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Effect of PCI on Quality of Life in Patients with Stable Coronary Disease

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ABSTRACT

BACKGROUND

It has not been clearly established whether percutaneous coronary intervention (PCI) can provide an incremental benefit in quality of life over that provided by optimal medical therapy among patients with chronic coronary artery disease.

METHODS

We randomly assigned 2287 patients with stable coronary disease to PCI plus optimal medical therapy or to optimal medical therapy alone. We assessed angina-specific health status (with the use of the Seattle Angina Questionnaire) and overall physical and mental function (with the use of the RAND 36-item health survey [RAND-36]).

RESULTS

At baseline, 22% of the patients were free of angina. At 3 months, 53% of the patients in the PCI group and 42% in the medical-therapy group were angina-free ($P < 0.001$). Baseline mean (\pm SD) Seattle Angina Questionnaire scores (which range from 0 to 100, with higher scores indicating better health status) were 66 ± 25 for physical limitations, 54 ± 32 for angina stability, 69 ± 26 for angina frequency, 87 ± 16 for treatment satisfaction, and 51 ± 25 for quality of life. By 3 months, these scores had increased in the PCI group, as compared with the medical-therapy group, to 76 ± 24 versus 72 ± 23 for physical limitation ($P = 0.004$), 77 ± 28 versus 73 ± 27 for angina stability ($P = 0.002$), 85 ± 22 versus 80 ± 23 for angina frequency ($P < 0.001$), 92 ± 12 versus 90 ± 14 for treatment satisfaction ($P < 0.001$), and 73 ± 22 versus 68 ± 23 for quality of life ($P < 0.001$). In general, patients had an incremental benefit from PCI for 6 to 24 months; patients with more severe angina had a greater benefit from PCI. Similar incremental benefits from PCI were seen in some but not all RAND-36 domains. By 36 months, there was no significant difference in health status between the treatment groups.

CONCLUSIONS

Among patients with stable angina, both those treated with PCI and those treated with optimal medical therapy alone had marked improvements in health status during follow-up. The PCI group had small, but significant, incremental benefits that disappeared by 36 months. (ClinicalTrials.gov number, NCT00007657.)

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CLINICAL TRIALS INVOLVING PATIENTS with chronic coronary artery disease, in contrast to those involving patients with acute coronary syndromes, have not shown that percutaneous coronary intervention (PCI) prevents major cardiovascular events.¹⁻⁵ The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial compared a strategy of PCI plus optimal medical therapy with optimal medical therapy alone and showed no significant difference in the rate of the primary end point (death or myocardial infarction) during a median follow-up period of 4.6 years.⁶

Among patients with stable coronary artery disease, PCI is indicated for the relief of angina.^{2,3,7,8} Therefore, as part of the COURAGE trial, we used the Seattle Angina Questionnaire to assess the effect of therapy on the relief of angina. In addition, we used the RAND 36-item health survey (RAND-36) to evaluate the effect of therapy on broader health status.

METHODS

STUDY DESIGN

The methods used in the trial have been described previously.^{6,9,10} Between 1999 and 2004, we screened 35,539 patients with stable coronary artery disease at 50 centers in the United States and Canada. Approval for the study was obtained from each local institutional review board. Entry criteria included stenosis of more than 70% in at least one major epicardial coronary artery with objective evidence of myocardial ischemia or stenosis of at least 80% in at least one coronary artery and classic angina without provocative testing. After obtaining written informed consent, we randomly assigned 2287 of 3071 eligible patients to PCI plus optimal medical therapy or to optimal medical therapy alone.

All the patients received aspirin, and those who were undergoing PCI also received clopidogrel in accordance with treatment guidelines.⁸ Anti-ischemic therapy included long-acting metoprolol, amlodipine, and isosorbide mononitrate, alone or in combination, together with simvastatin and either lisinopril or losartan for secondary prevention. Patients were followed for a minimum of 30 months.

Sponsorship and oversight of the trial were provided by the Department of Veterans Affairs Cooperative Studies Program, with additional

funding from the Canadian Institutes of Health Research. Supplemental support was received from several pharmaceutical companies, none of which had any role in the design, analysis, or interpretation of the quality-of-life study. An independent data and safety monitoring board monitored the trial for safety and efficacy. The study's executive committee had full access to the data and vouches for the accuracy and completeness of the analyses performed by the data-coordinating centers.

MEASUREMENT OF DISEASE-SPECIFIC HEALTH STATUS

Health status related to angina was assessed directly from patients at baseline; at 1, 3, 6, and 12 months; and at annual evaluations thereafter. Each assessment was performed with the use of the Seattle Angina Questionnaire, a 19-item questionnaire that quantifies physical limitations due to angina, any recent change in the severity of angina, the frequency of angina, satisfaction with treatment, and quality of life.¹¹⁻¹⁴ Scores range from 0 to 100; higher scores indicate better health status.

We defined clinically significant changes in each of the Seattle Angina Questionnaire scales according to criteria developed by Wyrwich et al.¹⁵ (for details, see the Supplementary Appendix, available with the full text of this article at www.nejm.org). On the basis of this method, we defined clinical significance as a difference of 8 points or more on the physical-limitation scale, 25 or more on the angina-stability scale, 20 or more on the angina-frequency scale, 12 or more on the treatment-satisfaction scale, and 16 or more on the quality-of-life scale.¹⁵

MEASUREMENT OF GENERAL HEALTH STATUS

General health status was measured with the use of the RAND-36 health survey, which includes the following domains: physical functioning, role limitation due to physical problems, role limitation due to emotional problems, vitality, emotional well-being, social functioning, pain, and general health.¹⁶ Scores for each domain range from 0 to 100, with higher scores reflecting better health status. A clinically significant change was defined as a difference of 10 points or more for each domain. The RAND-36 health survey contains the same items as the Medical Outcomes Study 36-item Short Form General Health Survey (SF-36)¹⁷ but is scored differently.¹⁸

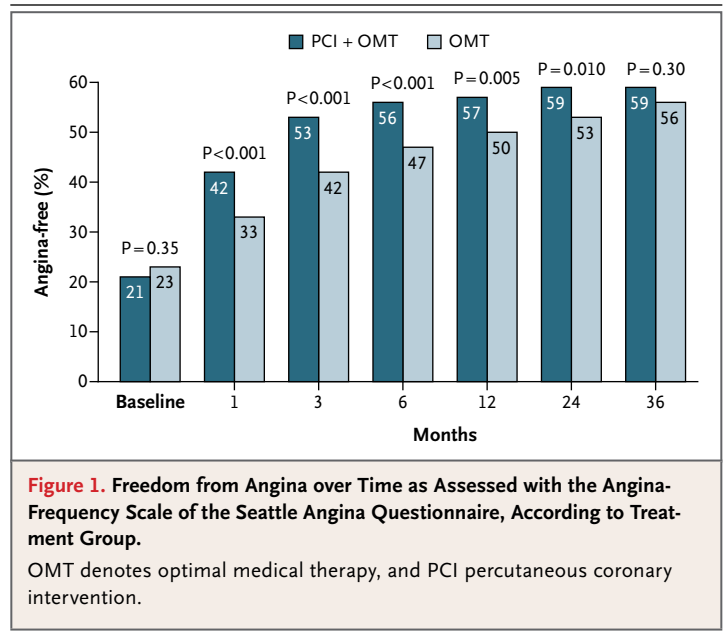
STATISTICAL ANALYSIS

All analyses were truncated at 36 months, because after that time, data were not available for an increasingly large proportion of patients owing to censoring, death, or failure to complete the health-status assessments. P values of less than 0.01 were considered to indicate statistical significance, with no formal correction for multiple comparisons. Of the multiple analyses performed, those that were specified before the initiation of trial enrollment are explicitly identified below.

The chi-square test was used to compare the proportions of patients in each treatment group who were angina-free as defined by the angina-frequency score on the Seattle Angina Questionnaire (with a score of 100 indicating that the patient was angina-free). Mean observed data for each of the domains of the Seattle Angina Questionnaire and the RAND-36 health survey were analyzed with the use of unpaired t-tests comparing the scores of patients in the PCI and medical-therapy groups at each visit (a prespecified end point). The chi-square test was used to assess the proportions of patients with clinically significant increases in scores from baseline (a post hoc analysis).

We performed prespecified longitudinal analyses with the use of linear mixed-effects models, assuming that any missing data were missing at random. Differences were assessed for interactions between treatment group and follow-up time. Quadratic and cubic terms of follow-up time were included in the models to account for non-linear trends along with their interactions with treatment group. As an additional strategy, a multiple partial-imputation strategy was used to account for missing scores.¹⁹ Intermittent missing data (e.g., a missing observation at 6 months but a valid observation at 12 months) were assumed to be missing at random and were imputed with the use of multivariate imputation by chained equations. The resulting data sets contained only monotone missing patterns, defined as dropout at a particular follow-up time for any reason, including death. Five imputed data sets were generated for analysis, and the results of each were combined to estimate regression parameters. These data were then analyzed by means of a pattern-mixture model (prespecified).²⁰ Further details of the approach to missing data are given in the Supplementary Appendix.

Additional prespecified sensitivity analyses were conducted by assigning zero to questionnaire



scores from the time of death to 36 months of follow-up and by grouping patients according to the treatment initially received. Repeated-measures analysis of variance was used to analyze trends to 36 months for patients with complete data. Outcomes with respect to health status for prespecified subgroups according to age (<65 years vs. ≥65 years), sex, race or ethnic group (self-reported), previous or no previous myocardial infarction, previous or no previous coronary-artery bypass surgery, and presence or absence of diabetes were analyzed for interactions between time and treatment group. In additional post hoc subgroup analyses, patients were grouped into thirds for each domain, on the basis of the distribution of the particular domain, with scores adjusted for regression to the mean.²¹

RESULTS

BASELINE CHARACTERISTICS AND PRIMARY END POINT

Baseline clinical characteristics were similar in the group of 1149 patients randomly assigned to PCI plus optimal medical therapy and the group of 1138 patients assigned to optimal medical therapy alone (Tables 1S and 2S in the Supplementary Appendix). No significant difference was observed for the primary end point of death or myocardial infarction (19.0% with PCI, as compared with 18.5% with medical therapy; P=0.62) during a median follow-up interval of 4.6 years.⁶

Table 1. Scores on the Seattle Angina Questionnaire from Baseline to 36 Months.*							
Domain	PCI plus OMT		OMT		P Value†	Missing Data‡	
	Score	No. of Patients	Score	No. of Patients		PCI plus OMT	OMT
% of patients							
Physical limitation							
Baseline	66±25	939	66±25	939	0.58	18	18
1 mo	73±24	850	70±24	850	0.003	26	25
3 mo	76±24	852	72±23	855	0.004	24	24
6 mo	77±23	878	72±24	820	<0.001	21	25
12 mo	75±24	844	73±24	812	0.21	24	25
24 mo	74±24	745	72±24	735	0.16	26	26
36 mo	74±24	573	74±24	583	0.68	33	32
Angina stability							
Baseline	54±33	953	53±32	947	0.56	17	17
1 mo	81±26	866	73±28	873	<0.001	24	23
3 mo	77±28	860	73±27	860	0.002	23	23
6 mo	76±28	883	73±28	827	0.02	20	25
12 mo	74±27	843	70±28	810	0.02	22	24
24 mo	73±27	746	69±27	733	0.003	26	27
36 mo	72±28	576	70±28	580	0.39	33	32
Angina frequency							
Baseline	68±26	969	69±26	969	0.20	16	15
1 mo	82±23	875	76±24	885	<0.001	24	22
3 mo	85±22	871	80±23	873	<0.001	22	22
6 mo	87±20	898	83±22	840	<0.001	19	23
12 mo	87±19	863	84±21	829	0.003	20	23
24 mo	89±18	764	86±19	746	0.002	24	25
36 mo	89±18	583	88±18	589	0.37	32	31
Treatment satisfaction							
Baseline	88±15	971	86±16	956	0.008	16	16
1 mo	92±12	873	88±15	882	<0.001	24	22
3 mo	92±12	869	90±14	873	<0.001	22	22
6 mo	92±13	894	90±14	839	0.007	19	23
12 mo	92±12	861	90±14	829	0.002	20	22
24 mo	92±13	761	92±13	740	0.35	24	26
36 mo	92±12	586	92±11	593	0.78	31	31
Quality of life							
Baseline	51±25	969	51±25	958	0.80	16	16
1 mo	68±24	873	62±24	882	<0.001	24	22
3 mo	73±22	869	68±23	872	<0.001	22	22
6 mo	75±22	897	70±23	838	<0.001	19	24
12 mo	76±21	862	73±22	827	0.008	20	22
24 mo	77±22	763	76±22	739	0.10	24	26
36 mo	79±20	586	77±20	591	0.32	31	31

* Plus-minus values are means ±SD. OMT denotes optimal medical therapy, and PCI percutaneous coronary intervention.

† P values were not adjusted for multiple testing.

‡ The denominator for the percentage of patients with missing data is the total number of patients in follow-up at each time point (patients who were no longer being followed or who had died — i.e., those whose data were censored — were excluded).

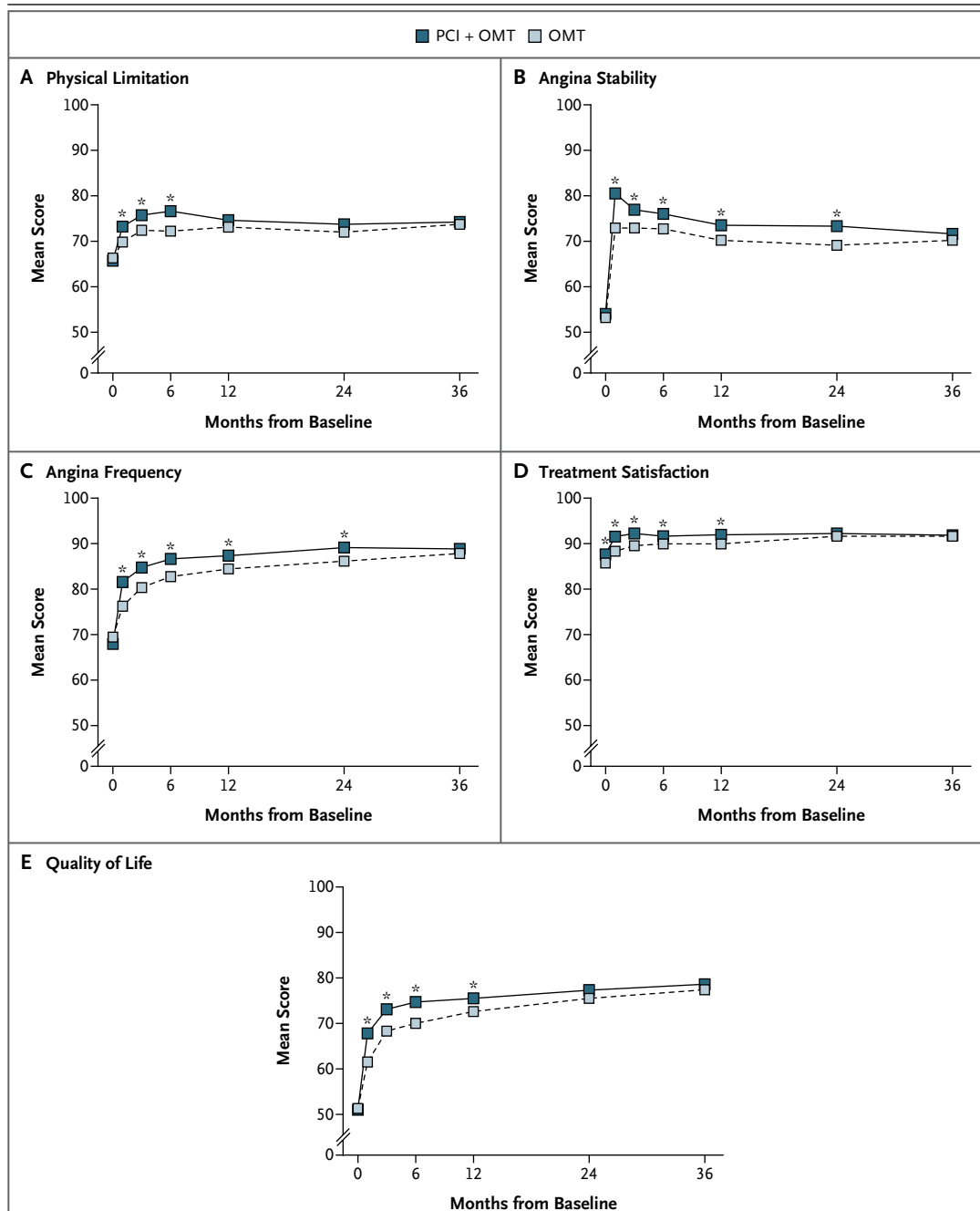


Figure 2. Mean Scores over Time in Five Domains of the Seattle Angina Questionnaire.

An asterisk indicates $P < 0.01$ for the difference between treatment groups. OMT denotes optimal medical therapy, and PCI percutaneous coronary intervention.

DISEASE-SPECIFIC HEALTH STATUS

At baseline, a minority of patients reported being angina-free (i.e., had an angina-frequency score of 100 on the Seattle Angina Questionnaire) (Fig. 1). In both groups, the percentage of patients who

became angina-free increased substantially by 1 month, with continuing improvement thereafter. During the follow-up period, the percentage of angina-free patients was significantly higher in the PCI group than in the medical-therapy group

Table 2. Patients with Clinically Significant Improvement from Baseline in Scores on the Seattle Angina Questionnaire.*

Domain	PCI plus OMT	OMT	P Value†
	% of patients with improvement		
Physical limitation			
1 mo	45	38	0.007
3 mo	49	43	0.008
6 mo	51	42	<0.001
12 mo	48	44	0.095
24 mo	49	44	0.08
36 mo	45	47	0.50
Angina stability			
1 mo	57	50	0.008
3 mo	56	51	0.06
6 mo	56	52	0.14
12 mo	51	50	0.46
24 mo	53	48	0.096
36 mo	51	46	0.14
Angina frequency			
1 mo	39	30	<0.001
3 mo	47	40	0.004
6 mo	50	44	0.010
12 mo	52	46	0.016
24 mo	54	47	0.012
36 mo	57	50	0.045
Treatment satisfaction			
1 mo	27	26	0.54
3 mo	28	29	0.77
6 mo	30	31	0.75
12 mo	39	33	0.23
24 mo	32	37	0.05
36 mo	31	34	0.28
Quality of life			
1 mo	52	43	0.001
3 mo	60	54	0.02
6 mo	64	56	0.001
12 mo	65	61	0.17
24 mo	65	67	0.65
36 mo	69	69	0.93

* OMT denotes optimal medical therapy, and PCI percutaneous coronary intervention.

† P values were not adjusted for multiple testing.

through 24 months but did not differ significantly between the two groups at 36 months.

Mean observed scores on the Seattle Angina Questionnaire are shown in Table 1 and Figure 2.

Scores were similar in the two treatment groups at baseline and improved in both groups for all domains of the Seattle Angina Questionnaire by 1 to 3 months ($P < 0.001$ for all comparisons); subsequent scores changed little. Scores were higher in the PCI group than in the medical-therapy group for 6 to 24 months, depending on the domain. By 36 months, the addition of PCI to optimal medical therapy no longer provided a significant advantage for any domain.

Table 2 shows the proportion of patients who had a clinically significant improvement (as defined in the Methods section) within each domain. A greater proportion of the PCI group had clinically significant improvements in the scores for physical function, angina frequency, and quality of life for the first 6 months after randomization, but these differences were no longer significant by 12 months.

SENSITIVITY AND SUBGROUP ANALYSES

To determine whether crossovers from optimal medical therapy to revascularization (Fig. 1S in the Supplementary Appendix) explained the improvement in health status over time, we assessed the 895 patients assigned to medical therapy who did not cross over within the first 3 months, which was the time of greatest improvement. Among the patients in this subgroup, from baseline to 3 months, physical-limitation scores improved from 67 ± 25 to 73 ± 23 , angina-frequency scores from 70 ± 26 to 80 ± 23 (Fig. 2S, Panel A, and Table 3S in the Supplementary Appendix), and quality-of-life scores from 52 ± 25 to 68 ± 23 . These results were similar to those for the entire medical-therapy group.

Baseline values for all five Seattle Angina Questionnaire scores were lower for the 68 patients in the medical-therapy group who required coronary revascularization within 3 months after randomization than for those who did not. For example, the mean baseline score for angina frequency was 55 ± 28 among those who crossed over within 3 months versus 69 ± 26 among those who did not ($P < 0.001$). By 3 months, angina-frequency scores had improved to 79 ± 26 and 83 ± 23 , respectively ($P = 0.27$). Similar patterns of baseline and 3-month scores were observed for the other domains.

Longitudinal analyses showed similar patterns, whether missing data were assumed to be missing at random (Fig. 2S, Panel B, and Table 4S in the Supplementary Appendix) or whether a pattern-mixture model was used (Fig. 2S, Panel C,

Table 3. Angina-Frequency Scores According to Thirds of Baseline Score.*

Third	Score [†]			Change from Baseline		Clinically Significant Improvement from Baseline [‡]		
	PCI plus OMT	OMT	P Value	PCI plus OMT <i>no. of scale points</i>	OMT	PCI plus OMT <i>% of patients</i>	OMT	P Value
First								
Baseline	35±14	35±14	0.75					
1 mo	68±27	58±25	<0.001	33	23	73	60	0.002
3 mo	74±27	65±26	<0.001	39	30	80	73	0.09
6 mo	78±25	72±25	0.02	43	38	85	81	0.26
12 mo	79±25	75±23	0.09	44	40	86	84	0.56
24 mo	84±21	79±23	0.03	49	45	90	89	0.74
36 mo	83±21	82±22	0.94	48	48	92	88	0.14
Second								
Baseline	71±8	71±8	0.18					
1 mo	81±19	76±20	0.002	9.5	5.3	44	35	0.02
3 mo	86±18	79±22	<0.001	15	8.8	61	50	0.009
6 mo	87±18	82±21	0.002	16	12	64	56	0.04
12 mo	88±17	85±20	0.02	17	14	67	58	0.04
24 mo	90±16	85±19	0.001	18	14	71	59	0.007
36 mo	89±18	87±17	0.28	17	16	71	64	0.11
Third								
Baseline	97±5	97±5	0.61					
1 mo	93±14	88±19	0.002	-4.4	-8.7	0	0	
3 mo	91±18	90±16	0.67	-6.0	-6.7	0	0	
6 mo	92±15	89±19	0.02	-4.9	-8.2	0	0	
12 mo	93±14	90±18	0.02	-4.3	-7.3	0	0	
24 mo	92±15	91±15	0.64	-5.0	-5.8	0	0	
36 mo	94±14	93±14	0.31	-2.8	-4.4	0	0	

* Plus-minus values are means ±SD. OMT denotes optimal medical therapy, and PCI percutaneous coronary intervention.

[†] The P value for the interaction for mean scores among time, baseline score according to thirds, and treatment group was 0.008.

[‡] The P value for the interaction for clinically significant improvement among time, baseline score according to thirds, and treatment group was <0.001.

and Table 5S in the Supplementary Appendix). As compared with observed mean scores, predicted mean scores from the longitudinal models showed similar but at times slightly less improvement in both groups from baseline to follow-up and slightly less difference between the groups. For example, baseline angina-frequency scores on the Seattle Angina Questionnaire were 71 for both treatment groups when either the missing-at-random or the pattern-mixture model was used. At 3 months, angina-frequency scores were 85 for the PCI group and 80 for the medical-therapy group with the missing-at-random model ($P<0.001$) and 84 and 80, respectively, with the pattern-mixture model

($P<0.001$), as compared with 85 and 80, respectively, for observed data ($P<0.001$).

When deaths were assigned a score of zero, the imputed mean scores were slightly lower than observed mean scores, with a greater effect over time as more deaths occurred (Fig. 3S, Panel D, and Table 6S in the Supplementary Appendix). However, there was no effect on the differences between groups. Analyses according to the treatment initially received also showed little effect on the differences between groups.

Complete data were available at 36 months for 328 patients in the PCI group and 303 patients in the medical-therapy group. Analysis of these

data showed that, for both groups, mean scores tended to be higher by about 2 to 3 scale points than the means presented in Table 1, but the patterns of change and the differences between the groups were similar.

The three domains of physical limitation, angina frequency, and quality of life are of particular importance in the analysis of the Seattle Angina Questionnaire because they most closely reflect the effect of angina on current health status and the change in health status over time. We examined these three domains for evidence of interactions between treatment group and baseline domain score according to thirds. For angina frequency, there was a greater improvement in the mean score from baseline to 3 months and a greater benefit from PCI in the lowest third (reflecting the most severe angina) than in the middle or highest third ($P=0.008$ for the interaction) (Table 3). The largest clinical improvement was in the lowest third, with no improvement in the highest third ($P<0.001$ for the interaction). The magnitude of improvement in the lowest and middle thirds was reduced by about one half after adjustment for regression to the mean (Table 7S in the Supplementary Appendix). The results for physical limitation and quality of life were similar ($P<0.001$ for the interactions in both domains) (Tables 8S to 11S in the Supplementary Appendix). There was an intermittent advantage of PCI with respect to the percentage of patients with clinically significant improvement in the lowest and middle thirds for up to 2 years, depending on the domain. No other subgroup interactions were consistently significant (see the Supplementary Appendix).

GENERAL HEALTH STATUS

There were no significant differences at baseline between the groups for any RAND-36 domain (Fig. 3, and Table 13S in the Supplementary Appendix). There was improvement in all domains in both groups between randomization and follow-up at 1 to 3 months ($P<0.001$ for all comparisons). There was also an incremental advantage of PCI over medical therapy at 3 months for the scores in five domains: physical functioning (69 ± 27 vs. 65 ± 26 , $P<0.001$), role limitation—physical (60 ± 42 vs. 52 ± 43 , $P<0.001$), vitality (56 ± 23 vs. 53 ± 23 , $P=0.008$), pain (72 ± 25 vs. 68 ± 26 , $P=0.006$), and general health (61 ± 21 vs. 58 ± 21 , $P<0.001$). The benefit across domains was less consistent than

Figure 3 (facing page). Mean Scores over Time in Eight Domains of Health Status as Assessed with the RAND-36 Health Survey.

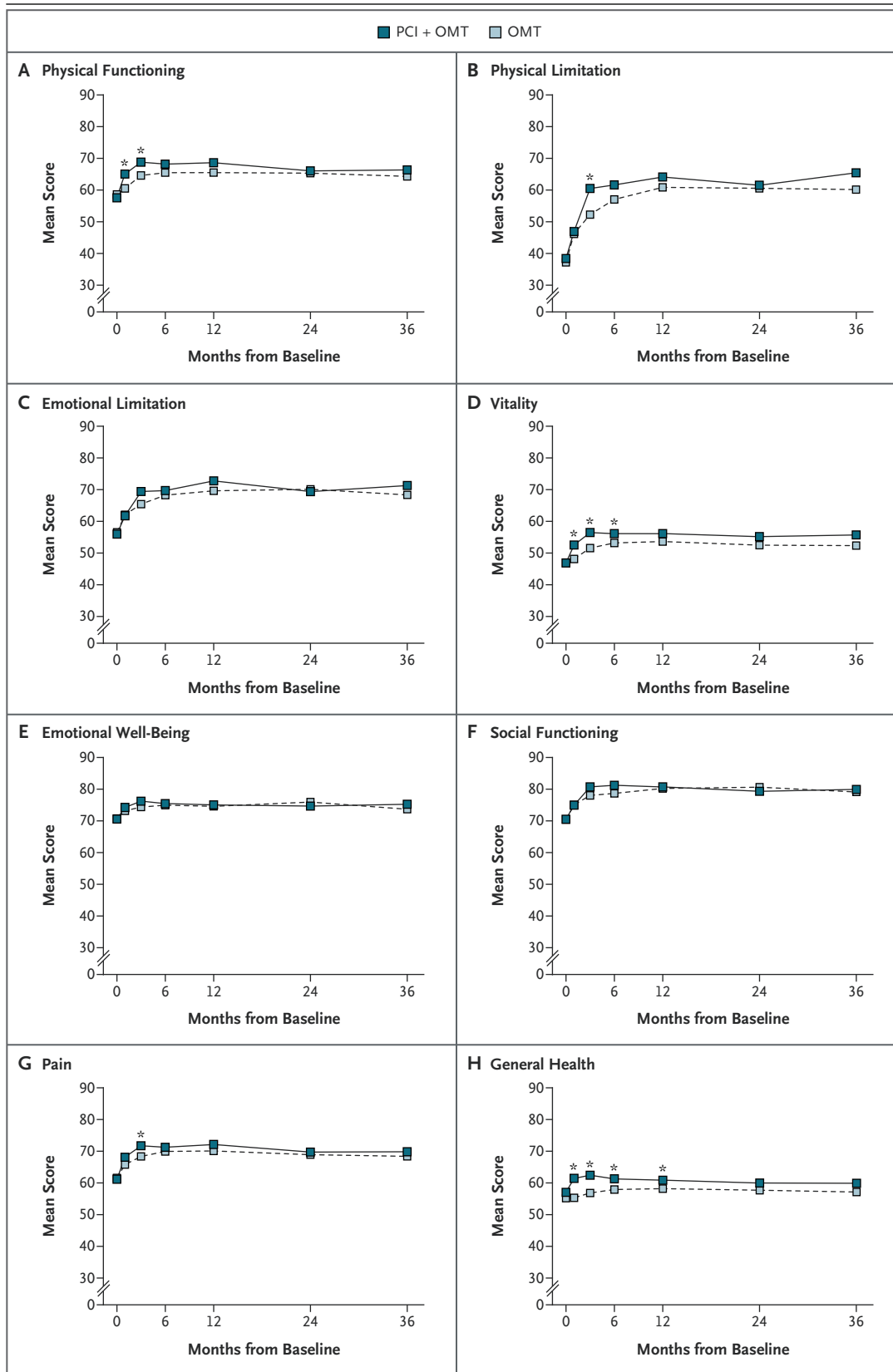
An asterisk indicates $P<0.01$ for the difference between treatment groups. OMT denotes optimal medical therapy, and PCI percutaneous coronary intervention.

that seen in the results for the Seattle Angina Questionnaire, with an advantage of PCI that was noted in most but not all domains and that had a shorter duration. At 6 months, the PCI group was more likely than the medical-therapy group to have a clinically significant improvement (as defined in the Methods section) in physical functioning (50% vs. 43%) and role limitation—physical (48% vs. 43%), but no advantage was observed at 12 months (Table 14S in the Supplementary Appendix). There were no significant subgroup interactions in the RAND-36 results (Table 15S in the Supplementary Appendix).

DISCUSSION

The primary results of the COURAGE trial showed that in patients with stable coronary disease and inducible ischemia who were treated with optimal medical therapy, the addition of PCI did not significantly reduce the risk of death or myocardial infarction.⁶ However, therapeutic procedures are performed not only to prevent events but also to improve health status. On the basis of the Seattle Angina Questionnaire analyses, patients had an incremental benefit from PCI for the first 12 to 24 months in the key domains of physical limitations, frequency of angina, and quality of life. The Seattle Angina Questionnaire data are supported by those from the RAND-36 survey, a general health questionnaire, which showed a less consistent benefit from PCI. These patient-reported outcomes are also consistent with the assessment of angina according to the Canadian Cardiovascular Society classification, as noted in the previous report on the COURAGE trial,⁶ as well as in earlier reports.^{7,22,23}

Although the differences in health status between the two treatment groups were significant, they were substantially smaller than the within-group differences noted for both groups. Somewhat unexpectedly, there was significant and rapid improvement in Seattle Angina Questionnaire scores among the patients in the medical-therapy group, including those who did not cross over



to revascularization treatment. This finding with respect to the benefit of optimal medical therapy alone shows that PCI is not always essential for the relief of symptoms in patients with stable angina.

Throughout the follow-up period, the mean differences between the treatment groups in the scores on all Seattle Angina Questionnaire scales were small (less than five points). However, the likelihood of a clinically significant improvement from baseline was greater in the PCI group for some domains during the first 6 months (though not thereafter). On the basis of these data, 17 patients would need to be treated with PCI plus optimal medical therapy as compared with optimal medical therapy alone for 1 to have a significantly greater amount of angina relief, 11 would need to be treated for 1 to have a significant benefit in physical function, and 12.5 would need to be treated for 1 to have a significant improvement in quality of life.

The benefit of therapy was influenced by the baseline frequency of angina, which was used to divide the patient population into thirds. In general, the data indicate that patients in the lowest third typically had multiple episodes of angina per week; those in the middle third had angina about once a week; and those in the highest third had angina only rarely. Among these subgroups, the patients in the lowest third had the greatest improvement over time and the greatest advantage with PCI, those in the middle third had less improvement and less advantage with PCI, and those in the highest third had no improvement and no advantage with PCI. In the small group of patients who required revascularization early in the trial, markedly low Seattle Angina Questionnaire scores were observed at baseline, and rapid, dramatic improvements were observed after revascularization, confirming that some patients have an especially marked benefit from PCI.

The most important limitation of this study is the amount of missing data. Data on quality of life are difficult to obtain and cannot be collected retrospectively. Although potential bias from missing data cannot be definitively ruled out, several analyses that were performed to account for missing data did not identify meaningful bias.

An additional potential concern is that patients were not unaware of treatment. Therefore, there may have been a placebo effect of PCI. However, the consistency and persistence of the incremen-

tal benefit from PCI with respect to angina make it less likely that a placebo effect could fully explain the observed differences, and it would not explain the substantial improvement in the medical-therapy group. Although we did not adjust for multiple testing in our analyses (except to set a P value of <0.01 as indicating statistical significance in order to be consistent with the report on the clinical results of the COURAGE trial), the consistency of the findings with multiple significant P values makes it unlikely that the results are due to chance.

As with any trial, there may be concerns about the generalizability of the findings. In particular, we enrolled a minority of women and nonwhites, and the effect of PCI plus optimal medical therapy on health-related quality of life in these important subgroups remains uncertain. In addition, the trial was designed and conducted such that high standards of treatment were established (and met), and free access was provided to many medications. Whether the substantial benefits of optimal medical therapy observed in this trial can be replicated outside the context of a clinical trial remains to be determined.

The benefit of PCI as currently practiced may be greater than that observed in this trial. Drug-eluting stents were used in only 31 patients in this study, because they became available only toward the end of the study. Although drug-eluting stents have not been shown to decrease the rate of death or of myocardial infarction, they do decrease the incidence of restenosis, and as a result, the likelihood of recurrent angina after PCI with drug-eluting stents is less than that after PCI with bare-metal stents. However, restenosis develops in only a minority of patients who receive bare-metal stents, and angina develops in only some of those patients (11% of the patients in our trial who were treated with PCI underwent a repeat procedure within 12 months). We did not quantify potential transient decrements in health-related quality of life associated with restenosis or other nonfatal events.

In conclusion, the COURAGE trial showed that patients with chronic coronary disease may expect relief from angina whether they are treated with PCI plus optimal medical therapy or with optimal medical therapy alone. However, an initial strategy of PCI added to optimal medical therapy relieved angina and improved self-assessed health status to a greater extent than an initial strategy

of optimal medical therapy alone for approximately 24 months. A greater benefit from PCI was observed in those patients with more severe and more frequent angina.

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