211 patients (53% of the original population). The median duration of follow-up for all patients was 6.2 years (range, 0 to 15); the median duration of follow-up for patients at the sites that permitted survival tracking was 11.9 years (range, 0 to 15). A total of 561 deaths (180 during the follow-up period in the original trial and 381 during the extended follow-up period) occurred: 284 deaths (25%) in the PCI group and 277 (24%) in the medical-therapy group (adjusted hazard ratio, 1.03; 95% confidence interval, 0.83 to 1.21; P=0.76).

CONCLUSIONS

During an extended-follow-up of up to 15 years, we did not find a difference in survival between an initial strategy of PCI plus medical therapy and medical therapy alone in patients with stable ischemic heart disease. (Funded by the VA Cooperative Studies Program and others; COURAGE ClinicalTrials.gov number, NCT00007657.)

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A Quick Take is available at NEJM.org

Percutaneous coronary intervention (PCI) relieves angina and reduces the extent of myocardial ischemia in patients with stable ischemic heart disease, but trials have not shown a survival benefit. By contrast, among patients with acute ST-segment elevation myocardial infarction, PCI has been shown to increase survival rates,[1,2] and among patients with non–ST-segment elevation myocardial infarction, PCI has been shown to improve long-term survival, with a reduction in both early and late cardiac events.[3,4] Nevertheless, uncertainty persists about the effect of PCI on long-term survival among patients with stable ischemic heart disease. In the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, we compared an initial management strategy of optimal medical therapy alone with optimal medical therapy plus PCI among patients with stable ischemic heart disease. We found no significant difference between the treatment groups with respect to the composite primary end point of death from any cause or nonfatal myocardial infarction or with respect to any of the other cardiac end points (including death from any cause or hospitalization for acute coronary syndrome) during a median follow-up period of 4.6 years.[5] In the current study, we performed an extended survival analysis to examine the potential long-term survival benefit from initial PCI among the patients with stable ischemic heart disease who were followed for up to 15 years after initial enrollment in the COURAGE trial.

Methods

Study Oversight

The COURAGE trial and the extended follow-up study were sponsored and overseen by the Department of Veterans Affairs (VA) Cooperative Studies Program. The COURAGE trial was designed by the members of the COURAGE Trial Executive Committee, who reviewed the results, were solely responsible for the analysis and for the decision to submit the manuscript for publication, and vouch for both the accuracy of all data analyses and the content of this article. The extended follow-up study was designed by the members of the COURAGE Trial Publications Committee. None of the companies or agencies that provided additional funding were involved in the review or analysis of the results or in the decision to submit the manuscript for publication, and no drugs, products, or equipment were donated for the extended follow-up study. The collection of the data in this extended follow-up study was performed by the investigators and study coordinators at each participating site, and the analysis of the data was performed by the study biostatistician (the second author). The first draft of the manuscript was written by the first and second authors, and all the coauthors provided input and approved the manuscript. The study protocol (available with the full text of this article at NEJM.org), including the protocol for the extended survival analysis, was approved by the human rights committee at the coordinating center and by the local institutional review board at each participating center.

Patients

The design and main trial results of the COURAGE trial have been published previously.[5-7] In brief, 2287 patients (1355 from the United States and 932 from Canada) were enrolled in the COURAGE trial; all the patients had chronic stable angina or silent ischemia, objective findings of inducible myocardial ischemia as assessed by stress testing or new ischemic electrocardiographic ST-T wave changes at rest, and coronary angiographic findings of at least 70% stenosis of an epicardial coronary artery. The patients had had angina for a mean of 26 months (averaging six episodes per week) before enrollment; 58% had Canadian Cardiovascular Society class II or III angina, indicating slight to moderate limitations associated with the angina. The patient population had a clinically significant cardiac risk-factor profile at baseline (67% of patients had hypertension, 71% had dyslipidemia, 34% had diabetes, 29% were active smokers, 39% had prior myocardial infarction, and 26% had undergone prior PCI or coronary-artery bypass grafting [CABG] surgery). Coronary angiography revealed multivessel disease in 69% of the randomly assigned patients, 68% of whom had involvement of the left anterior descending coronary artery; 24% of the randomly assigned patients had greater than 50% stenosis of the proximal left anterior descending coronary artery. The annualized rate of death or myocardial infarction was 4.3% during the original follow-up period.

TREATMENT AND FOLLOW-UP

After providing written informed consent, the participants in the original COURAGE trial were randomly assigned to an initial management strategy of optimal medical therapy alone (medical-therapy group) or optimal medical therapy plus PCI (PCI group). Pharmacologic and lifestyle interventions consistent with existing clinical practice guidelines were applied equally in the two treatment groups.[8] The cardiac risk-factor goals in the COURAGE trial initially included an on-treatment low-density lipoprotein cholesterol goal between 60 and 85 mg per deciliter (between 1.6 and 2.2 mmol per liter) — later revised to less than 70 mg per deciliter (1.8 mmol per liter) — and a blood pressure goal of less than 130/85 mm Hg. Lifestyle counseling included strategies for smoking cessation and advice on exercise, nutrition, and weight control. PCI was performed according to the judgment of the operator and prevailing best practice. The operator was free to choose any primary or adjunctive catheter-based technique approved by the Food and Drug Administration to safely and effectively accomplish myocardial revascularization. Complete revascularization was encouraged but not mandated if, in the judgment of the operator, this posed undue risk to the patient. Drug-eluting stents were not available until the last 6 months of enrollment and were used in only 3% of the randomly assigned patients.

In the original COURAGE trial, patients were followed up monthly for the first 3 months of the trial, at 6 months, and every 6 months thereafter for 2.5 to 7 years (median follow-up, 4.6 years). Clinical end points until the end of the study were adjudicated by an independent committee whose members were unaware of the randomized treatment assignments.

LONG-TERM SURVIVAL

The patients in the United States were asked, as part of the initial informed-consent process, to provide their Social Security numbers for survival tracking. This was not permitted by the institutional review boards in Canada and at some non-VA enrolling sites in the United States. Almost all the patients (99.4%) at the participating sites that permitted the collection of Social Security number information consented to survival tracking, and these patients were included in the "extended follow-up" cohort. For veterans, Social Security numbers were submitted to the VA national Corporate Data Warehouse system to ascertain the date of death in the case of patients who died and the date last seen at any VA facility in the case of surviving patients. For all the patients in the extended follow-up cohort, Social Security numbers were submitted to the National Death Index, and the database was searched for deaths from any cause between 1999 and 2012, which was the latest year with complete data. Patients with Social Security numbers that were not matched in the National Death Index and who were not veterans were presumed to be alive on December 31, 2012. As a data-quality check, we also submitted the Social Security numbers to the national databases for the 125 patients with Social Security number information who had died during the course of the COURAGE trial, and in all cases the date of death in the database matched trial records. Figure 1 shows the completeness of follow-up for all groups.

STATISTICAL ANALYSIS

We used a chi-square test or the Wilcoxon rank-sum test to compare the baseline categorical variables between the medical-therapy group and the PCI group and Student's t-test to compare the baseline continuous variables between the treatment groups. We used the Kaplan–Meier method to estimate the cumulative death rate and the stratified log-rank statistic to assess the efficacy of PCI as compared with medical therapy with respect to the composite primary end point of the COURAGE trial. A Cox proportional-hazards regression model that included all baseline variables with a P value of 0.05 or less for the between-group comparison was used to perform an adjusted analysis of survival, and interactions between treatment assignment and the design variable (availability of Social Security number) were also assessed. Analyses were performed according to the intention-to-treat principle. P values of 0.01 or less were considered to indicate statistical significance for all subgroup and interaction analyses.

RESULTS

BASELINE CHARACTERISTICS

Extended follow-up data (i.e., post-trial survival information) were available for 1211 patients

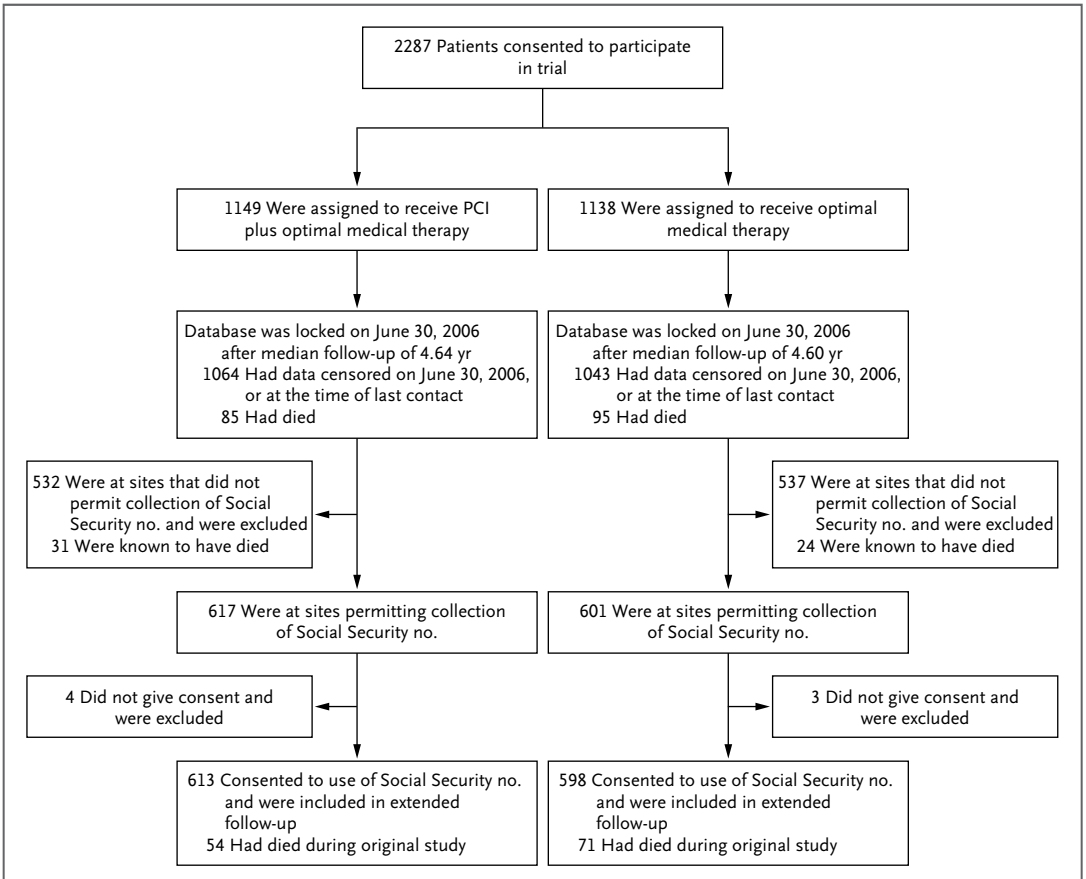

Figure 1. Patient Selection Process for the Extended Follow-up Analysis.

Patients at U.S. sites were asked, as part of the initial informed-consent process, to provide their Social Security number for survival tracking. The use of identifiers for long-term survival tracking was not permitted by the institutional review boards in Canada and at some non-VA enrolling sites in the United States. Patients who consented to the use of their Social Security numbers for survival tracking were included in the extended follow-up cohort. PCI denotes percutaneous coronary intervention.

(53% of the original study population). The baseline characteristics of the patients with and those without extended follow-up, stratified according to treatment assignment, are shown in Table 1. There were numerous significant differences in the baseline characteristics between the patients with and those without extended follow-up. However, none of the baseline characteristics, except for the incidence of pulmonary disease in the cohort without extended follow-up, differed significantly between the medical-therapy group and the PCI group within each cohort.

The baseline characteristics of the patients with and those without extended follow-up, stratified according to health care system, are shown in Table S1 in the Supplementary Appendix, available at NEJM.org. As expected, there were far more men in the VA population than in the Canadian population or non-VA population in the United States (98% vs. 78% and 71%, respectively). There were few other major differences between the patients with and those without extended follow-up, but one such difference was that the patients at the VA sites with extended follow-up had more coexisting clinical diseases at baseline than did the patients at the non-VA sites without extended follow-up.

FOLLOW-UP

The median duration of follow-up in the original trial was 4.6 years (mean, 4.4 years; range, 0 to 7). The median duration of follow-up for all study patients, including those with and those without extended follow-up, was 6.2 years (mean, 7.6 years;

range, 0 to 15.3). The median duration of follow-up for patients with extended follow-up was 11.9 years (mean, 10.5 years; range, 0 to 15.3).

In the original trial, 46 of the 1149 patients in the PCI group did not undergo the initially assigned PCI. During the original follow-up period, 228 patients in the PCI group and 348 in the medical-therapy group underwent revascularization (excluding the initially assigned procedures). No data were available concerning subsequent revascularization during the extended follow-up.

SURVIVAL ANALYSIS

A total of 561 patients (25% of the study population) died during follow-up; 180 patients had died during the original follow-up period and 381 died during the extended follow-up period. A total of 284 deaths (25%) occurred in the PCI group and 277 (24%) in the medical-therapy group (unadjusted hazard ratio for the PCI group as compared with the medical-therapy group, 0.98; 95% confidence interval [CI], 0.83 to 1.15; P=0.77). Figure 2A shows survival curves for up to 12 years of follow-up for patients in the PCI group and the medical-therapy group as compared with expected survival for an age- and sex-matched U.S. population.[9] In the cohort of patients with extended follow-up, there were 253 deaths (41%) in the PCI group and 253 (42%) in the medical-therapy group (unadjusted hazard ratio, 0.95; 95% CI, 0.79 to 1.13; P=0.53) (Fig. 2B). Survival curves, stratified according to treatment assignment, for the patients without extended follow-up are shown in Figure S1 in the Supplementary Appendix.

MULTIVARIABLE AND SUBGROUP ANALYSES

The number of deaths among the patients, stratified according to the availability of extended follow-up data, health care system, and treatment assignment, is shown in Table S2 in the Supplementary Appendix. Among the non-VA patients with extended follow-up, there were 45 deaths in the PCI group (34%) and 41 deaths in the medical-therapy group (34%), whereas among the VA patients with extended follow-up, there were 208 deaths (43%) and 212 deaths (44%), respectively.

When all the baseline variables, as well as a design variable (availability of Social Security number), were included in the Cox regression analysis, the hazard ratio for death from any cause in the PCI group versus the medical-therapy group was 1.03 (95% CI, 0.83 to 1.21; P=0.76). Figure 3 shows the treatment effect in the various subgroups of interest; there was no significant interaction between treatment effect and any of the subgroup variables.

DISCUSSION

In this extended follow-up analysis, we observed that an initial strategy of PCI, as compared with a strategy of medical therapy alone, was not associated with lower mortality among the patients in the COURAGE trial for whom long-term survival could be ascertained. Our findings are based on data collected over a median follow-up period of 6.2 years and are consistent with the results of the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D)[10] trial, which involved 2368 patients with both diabetes and stable ischemic heart disease; the BARI 2D trial also did not show a survival benefit with PCI with respect to the trial primary end point of death from any cause during a median follow-up of 5.3 years.

Previous prespecified and post hoc analyses of data from the COURAGE trial have attempted to define specific subgroups of patients who would benefit from an initial strategy of PCI, but none of these investigations, including those that evaluated high-risk subgroups of patients, have been able to identify any subgroup that derived a survival benefit.[11-15] Similarly, in our extended survival analysis that included a cohort with a slightly higher risk profile than the risk profile of the overall study population, no survival benefit with initial PCI could be discerned during the extended follow-up; in addition, no treatment-by-subgroup interactions were detected.

In the original trial, the survival curves appeared to separate at 5 years in favor of PCI (hazard ratio for death, 0.87; 95% CI, 0.65 to 1.13), which suggested that a late survival benefit with an initial management strategy of PCI may have emerged toward the end of the follow-up period. However, after 15 years of extended follow-up, nearly half the VA patients and one quarter of the non–VA patients in the study had died, and no late trend had emerged to suggest a survival benefit with initial PCI. The higher mortality among VA patients reflects a higher risk profile that included older age, male sex, and a higher frequency of the variables that predict mortality in a Cox regression model.[16]

Observational data from large registries sug-

Table 1. Baseline Characteristics of the Patients According to Treatment Group and Follow-up Cohort.*

Characteristic	No Extended Follow-up		Extended Follow-up	
	Optimal Medical Therapy Alone (N=540)	PCI plus Optimal Medical Therapy (N=536)	Optimal Medical Therapy Alone (N=598)	PCI plus Optimal Medical Therapy (N=613)
Age — yr	61±10	61±10	63±10	63±10
Male sex — %	80	77	90	93
White race — %†	93	93	80	81
Body-mass index‡	29±5	29±5	30±5	30±5
Never smoked — %	25	23	17	15
Hypertension — %	55	55	79	77
Diabetes — %	29	26	42	39
Family history of coronary artery disease — %§	53	55	51	55
Cardiac history — %				
Heart failure	4	5	5	5
Prior MI	41	43	37	35
Prior PCI	10	10	22	20
Prior CABG	6	6	15	15
Coexisting disease — %				
Renal disease	2	2	4	3
Liver disease	2	2	2	2
Cancer	3	3	6	7
Pulmonary disease				
None	89	94	87	88
Mild	9	4	9	8
Moderate	2	1	4	4
Severe	<1	<1	1	<1
Symptoms — %				
Angina	87	87	87	89
Canadian Cardiovascular Society Class¶				
0	13	13	13	11
I	30	31	30	28
II	42	38	34	34
III	16	18	23	27
Angiographic findings — %				
No. of diseased vessels				
1	32	35	29	29
2	37	38	40	40
3	31	28	31	32
LVEF	63±10	62±11	59±11	60±12
Blood pressure — mm Hg				
Systolic	129±18	130±19	135±19	135±21
Diastolic	74±10	75±11	74±11	74±12
Laboratory values — mg/dl				

Table 1. (Continued.)

Characteristic	No Extended Follow-up		Extended Follow-up	
	Optimal Medical Therapy Alone (N=540)	PCI plus Optimal Medical Therapy (N=536)	Optimal Medical Therapy Alone (N=598)	PCI plus Optimal Medical Therapy (N=613)
LDL cholesterol	107±34	103±34	104±33	105±35
HDL cholesterol	43±12	43±12	39±11	39±11
Triglycerides	173±103	166±99	175±103	173±107

* Plus–minus values are means ±SD. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. There were no significant differences between the treatment groups within each follow-up category except for pulmonary disease among those with no extended follow-up ($P=0.01$; $P\leq0.01$ was considered to indicate significance in these between-group comparisons). All the differences between the patients with and those without extended follow-up were significant except for family history, history of heart failure, liver disease, angina, number of diseased vessels, diastolic blood pressure, low-density lipoprotein (LDL) cholesterol, and triglycerides. CABG denotes coronary-artery bypass grafting, HDL high-density lipoprotein, LVEF left ventricular ejection fraction, MI myocardial infarction, and PCI percutaneous coronary intervention.

† Race was self-reported.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ A participant was considered to have a family history of coronary artery disease if a male relative younger than 55 years old or a female relative younger than 65 years old had the disease.

¶ Canadian Cardiovascular Society Class ranges from class 0, which indicates no symptoms, to class IV, which indicates angina at any level of physical exertion.

gest that PCI provides a survival benefit among patients with coronary heart disease,[17-19] but meta-analyses that have used various methods and have included both observational and randomized studies have yielded conflicting results, largely because of the inclusion of patients with acute coronary syndromes or acute myocardial infarction and, in some instances, an admixture of patients who had undergone either PCI or CABG surgery.[20,21] Observational studies and meta-analyses that include observational data are typically confounded by selection bias, by significant differences in unmeasured variables, and often by the inclusion of patients with acute coronary syndromes who benefit from PCI but are not clearly distinguished from patients with stable ischemic heart disease.

Almost one third of the patients (32.6%) in the COURAGE trial crossed over to coronary revascularization during the original follow-up period of 2.5 to 7 years. The median time to crossover was 11 months,[5,22] and the rate of crossover after 1 year was only 2.7% per year. Nevertheless, we have no data on how many patients received subsequent revascularization during the extended follow-up period. The lack of these data is an important limitation of the current analysis, because it is not possible for us to determine the likelihood that, after receiving initial treatment with medical therapy alone, a patient will be considered to require PCI or CABG surgery in the longer term. A high rate of revascularization during the extended follow-up period would also reduce the likelihood of a divergence in mortality between the two study groups; therefore, the late follow-up data may be less reflective of the initial treatment assignment than of a convergence of management strategies over time.

Several other limitations of our trial should be noted. First, we were able to ascertain survival during the extended follow-up period in just over one half of the original study population. The extended follow-up cohort included mostly veterans and only a small number of the non-VA trial participants in the United States; none of the Canadian enrollees were included. Thus, the inability to obtain informed consent for extended follow-up among the nonveteran participants in the COURAGE trial is a shortcoming. Second, the use of death from any cause as an end point is a limitation because it does not permit a distinction between cardiac and noncardiac causes of death. Third, the evaluated therapies, such as the stent platform and device technology and pharmacologic treatments, were older and, in some cases, have been further refined and improved since the initiation of the trial; this type of limitation is common to all long-term outcome studies. There was little use of drug-eluting

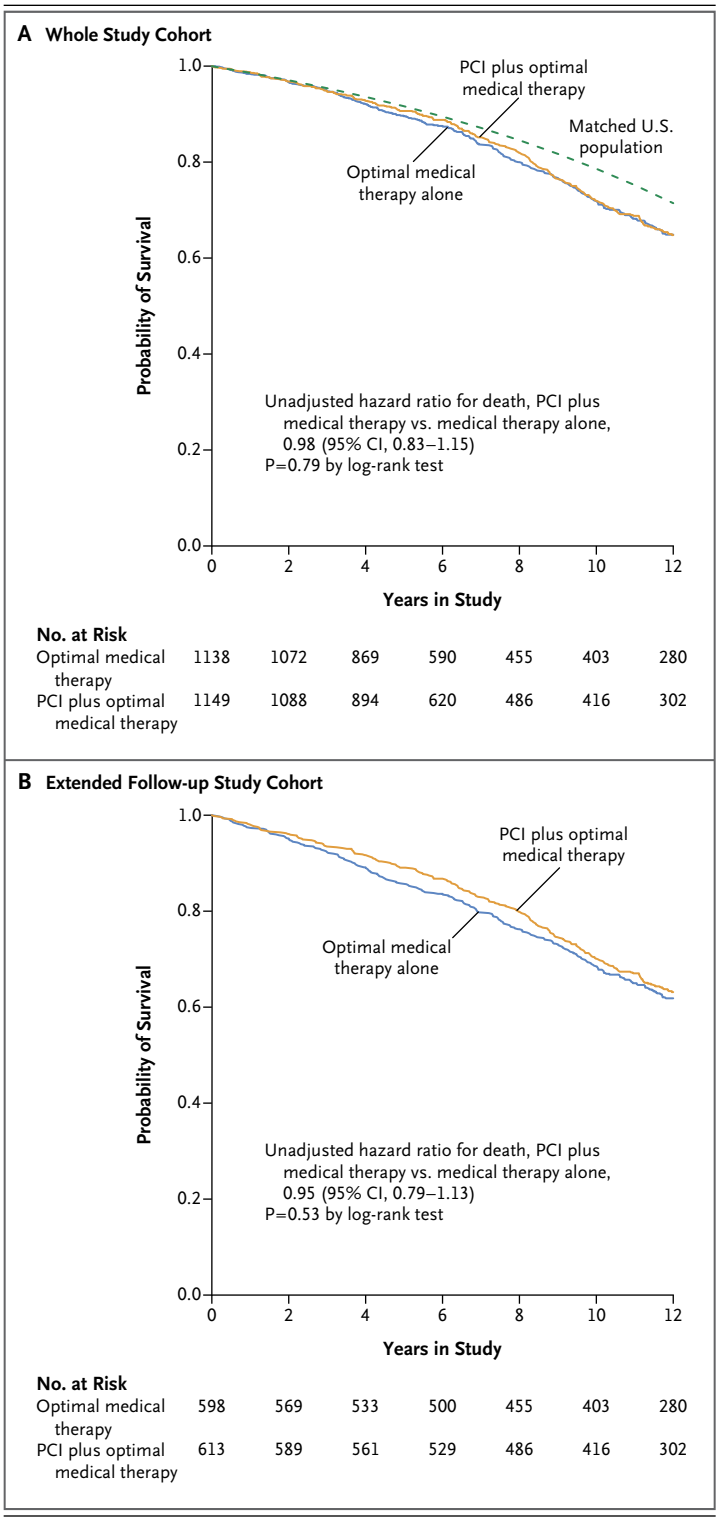

Figure 2. Kaplan–Meier Estimates of Survival in the Two Treatment Groups.

Panel A shows the number of patients at risk in the whole study cohort. It also shows the expected survival (without censoring of data) of 2287 persons who were matched by age and sex to the COURAGE population according to data from the U.S. vital statistics report for 2009.[9] Panel B shows the number of patients at risk in the cohort of patients with extended follow-up. The curves in both panels have been truncated at 12 years, which is the approximate median duration of follow-up in the extended follow-up cohort.

stents during the enrollment period, and CABG surgery was not a revascularization option according to the protocol design. Fourth, because the use of fractional flow reserve was still in its infancy during the time the COURAGE trial was conducted, there was little, if any, use of invasive physiologic measurements; coronary stenoses were evaluated solely on the basis of visual assessment.[23,24] Similarly, there was little use during the trial enrollment period of coronary intravascular ultrasonography or other new coronary imaging methods that have prognostic significance.[25,26] Finally, it must be acknowledged that certain baseline clinical and demographic characteristics, such as the low percentage of women (15%) and the sizable minority of veterans (42%) enrolled in the original trial, could have played a role in the findings we report.

All these limitations, as well as the relatively high late mortality associated with stable ischemic heart disease despite intensive medical therapy, underscore the importance of the ongoing International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) Trial (ClinicalTrials.gov number NCT01471522). This trial is currently evaluating whether, in patients with stable ischemic heart disease and at least moderate ischemia, an initial strategy of optimal medical therapy combined with cardiac catheterization and contemporary revascularization techniques (including second-generation drug-eluting stents, CABG surgery, and appropriate use of fractional flow reserve measurements) reduces the rate of death from cardiovascular causes or of myocardial infarction, as compared with an initial conservative strategy of optimal medical therapy only, with catheterization and revascularization reserved for the patients in whom optimal medical therapy fails.

Subgroup	All Patients	Optimal Medical Therapy Alone	PCI plus Optimal Medical Therapy	Estimated Mortality at Median Follow-up of 6.2 yr	P Value for Interaction
	no. of deaths/total no. of patients (%)			*(%)*	
Extended follow-up					0.30
No	55/1076 (5)	24/540 (4)	31/536 (6)	6.8	
Yes	506/1211 (42)	253/598 (42)	253/613 (41)	15.4	
Age					0.26
≤60 yr	163/990 (16)	86/486 (18)	77/504 (15)	7.7	
>60 yr	398/1296 (31)	191/651 (29)	207/645 (32)	15.7	
Ever smoked					0.70
No	71/452 (16)	35/236 (15)	36/216 (17)	7.1	
Yes	490/1832 (27)	242/900 (27)	248/932 (27)	13.7	
Sex					0.05
Female	57/338 (17)	26/169 (15)	31/169 (18)	13.2	
Male	504/1948 (26)	251/968 (26)	253/980 (26)	12.6	
Diabetes mellitus					0.76
No	290/1482 (20)	139/723 (19)	151/759 (20)	9.9	
Yes	261/766 (34)	133/399 (33)	128/367 (35)	16.9	
Multivessel CAD					0.65
No	141/704 (20)	68/343 (20)	73/361 (20)	10.7	
Yes	420/1582 (27)	209/794 (26)	211/788 (27)	13.8	
LVEF ≤50%					0.57
No	419/1888 (22)	208/952 (22)	211/936 (23)	10.4	
Yes	142/394 (36)	69/184 (38)	73/210 (35)	21.7	
Ischemia, moderate or severe					0.69
No	241/913 (26)	120/454 (26)	121/459 (26)	12.5	
Yes	130/468 (28)	67/245 (27)	63/223 (28)	14.1	
Pulmonary disease					0.07
No	449/2036 (22)	224/997 (22)	225/1039 (22)	10.5	
Yes	111/248 (45)	53/140 (38)	58/108 (54)	27.1	
Liver disease					0.17
No	545/2241 (24)	271/1117 (24)	274/1124 (24)	12.2	
Yes	15/43 (35)	6/20 (30)	9/23 (39)	17.7	
Renal disease					0.68
No	525/2214 (24)	258/1100 (23)	267/1114 (24)	12.0	
Yes	35/70 (50)	19/37 (51)	16/33 (48)	24.4	
Overall	561/2287 (25)	277/1138 (24)	284/1149 (25)	12.7	

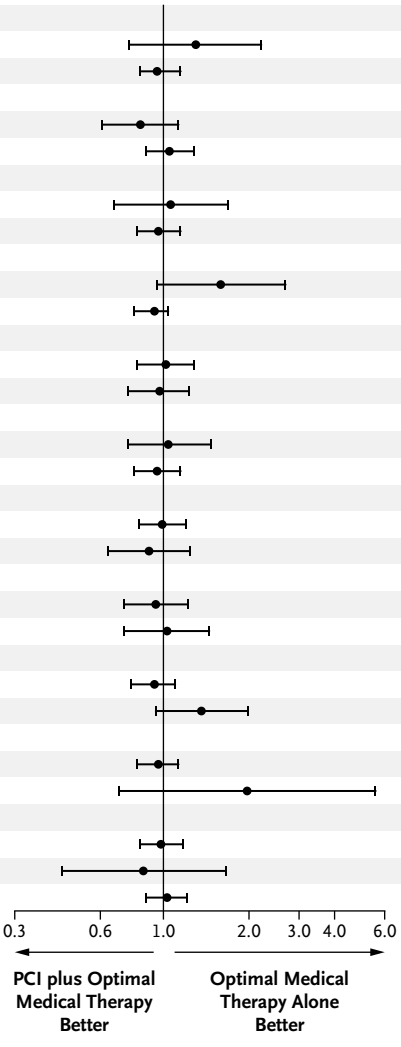

Figure 3. Forest Plot of the Treatment Effect with Respect to Death from Any Cause in Various Subgroups.

The treatment effect compared PCI plus optimal medical therapy with optimal medical therapy alone. The median duration of follow-up for all patients (including those with and those without extended follow-up) was 6.2 years. CAD denotes coronary artery disease, and LVEF left ventricular ejection fraction.

In the current study, we performed an extended survival analysis of data from a cohort of participants in the COURAGE trial who were followed for up to 15 years. We found that among patients with stable ischemic heart disease, objective evidence of ischemia, significant coronary artery disease, and a substantial risk of death (with mortality of approximately 4% per year), there was no difference in rates of long-term survival with an initial strategy of optimal medical therapy plus PCI as compared with optimal medical therapy alone.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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