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CLINICAL RESEARCH

Percutaneous Coronary Intervention Plus Medical Therapy Reduces the Incidence of Acute Coronary Syndrome More Effectively Than Initial Medical Therapy Only Among Patients With Low-Risk Coronary Artery Disease

A Randomized, Comparative, Multicenter Study

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Objectives This study sought to determine whether initial medical therapy (MT) only or percutaneous coronary intervention plus medical therapy (PCI+MT) is better for patients with low-risk stable coronary artery disease (CAD) indicated for intervention in Japan.

Background Several multicenter studies have suggested that in the above patients, an initial management strategy of PCI+MT does not reduce the long-term risk of cardiovascular events more effectively than initial MT only.

Methods We conducted a randomized comparative study (JSAP [Japanese Stable Angina Pectoris] study) in the previously mentioned patients.

Results The patients were randomized to PCI+MT (n = 192) or initial MT only group (n = 192), and the patient characteristics were very similar in the 2 groups. During the 3.3-year follow-up, there was no significant difference in the cumulative death rate between PCI+MT (2.9%) and MT (3.9%). However, the cumulative risk of death plus acute coronary syndrome was significantly smaller in PCI+MT.

Conclusions In stable low-risk CAD, PCI+MT may improve long-term prognosis more effectively than MT. (J Am Coll Cardiol Intv 2008;1:469–79) © 2008 by the American College of Cardiology Foundation

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Coronary artery disease (CAD), consisting of stable CAD and acute coronary syndrome (ACS) (unstable angina pectoris [UAP] and acute myocardial infarction [AMI]), is a serious and common ailment that can profoundly influence a patient's prognosis and quality of life. Stable CAD is classified into 2 types, depending on the lesion site and the number of affected vessels. One type is high-risk CAD, which includes 3-vessel disease, left main trunk lesions, and ostial lesions of the left anterior descending artery (LAD) and carries a high risk of death. The other type is low-risk CAD and involves disease of 1 or 2 vessels other than those associated with high-risk CAD. This type accounts for the majority of CAD patients and carries a low risk of death. Justification for performing percutaneous coronary intervention (PCI) on patients with stable and low-risk CAD is the reduction of anginal pain and the prevention of cardiac events such as ACS and cardiac death.

Abbreviations and Acronyms

ACS = acute coronary syndrome
AMI = acute myocardial infarction
CAD = coronary artery disease
CAG = coronary arteriography
CI = confidence interval
CVA = cerebrovascular accidents
ECG = electrocardiogram
LAD = left anterior descending artery
MT = medical therapy
PCI = percutaneous coronary intervention
UAP = unstable angina pectoris

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According to American College of Cardiology/American Heart Association/American College of Physicians–American Society of Internal Medicine guidelines for the treatment of patients with low-risk stable CAD (1), which are based on many multicenter studies (2), antianginal agents should be administered initially to control anginal attacks, and much effort should be made toward reduction of risk factors and lifestyle intervention. A percutaneous coronary intervention (PCI) should be considered only when medical therapy does not adequately control the symptoms (initial medical therapy [MT] only). Nevertheless, in North America, Japan, and elsewhere, PCI combined with medical therapy has generally been selected as the initial treatment for low-risk stable CAD (PCI plus medical therapy; PCI+MT). Notably in that regard, the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) study by Boden et al. (3) recently showed that PCI+MT does not yield a better long-term prognosis than initial MT. On the other hand, the SWISSI II (Swiss Interventional Study on Silent Ischemia Type II) study by Erne et al. (4) reported that PCI+MT does indeed improve prognosis. In addition, the medical therapy in PCI+MT and in initial MT was intensive in many trials such as the COURAGE study, although PCI plus standard medical therapy has been clinically selected for CAD patients. Thus, an initial management strategy for low-risk stable CAD has not yet been definitively established, especially in Asian countries such as Japan.

In the present study, therefore, we conducted a randomized trial in which the long-term prognoses obtained with PCI+MT and initial MT only, in which medical means standard medical therapy, were compared in Japanese patients with stable low-risk CAD (JSAP [Japanese Stable Angina Pectoris] Study).

Methods

Study design. The study protocol was approved by the human rights committees at all of the participating institutions, and ample consideration was given to patient privacy. Only physicians at designated institutions reviewed data, and data were obtained directly from those physicians. Medical records were not investigated by a third party. Consequently, the likelihood of privacy intrusion was very low. In this study, 24-h random allocation, data collection, and statistical analysis were performed using a host computer in the data center (International Medical Center of Japan [IMCJ], Tokyo, Japan). Discrimination among individual data was not possible. Computerized data were protected by multiple defense systems, and data leakage or data correction by individuals other than the physicians in charge at the institutions was not possible.

This study was performed with written consent of the patients after informing them of the content, importance, and risks of the study, and in the absence of privacy intrusion. Whenever a patient expressed a desire to discontinue registration, the registration was deleted.

Study population. Seventy-eight institutions, nationwide, in Japan that fulfilled the criteria proposed by the Ministry of Health, Labour, and Welfare for institutions performing PCI were requested to cooperate in the JSAP study (Online Appendix).

The subjects were patients (age 30 to 75 years) with stable low-risk CAD consisting of 1- or 2-vessel disease in whom coronary arteriography (CAG) showed significant stenosis (≥75% according to the American Heart Association classification or ≥60% on quantitative CAG) at the culprit lesion. A PCI was indicated based on vessel lesion, objective myocardial ischemia (substantial changes in ST-segment depression or T-wave inversion on a resting electrocardiogram (ECG), or inducible ischemia with either exercise or pharmacologic vasodilator stress), and/or chest pain on exercise. Exclusion criteria are listed in Table 1. Stable angina was defined as angina that was not UAP, which was defined as rest angina, severe new-onset angina within 2 months of initial presentation, or worsening angina that was distinctly more frequent, longer in duration, or lower in threshold than before.

Table 1. Criteria for Exclusion From the Japanese Stable Angina Pectoris Study

High-risk coronary artery disease: 3-vessel disease, lesions in the left main trunk or ostial left anterior descending artery (within 5 mm of the bifurcation)
Chronic total obstruction
Acute coronary syndrome: myocardial infarction or unstable angina
Left ventricular ejection fraction <50%
Lesions not indicated for percutaneous coronary intervention (thin lateral branches, peripheral branches, and so on)
Complications such as a tendency to bleed, disseminated intravascular coagulation, or severe pneumonia
Impaired renal function (creatinine >1.5 mg/dl)
Coronary artery bypass graft surgery patients with graft stenosis as the responsible lesion
Low-risk coronary artery disease patients for whom percutaneous coronary intervention plus medical therapy or initial medical therapy only had already been prescribed by a previous physician

Patients were randomly allocated to the initial MT only group or the PCI+MT group so that the 2 groups were matched with respect to gender, age, risk factors (hypertension, hyperlipidemia, and diabetes mellitus), and the number of culprit coronary arteries.

Registration methods. The JSAP study was a randomized comparative study using a host computer in the IMCJ that enabled 24-h randomized allocation. The registration period was 26 months long, extending from February 1, 2002, to March 31, 2004. When a physician in charge considered a patient to be a candidate for this study, that physician could gain access to the JSAP home page by using a password provided to each institution and known only by the data center. The physician could then obtain a temporary registration, with automatic input of the institution name, by inputting the password, an arbitrary 4-digit identification number, and the patient's age and gender. Subsequently, the study methods were explained to the patient, and his or her informed consent was obtained. Initial MT only or PCI+MT group was selected after again accessing the home page and inputting gender, age, and the presence or absence of the risk factors (hypertension, hyperlipidemia, and diabetes mellitus) and the number of culprit coronary arteries. The selection was immediately displayed on the screen, and the patient was informed of the treatment method. With patients who did not give consent for random allocation, consent to input their data into the home page was sought, and the home page was accessed again. The reason and the arbitrarily selected treatment method were entered, and symptoms and survival were evaluated after 1 month, 6 months, 1 year, 2 years, and 3 years (follow-up survey group). When even consent for input of data into the home page was denied, the temporary registration was deleted. With patients from whom consent was obtained according to the instructions on the home page, the final registration was performed by inputting the classification of their angina symptoms, the oral medications being taken, and the findings of CAG. Additional input of data to the home page was performed periodically, as necessary.

Clinical outcome. Clinical outcome was adjudicated by an independent outside committee whose members were unaware of the treatment assignment (Online Appendix: JSAP Study Evaluation Committee). The primary end points were death (total death, cardiac death, and sudden death), ACS (AMI or UAP), cerebrovascular accidents (CVA; cerebral infarction or cerebral hemorrhage), and emergency hospitalization. The secondary end point was evaluation of the angina severity grade 1 month, 6 months, 1 year, 2 years, and 3 years after registration (Table 2), and elective repeat revascularization.

We defined ACS as AMI or UAP requiring emergency hospitalization, which is caused by the same mechanisms: plaque rupture, intimal erosion, and/or thrombus formation in a coronary artery. Patients who received elective PCI for uncontrollable angina in the initial MT group or for restenosis after PCI in the PCI+MT group were excluded from the ACS patients.

An AMI was definitively diagnosed if new abnormal Q waves appeared in 2 or more ECG leads during follow-up, or if a convincing clinical history was associated with ECG changes compatible with non–Q-wave infarction, and the serum activities of at least 2 cardiac enzymes were greater than twice normal. A UAP was defined as emergency admission for ischemic cardiac pain associated with ECG signs of myocardial ischemia and presentation of coronary stenosis of >90% on CAG in the absence of elevation of serum cardiac enzymes to more than twice normal or the appearance of new Q waves. A CVA was defined as a sudden focal disturbance in brain function of presumed vascular origin persisting for longer than 24 h. Hospitalization was defined as the state to require intensive care by emergency hospitalization on the JSAP study, for example, severe heart failure, critical arrhythmia, and so on.

Drugs and intervention methods. For each patient in the PCI+MT and initial MT groups, medical therapy with antiangina and antirisk factor drugs that was based on evidence from the patient was recommended to the physician in charge. In both groups, the physician in charge could

Table 2. Classification of Severity of Angina*

Class 0: No angina, even during strenuous or prolonged physical activity
Class 1: Angina only during strenuous or prolonged physical activity
Class 2: Slight limitation, with angina only during vigorous physical activity
Class 3: Symptoms during occasional living activities, i.e., mild limitation
Class 4: Symptoms during everyday living activities, i.e., moderate limitation
Class 5: Inability to perform any activity without angina or angina at rest, i.e., severe limitation

*Canadian Cardiovascular Society classification was modified.

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add to or change the prescription at his or her discretion to relieve the signs and symptoms of the patients.

There were no restrictions on the device used for PCI, but the use of a stent was recommended. Drug-eluting stents were not used, however, because at the time of the study they were not yet covered by insurance in Japan.

In Japan, follow-up CAG is performed in nearly all PCI patients 3 to 12 months after PCI, whether or not ischemic signs and/or symptoms are present. Generally, PCI is added when restenosis at the PCI site and/or new significant stenosis at a non-PCI site are found on the follow-up CAG. The same procedures were followed for patients in the PCI+MT group. In the initial MT group, myocardial revascularization procedures were reserved for patients whose symptoms were not adequately controlled by intensive medical therapy. In addition, follow-up CAG within 1 or 2 years was recommended in the group.

Statistical analysis. In the RITA-2 (Second Randomised Intervention Treatment of Angina) trial (5), the hazard ratio of the PCI+MT to the intitial MT group was 1.92 with a 95% confidence interval (CI) 1.08 to 3.41 ($p = 0.02$) (in all-cause death plus nonfatal AMI), and the event rate per 5 years was 15% with PCI+MT and 8% with initial MT. If this was applied to the present study, which had 384 participating patients, an expected event number of 74 and a follow-up period extending until September 2010 would be needed to keep the power at 80% ($\alpha = 0.05$, $\beta = 0.2$). However, the primary end points in the JSAP study were all causes of death plus ACS plus cerebrovascular accident plus emergency hospitalization. Therefore, independent JSAP study statistics and JSAP study evaluation committees performed an interim analysis in May 2006 (mean follow-up period: 3.3 years). The result showed the number of events to be 103 with a power point of 90%, and the difference in the primary end points between the PCI+MT and initial MT groups was significant ($p < 0.05$). Consequently, further follow-up was deemed unnecessary. Based on the above interim analysis, those committees recommended stopping the follow-up because continuing the JSAP study might not benefit the prognosis of patients in the initial MT group.

The cumulative event rate was calculated using the Kaplan-Meier method, and the 2 groups were compared using the log rank statistic. The treatment effects on the hazard ratio and its associated 95% CI were estimated using the Cox proportional hazards model. Data collection and statistical analyses were entrusted to the IMCJ. Analyses were performed according to the intention-to-treat principle. Categorical variables were compared using the chi-square test; continuous variables were compared using the unpaired Student *t* test or Wilcoxon test. A significance level of <0.05 was used for all subgroup analyses and interactions.

Organization of evaluation committee. The JSAP study was evaluated by a committee consisting of a central chairperson, central committee members, statistics committee members, and outside committee members independent of the study (Online Appendix).

Results

Baseline characteristics and angiographic data. Between February 1, 2002, and March 31, 2004, a total of 469 patients were enrolled in this study at 78 institutions, nationwide, in Japan (Fig. 1). Of those, 85 did not give consent for random allocation but did give consent to input their data into the home page; the reason and the arbitrarily selected treatment method were entered, and their symptoms and survival were evaluated after 1 month, 6 months, 1 year, 2 years, and 3 years (follow-up survey group). The remaining 384 patients, from whom informed consent was obtained, were randomly allocated to the initial MT group (n = 192) or the PCI+MT group (n = 192).

This report concerns follow-up to May 31, 2006, which was completed for 98.7% of the patients (379 of 384 patients: 4 of 192 in the PCI+MT group and 1 of 192 in

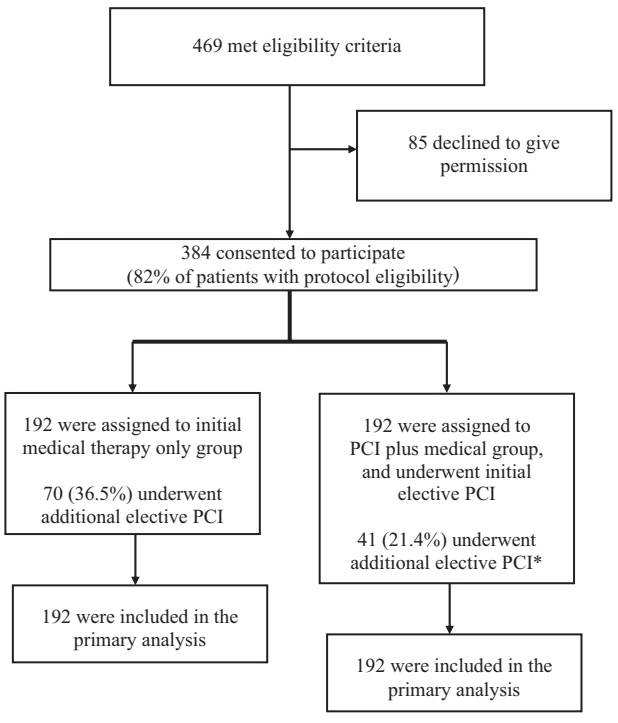

Figure 1. Enrollment of the Patients and the Outcomes

Note that additional elective percutaneous coronary intervention (PCI) was significantly lower in the PCI plus medical group than the initial medical therapy only group. *The percentage of repeat revascularization in the PCI plus medical group was significantly lower than that in the initial medical therapy only group ($p = 0.001$).

the initial MT group were dropped). The minimum and average follow-up periods were 126 days and 1,187 ± 252 days, respectively (mean ± SD; median: 3.3 years, interquartile range: 2.9 to 3.8 years, average: 3.2 years, 95% CI: 3.14 to 3.29 years).

The characteristics of the patients in the 2 groups are shown in Table 3. Overall, there was close similarity between the initial MT and PCI+MT groups with respect to age, gender, risk factors, number of affected vessels, and so on. The percentage of patients with class 0 angina (no angina, even during strenuous or prolonged physical activity) on the classification of severity of angina scale at the time of randomization was 12.9% in the initial MT group and 11.7% in the PCI+MT group.

The distribution of underlying diseases such as hypertension, hyperlipidemia, and diabetes mellitus was also similar in the 2 groups. A previous MI had occurred in 15.1% of patients in the initial MT group and in 14.0% of patients in the PCI+MT group. Patients with previous coronary artery bypass grafting were rare in both groups (1.6% in the initial MT group and 2.8% in the PCI+MT group). In both groups, approximately two-thirds of the patients had 1-vessel disease, and the remaining one-third had 2-vessel disease.

Medication and treatment. Clinical status, risk and lifestyle, and the type of medications used are shown in Table 4. Mean systolic and diastolic blood pressures during follow-up were controlled at 128 to 135 mm Hg and 73 to 75 mm Hg, respectively, in both the PCI+MT and initial MT groups. During follow-up, the mean serum total cholesterol level was 183 to 192 mg/dl in both groups and hemoglobin-A_1C was 6.2 to 6.4 in each group.

At entry into the study, serum total cholesterol and low-density lipoprotein cholesterol were significantly higher in the PCI+MT group than in the initial MT group, and the number of current smokers was higher in the initial MT group than in the PCI+MT group. However, these differences were not seen after 6 months, 1 year, and 3 years of follow-up.

There were no significant differences in the use of medication between the initial MT and PCI+MT groups after randomization or during follow-up, except for nitrate, which was used less in the PCI+MT group at the 6-month, 1-year, and 3-year follow-ups.

Intended randomized PCI. Intended randomized PCI was performed in all patients in the PCI+MT group. The average time from randomization to PCI was 33 days; 31% of PCIs were performed within 1 week, 66% within 1 month, and 91% within 3 months of randomization. The initial success rate was 99.5% for a total of 209 vessel segments. Only 1 case was unsuccessful (from 75% stenosis to 75% stenosis angiographically). On average, the degree of stenosis improved from 86 ± 9% before PCI to 5 ± 11% after PCI in stent-treated vessels (<25% in each) and from 87 ± 10% to 24 ± 15% in

Table 3. Baseline Clinical and Angiographic Characteristics

	Initial MT Only Group (n = 192)	PCI+MT Group (n = 192)	p Value
Characteristic			
Age, yrs	64.2 ± 7.6	64.5 ± 7.2	0.755
Minimum, median, maximum	41, 65, 75	41, 65, 75	
<65 yrs, n (%)	90 (47.2)	87 (46.3)	0.869
Male, n (%)	144 (75.4)	141 (75.0)	0.930
Physique			
Height, cm	160.4 ± 8.4	160.2 ± 8.3	0.784
Weight, kg	62.3 ± 9.8	62.6 ± 10.5	0.818
Body mass index, kg/m^2	24.1 ± 2.8	24.3 ± 3.3	0.574
Clinical			
Initial angina grade, n (%)			0.396
0*	24 (12.9)	21 (11.7)	
1	69 (37.1)	64 (35.8)	
2	74 (39.8)	68 (38.0)	
3	16 (8.6)	19 (10.6)	
4	3 (1.6)	6 (3.3)	
5	0 (0.0)	1 (0.6)	
Missing data	6	13	
History, n (%)			
Diabetes	76 (39.8)	76 (40.4)	0.900
Hypertension	121 (63.4)	119 (63.3)	0.992
Hyperlipidemia	121 (63.4)	120 (63.8)	0.923
Hyperuricemia	24 (12.9)	20 (11.2)	0.612
Menopause of female	29 (61.7 of female)	31 (66.0 of female)	0.668
Myocardial infarction	28 (15.1)	25 (14.0)	0.768
Previous PCI	54 (29.0)	44 (24.6)	0.337
CABG	3 (1.6)	5 (2.8)	0.441
Cerebrovascular disease	10 (5.4)	13 (7.3)	0.459
Stress test, n (%)			
Total patients	149 (80.1)	146 (81.6)	0.724
Treadmill test	76 (40.9)	68 (38.0)	0.575
Duration of treadmill test, min, n (%)	7.0 ± 3.5	6.4 ± 2.7	0.255
Nuclear medicine	55 (29.6)	63 (35.2)	0.251
Echocardiography	13 (7.0)	13 (7.3)	0.919
Angiographic			
Vessels with disease, n (%)			0.998
1	129 (67.5)	127 (67.6)	
2	62 (32.5)	61 (32.5)	
Ejection fraction	65.8 ± 9.6	64.0 ± 9.7	0.171
Cardiac index	3.1 ± 0.8	3.1 ± 0.8	0.742

Plus-minus values are mean ± SD. *These included patients with any arrhythmia, untypical chest discomfort, or dyspnea on effort, and asymptomatic patients with any abnormal cardiac findings on mass examination, among others. Objective myocardial ischemia (substantial changes in ST-segment depression or T-wave inversion on a resting electrocardiogram, or inducible ischemia with either exercise or pharmacologic vasodilator stress) was found in all of these patients, after which coronary arteriography showed 1- or 2-vessel disease in each.

CABG = coronary artery bypass grafting; MT = medical therapy; PCI = percutaneous coronary intervention.

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Table 4. Clinical Status, Risk and Life-Style, and Use of Medication

Variable	Initial MT Only Group (n = 192)				PCI+MT Group (n = 192)				p Value	
	Baseline	6 Months	1 Yr	3 Yrs	Baseline	6 Months	1 Yr	3 Yrs	Baseline	Through 3 Yrs*
Clinical status										
No. evaluated	192	181	172	125	192	168	158	106		
Blood pressure, mm Hg										
Systolic	140 ± 24	132 ± 17	132 ± 17	130 ± 14	142 ± 25	136 ± 19	133 ± 17	135 ± 14	0.344	0.401
Diastolic	73 ± 13	74 ± 10	74 ± 10	75 ± 9	73 ± 12	75 ± 10	74 ± 10	75 ± 9	0.704	0.334
Heart rate, beats/min	68 ± 12	68 ± 11	68 ± 10	67 ± 10	69 ± 11	69 ± 11	70 ± 10	69 ± 10	0.290	0.469
Cholesterol, mg/dl										
Total	196 ± 37	186 ± 36	186 ± 31	186 ± 30	206 ± 43	192 ± 35	193 ± 36	183 ± 27	0.038	0.328
LDL	116 ± 32	109 ± 33	110 ± 26	106 ± 27	125 ± 32	113 ± 31	115 ± 33	106 ± 26	0.007	0.354
HDL	49 ± 15	48 ± 11	49 ± 13	50 ± 14	48 ± 13	49 ± 14	50 ± 15	51 ± 12	0.349	0.123
Triglycerides, mg/dl	153 ± 95	143 ± 79	145 ± 86	137 ± 75	167 ± 171	153 ± 103	136 ± 102	144 ± 69	0.429	0.278
Uric acid, mg/dl	5.7 ± 1.5	5.7 ± 1.5	6.0 ± 2.2	5.7 ± 1.4	5.7 ± 1.4	5.7 ± 1.4	5.8 ± 1.3	5.7 ± 1.5	0.607	0.057
Risk or life-style factor										
Current smoker, %	23.7	12.4	12.6	10.6	13.1	8.9	7.4	5.2	0.009	0.079
Fasting blood sugar	123 ± 45	129 ± 52	131 ± 51	124 ± 47	122 ± 44	120 ± 47	120 ± 40	126 ± 48	0.656	0.550
HbA1c	6.2 ± 1.2	6.2 ± 1.0	6.2 ± 1.0	6.2 ± 1.0	6.3 ± 1.3	6.2 ± 1.3	6.3 ± 1.4	6.3 ± 1.3	0.637	0.635
Patients with diabetes										
No. evaluated (FBS)	67	48	46	30	67	54	41	26		
No. evaluated (HbA1c)	66	53	49	31	67	55	41	24		
Fasting blood sugar	156 ± 54	159 ± 65	163 ± 64	153 ± 51	152 ± 53	143 ± 60	151 ± 48	155 ± 64	0.664	0.390
HbA1c	7.0 ± 1.2	6.7 ± 1.0	6.8 ± 1.0	6.9 ± 1.1	7.0 ± 1.2	6.9 ± 1.3	7.1 ± 1.4	7.4 ± 1.2	0.512	0.620
Other laboratory data										
RBC	438 ± 44	441 ± 50	434 ± 49	427 ± 45	442 ± 52	432 ± 50	435 ± 50	434 ± 47	0.393	0.581
WBC	6,210 ± 1,496	6,207 ± 1,761	5,863 ± 1,476	5,785 ± 1,471	6,201 ± 1,319	6,029 ± 1,384	5,874 ± 1,325	5,831 ± 1,339	0.872	0.570
Hb	13.8 ± 1.4	13.7 ± 1.5	13.6 ± 1.4	13.3 ± 1.4	13.7 ± 1.8	13.5 ± 1.6	13.6 ± 1.6	13.5 ± 1.5	0.705	0.417
Ht	40.9 ± 4.0	40.8 ± 4.9	40.8 ± 3.9	40.0 ± 3.9	40.8 ± 5.2	40.3 ± 4.5	40.6 ± 4.6	40.6 ± 4.3	0.753	0.445
Platelet	22.4 ± 6.5	21.4 ± 6.0	20.9 ± 5.5	21.4 ± 5.3	21.8 ± 5.8	21.7 ± 6.4	21.2 ± 5.7	20.3 ± 5.8	0.624	0.801
BUN	16.1 ± 4.2	16.4 ± 4.2	16.0 ± 4.2	16.4 ± 4.4	16.0 ± 5.3	16.4 ± 4.5	16.3 ± 4.7	16.8 ± 5.1	0.355	0.933
Cr	0.83 ± 0.21	0.82 ± 0.21	0.82 ± 0.23	0.96 ± 0.83	0.86 ± 0.37	0.84 ± 0.25	0.86 ± 0.26	0.85 ± 0.28	0.951	0.606
AST	26 ± 14	25 ± 11	28 ± 26	25 ± 10	27 ± 20	25 ± 11	27 ± 28	27 ± 15	0.681	0.087
ALT	28 ± 19	26 ± 16	25 ± 19	23 ± 12	27 ± 17	27 ± 17	26 ± 15	28 ± 23	0.623	0.198
LDH	236 ± 103	233 ± 96	229 ± 91	203 ± 50	239 ± 102	231 ± 107	224 ± 93	207 ± 58	0.616	0.232
gamma-GTP	57 ± 77	66 ± 108	64 ± 112	54 ± 80	50 ± 75	52 ± 60	51 ± 75	52 ± 91	0.287	0.647
ALP	222 ± 87	230 ± 84	222 ± 74	251 ± 93	228 ± 96	222 ± 87	224 ± 80	249 ± 103	0.488	0.304
CRP	0.22 ± 0.44	0.21 ± 0.65	0.28 ± 0.65	0.10 ± 0.17	0.28 ± 0.61	0.20 ± 0.46	0.20 ± 0.63	0.18 ± 0.31	0.260	0.150
CPK	110 ± 61	109 ± 71	113 ± 81	121 ± 87	103 ± 57	105 ± 62	109 ± 69	117 ± 82	0.233	0.137

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nonstent-treated vessels (<50% in each except for 1 vessel with unsuccessful PCI). Seventy-six percent of PCIs were performed with coronary bare-metal stents and 15% with plain balloon angioplasty. A cutting balloon was used in 10% of cases, directional atherectomy in 5.9%, and rotational atherectomy in 5.3%.

Primary and secondary end points. There were no deaths within 7 days after PCI among the 192 patients who received PCI; ACS occurred in 1 patient within 7 days after PCI.

Kaplan-Meier survival curves for the primary end point are shown in Figure 2. During the 3.3-year follow-up, there was no significant difference in the survival curves free of all causes of death between the initial MT and PCI+MT groups. However, the survival curve free of all causes of death and ACS in the PCI+MT group was shifted significantly upward relative to that in the initial MT group. In addition, the survival curves free of all causes of death, ACS, and cerebral vascular accidents, and free of all causes of death, ACS, cerebral vascular accidents, and emergency hospitalization were each significantly higher in the PCI+MT group than the initial MT group, respectively.

Table 4. Continued

Variable	Initial MT Only Group (n = 192)				PCI+MT Group (n = 192)				p Value	
	Baseline	6 Months	1 Yr	3 Yrs	Baseline	6 Months	1 Yr	3 Yrs	Baseline	Through 3 Yrs*
Medication										
No. evaluated	186	181	172	127	181	168	158	107		
Aspirin or other antiplatelet, n (%)	170 (91.4)	171 (94.5)	160 (93.0)	114 (89.8)	166 (91.7)	164 (97.6)	153 (96.8)	101 (94.4)	0.914	0.197
Warfarin, n (%)	2 (1.1)	2 (1.1)	3 (1.7)	3 (2.4)	7 (4.2)	6 (3.6)	6 (3.8)	6 (5.6)	0.101	0.307
Calcium-channel blocker, n (%)	109 (58.6)	113 (62.4)	109 (63.4)	75 (59.1)	103 (56.9)	96 (57.1)	86 (54.4)	53 (49.5)	0.742	0.145
KATP-channel opener, n (%)	47 (25.3)	51 (28.2)	44 (25.6)	40 (31.5)	40 (22.1)	37 (22.0)	36 (22.8)	24 (22.4)	0.475	0.121
Beta-blocker, n (%)†	96 (51.6)	96 (53.0)	93 (54.1)	72 (56.7)	79 (43.6)	82 (48.8)	76 (48.1)	50 (46.7)	0.126	0.129
Alpha-blocker, n (%)	9 (4.8)	9 (5.0)	8 (4.7)	6 (4.7)	9 (5.0)	9 (5.4)	9 (5.7)	5 (4.7)	1.000	1.000
Nitrates, n (%)	106 (57.0)	108 (59.7)	101 (58.7)	68 (53.5)	93 (51.4)	80 (47.6)	70 (44.3)	39 (36.4)	0.281	0.009
Diuretics, n (%)	13 (7.0)	12 (6.6)	16 (9.3)	11 (8.7)	8 (4.4)	11 (6.5)	12 (7.6)	11 (10.3)	0.289	0.673
ACE inhibitor, n (%)	26 (14.0)	26 (14.4)	25 (14.5)	15 (11.8)	39 (21.5)	35 (20.8)	34 (21.5)	22 (20.6)	0.058	0.068
ARB, n (%)	47 (25.3)	48 (26.5)	50 (29.1)	48 (37.8)	37 (20.4)	42 (25.0)	42 (26.6)	37 (34.6)	0.271	0.610
Statin, n (%)	84 (45.2)	91 (50.3)	93 (54.1)	71 (55.9)	89 (49.2)	100 (59.5)	98 (62.0)	70 (65.4)	0.442	0.138
Other antilipid, n (%)	13 (7.0)	13 (7.2)	11 (6.4)	8 (6.3)	10 (5.5)	13 (7.7)	11 (7.0)	3 (2.8)	0.563	0.208

Plus-minus values are means ± SD. *The interaction between treatment and time was tested in repeated measurement MANOVA for complete cases in vital signs and laboratory results. †Because of the high frequency in side effects such as heart failure and bradycardia, beta-blockade is not used in Japan as much as in western countries. This is reflected by the lower frequency of beta-blockade in the JSAP study, compared with the COURAGE study.

ACE = angiotensin-converting enzyme; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ARB = angiotensin receptor blocker; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; Cr = creatinine; CRP = C-reactive protein; FBS = fasting blood sugar; gamma-GTP = gamma-glutamyl transpeptidase; Hb = hemoglobin; HbA1C = hemoglobin-A1C; HDL = high-density lipoprotein; Ht = hematocrit; KATP = adenosine triphosphate-dependent potassium; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; RBC = red blood cells; WBC = white blood cells; other abbreviations as in Table 3.

The cumulative death rate at 3.3 years was 3.9% in the initial MT group and 2.9% in the PCI+MT group, which was not a significant difference (Table 5). In addition, there was no significant difference in the rates of cardiac death, including sudden death, or noncardiac death between the 2 groups. On the other hand, ACS occurred significantly less frequently in the PCI+MT group (cumulative rate at 3.3 years: 5.0%) than in the initial MT group (11.7%). Although there was no significant difference in the cumulative rates of nonfatal AMI between the PCI+MT and initial MT groups (1.6% vs. 3.7%, respectively), the rate of UAP was significantly lower in the PCI+MT group than in the initial MT group (3.2% vs. 7.3%, respectively). Likewise, the rate of emergency hospitalization was significantly lower in the PCI+MT group (20.6%) than the initial MT group (31.6%). All of the emergency hospitalizations were attributable to ACS or CVA; none were attributable to heart failure or arrhythmia. There was no significant difference in the rates of CVA between the 2 groups (Table 5).

As shown in Figure 3, the severity of angina symptoms, which was similar in the initial MT and PCI+MT groups at entry into the study, was much reduced in both groups (Fig. 3). However, the severity was significantly lower in the PCI+MT group than the initial MT group at the 1-month, 6-month, 1-year, 2-year, and 3-year follow-ups in overall and both mild and severe initial symptoms groups.

In the present study, elective repeat revascularization was performed in 21.4% of patients in the PCI+MT group, but elective revascularization was needed in 36.5% of patients in the initial MT group (Fig. 1). This difference was significant ($p = 0.0011$). Likewise, the frequency of emergency revascularization during an attack of ACS was also significantly lower in the PCI+MT group (5%) than the initial MT group (12%) (Table 5).

ACS and ACS-related coronary lesions. Emergency CAG after an attack of ACS was performed in 32 patients in whom ACS developed during 3.3-year follow-up. As shown in Table 5, the percentage of patients with ACS originating from a lesion that had caused significant stenosis at entry into the JSAP study was significantly lower in the PCI+MT (3.2%) than in the initial MT (8.8%) group. On the other hand, there was no significant difference between the 2 groups in the percentages of patients with ACS originating from a lesion other than the initial target lesion noted at entry. In the initial MT group, the percentage of patients with ACS originating from a site that had shown significant stenosis at entry was significantly higher (8.8%) than that from a different site (4.3%). In the PCI+MT group, however, there was no significant difference between the percentages of ACS originating from the initial target lesion at entry and other sites.

For those in the PCI+MT group with ACS originating from the initial target site, the degree of stenosis in the ACS-related coronary artery was 81.5 ± 10.5% at entry into the study, before the first PCI; it was reduced to 8.3 ± 12.9% after the PCI, but had increased to 94.0 ± 10.1% at

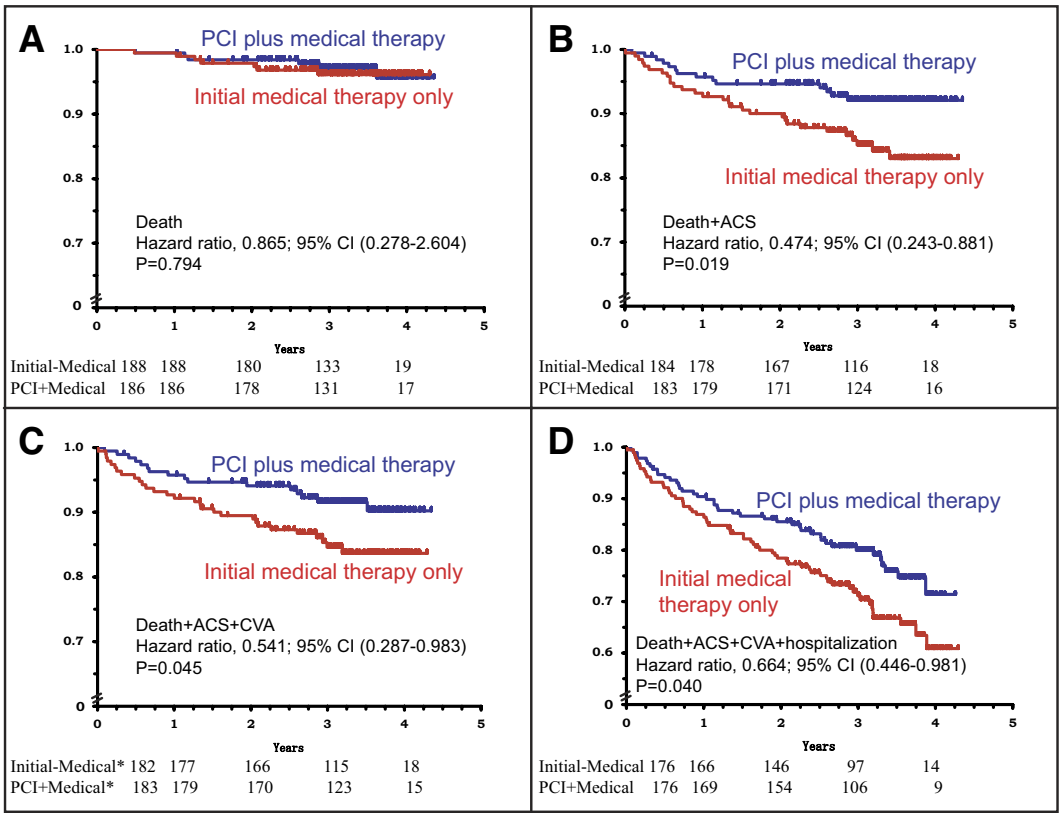

Figure 2. Kaplan-Meier Survival Curves for the Primary End Point

Note that the survival curves free of all causes of death (Death) + acute coronary syndrome (ACS), Death + ACS + cerebrovascular accidents (CVA), and Death + ACS + CVA + Hospitalization (emergency hospitalization) in the PCI plus medical therapy group was shifted significantly upward to that in the initial medical therapy only group, although Death was similar in the 2 groups. *The number of patients in each of the PCI plus medical therapy and initial medical therapy only groups. Abbreviations as in Figure 1.

the time of the ACS attack. For those with ACS originating from a nontarget lesion, the degree of stenosis was 16.7 ± 28.9% at entry, but it had progressed to 93.0 ± 5.2% by the time of ACS attack. For those in the initial MT group with ACS originating from a coronary site that showed significant stenosis at entry, the degree of stenosis in the ACS-related coronary artery had progressed significantly from 89.3 ± 6.7% at entry to 95.1 ± 6.9% at the time of ACS attack. For those with ACS originating from a coronary site that did not show significant stenosis at the entry, the degree of stenosis progressed from 32.1 ± 12.2% at entry to 94.6 ± 9.3% at the time of ACS attack.

Discussion

Reduction of ACS in the PCI+MT group. Studies carried out in Western countries have generally found that long-term prognoses with respect to death or ACS are not significantly better with PCI+MT than with initial MT (2,3,5). In the present study, however, the cumulative rate of cardiac events (e.g., ACS) was smaller in the PCI+MT group than the initial MT group, although there was no significant difference on death. This finding is consistent with those of the SWISSI II study (4), which reported that PCI+MT reduced the long-term risk of major cardiac events in patients with silent MI after MI.

For the patients in the present study, who had 1- or 2-vessel disease, the cumulative rate of ACS during the 3.3-year follow-up was 5.0% in the PCI+MT group and 11.7% in the initial MT group. In the RITA-2 trial (5), in which most of the patients had 1- or 2-vessel disease, the cumulative rates of ACS in the PCI+MT and initial MT groups were 13.6% and 11.4%, respectively, during the 2.7-year follow-up. In the COURAGE trial (3), in which approximately one-third of the patients had 3-vessel disease, the cumulative rates of ACS were 20.0% and 18.7%, respectively, during the 4.6-year follow-up. Thus, the key finding of the present study is the clear reduction of the incidence of ACS in the PCI+MT group.

Table 5. Estimate of the Hazard Ratio for the Primary Efficacy Outcome Measures

Outcome	Number of Events		Hazard Ratio (95% CI)	p Value	Cumulative Rate at 3.3 Yrs	
	Initial MT Only Group (n = 191)	PCI+MT Group (n = 188)			Initial MT Only Group (%)	PCI+MT Group (%)
Deaths	7	6	0.865 (0.278–2.604)	0.794	3.9	2.9
Cardiac	3	2				
Noncardiac	4	3				
Unknown	0	1				
Death and ACS	29	14	0.474 (0.243–0.881)	0.018	14.9	7.9
Death, ACS, and stroke	29	16	0.541 (0.287–0.983)	0.044	16.4	8.5
Death, ACS, stroke, and emergency hospitalization	61	42	0.664 (0.446–0.981)	0.040	33.2	22
ACS	23	9	0.384 (0.168–0.802)	0.012	11.7	5.0
Myocardial infarction	7	3	0.429 (0.092–1.542)	0.200	3.8	1.6
Unstable angina	16	6	0.370 (0.133–0.899)	0.028	8.9	3.4
Originating from target lesion*	16	6	0.373 (0.134–0.907)	0.029	8.8	3.2
Originating from nontarget lesion	7	3	0.408 (0.088–1.470)	0.175	4.3	1.9
CVA	2	2	1.028 (0.123–8.561)	0.978	1.1	0.6
Cerebral infarction	2	0				
Cerebral hemorrhage	0	2				
Emergency hospitalization	58	39	0.658 (0.435–0.983)	0.042	31.6	20.6

*PCI target site of coronary artery with significant stenosis at the entry into Japanese Stable Angina Pectoris Study.
ACS = acute coronary syndrome; CVA = cerebrovascular accident; other abbreviations as in Table 3.

Possible mechanism underlying the reduced ACS in the PCI+MT group. In Table 3, use of nitrates was significantly smaller in the PCI+MT group than in the initial MT group, suggesting it is unrelated with the reduction in ACS in the PCI+MT group. Other variables showed no significant difference. Thus each of the variables in Table 3 seems to be independent of the beneficial effect seen in the PCI+MT group.

Two types of ACS occurred in patients entered into this study. One type was caused by progression of a PCI target lesion already showing significant stenosis at the time of entry to more severe stenosis as a result of thrombus formation via plaque rupture detected at the time of ACS onset during the follow-up. The PCI target lesion was treated with PCI at entry in the PCI+MT group, but not in the initial MT group. If a patient at entry had an acute occlusion or rapidly narrowing lesion, then he or she would not have met the study's inclusion criteria as a low-risk and stable patient. The second type was caused by progression of a non-PCI target lesion at entry to severe stenosis by thrombus formation via plaque rupture. We found that the incidence of ACS stemming from the PCI target lesion was significantly lower in the PCI+MT group than the initial MT group. Moreover, a number of studies, including those by Cutlip et al. (6) and Kimura et al. (7), have shown that the PCI target lesion may remain stable for more than 1 year after PCI. Therefore, the reduced incidence of ACS stemming from the PCI target lesion in the PCI+MT group may be caused by stabilization of PCI target coronary artery by PCI.

Generally, vulnerable plaques (ACS precursors) have a thinner fibrous cap and a larger lipid core than stable plaques and do not cause significant stenosis before they rupture, precipitating ACS. By contrast, stable plaques may narrow the coronary lumen and produce ischemia and anginal symptoms but are less likely to result in ACS. This has been claimed as the main reason why focal management of coronary lesions with significant stenosis using PCI does not improve long-term prognosis. That explanation is doubtful, however, because: 1) approximately one-third of AMIs stem from a coronary site that already shows significant stenosis (8); 2) approximately 40% of ACS cases observed during an 8-month follow-up reportedly originated from the PCI target lesion in patients with stable angina pectoris (9), and in approximately 40% of ACS cases originating from a non-PCI target lesion, the ACS-related site already had significant stenosis at the initial PCI (10); and 3) because of the widespread use of PCI to treat low-risk angina, there have been no reliable comparative studies of the rates of ACS originating from PCI target and non-PCI target lesions in the initial MT group. In fact, that analysis was omitted in earlier multicenter studies, such as the RITA-2 and the COURAGE trials. In the present initial MT group, more than one-half of ACS originated from the PCI target lesion. Thus, the present finding that a considerable number of ACS cases may originate from coronary sites with already severe stenosis makes it reason-

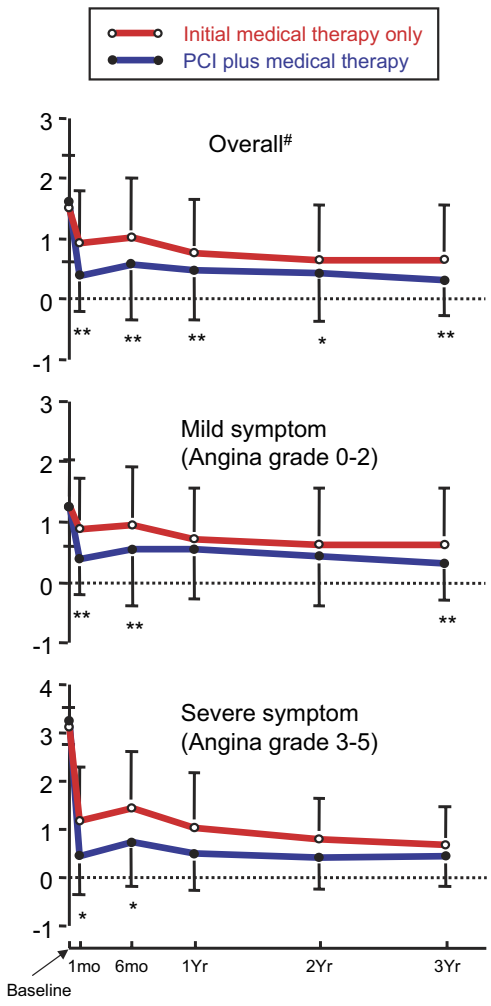

Figure 3. Changes in the Severity of Angina Symptoms During the Follow-Up

Note that the severity was significantly lower in the PCI plus medical therapy group than in the initial medical therapy only group. *$p < 0.05$. **$p < 0.01$ vs. the PCI plus medical therapy group. #Overall, the interaction between treatment and time was tested in repeated-measurement multivariate analysis of variance for complete cases. After missing observations were imputed using the last observation carried forward method, the p value was <0.0001. Abbreviations as in Figure 1.

able to expect that PCI therapy would protect against a future ACS attack by stabilizing the PCI target lesion as well as reducing stenosis.

The lower frequency of ACS in the PCI+MT group is compatible with that of the SWISSI II study but not with the majority of studies in the published literature, including the COURAGE trial, the RITA-2 trial, and the meta-analysis by Katritsis et al. (2). Possible explanations for this discrepancy may be as follows. Kaplan-Meier event-free survival curves for the PCI+MT groups in the COURAGE and RITA-2 trials seem to show curious biphasic changes that are clearly different from those obtained in the present study and the SWISSI II study, although we have no data with which to determine whether the biphasic changes were statistically significant. In the COURAGE and RITA-2 trials, there seems to be a marked downward shift in the curves for the PCI+MT group relative to those for the initial MT group during the initial 4 months, and this downward shift gradually disappeared in the later stages of the follow-up period. By contrast, such biphasic changes in the Kaplan-Meier event-free survival curves were not seen in the present study or the SWISSI II study; instead, the curve for the PCI+MT group was shifted upward relative to that of the initial MT group at the initial stage of follow-up, and that upward shift became greater at the later stages. If cardiac events occurring during the early stages are excluded, the incidence of late cardiac events would be smaller in the PCI+MT group, even in the COURAGE and RITA-2 trials, and the data from the late stages support the idea expressed in the present study; that is, PCI+MT treatment can improve long-term prognosis, probably by stabilizing the plaque at the PCI site. In addition, we suggest that a device such as the drug-eluting stent, which can strongly protect against cardiac events early after PCI (11,12), may further improve the total long-term prognosis obtained with PCI+MT, compared with that obtained with initial MT treatment.

We will now consider the increased incidence of ACS early during follow-up in the PCI+MT group in the RITA-2 study and the COURAGE study, which was indicated by the marked downward shift of the Kaplan-Meier curve (ACS incidence in the PCI+MT group at 4 months after PCI: 1% in the JSAP study vs. approximately 7% in the COURAGE study; in the initial MT group: 3% in the JSAP study vs. approximately 4% in the COURAGE study). In the RITA-2 study, the increase in ACS during the initial stage of follow-up could be explained by technical problems with the stents, which were used only rarely at that time but had become popular by the time of the present study. In addition, patients with 3-vessel disease were included in the COURAGE study (approximately one-third), and it is now established that 3-vessel disease is the most important risk factor for cardiac events after PCI (6,7). All of the subjects in the present study were stable CAD patients with 1- or 2-vessel disease, so that differences in the backgrounds of the patients may have contributed to the lower incidence of ACS seen in the present study, compared with the COURAGE study. Follow-up CAG is routinely carried out 3 to 12 months after PCI in Japan, which may be important for prevention of ACS. However, the marked downward shift of the Kaplan-Meier curve seen in the RITA-2 and COURAGE studies occurred within 3 months after PCI. In addition, the follow-up CAG was performed in both groups in the JSAP study (100% in the PCI+MT group and 96% in the initial MT group).

Therefore, it would not serve to offset the difference between the 2 groups in the JSAP study.

Finally, we will discuss PCI carried out under intravascular ultrasound (IVUS), which can enable prediction of and protection from various complications such as subacute thrombosis after PCI (13). In Japan, PCI is generally performed under IVUS. In the present study, this was true for all of the patients in the PCI+MT group, but it is not always true in the U.S. and elsewhere. The initial success rate per vessel for PCI was higher in the JSAP trial (99.5%) than in the COURAGE trial (93%), despite similar reductions in stenosis achieved with PCI (from 86% to 5% vs. from 82% to 2% in stent-treated vessels, and from 87% to 24% vs. from 83% to 31% in nonstent-treated vessels, respectively). Perhaps the better initial success rate in the JSAP trial reflects differences in the technical aspects of the PCI procedure (e.g., whether the PCI was IVUS-guided) rather than the degree of coronary atherosclerosis. Thus, the backgrounds of the patients and the PCI procedure may be important contributors to the differences between the present study and the RITA-2 or the COURAGE trial.

Study limitations. This study was not blinded. To limit the risk of bias, the patients were randomized by computer, objective outcomes were used, and a committee blinded to the treatment groups adjudicated the end points and based its decisions on hospital case records from other physicians not involved in the study.

In addition, despite formal power calculations, the sample size was relatively small. However, the follow-up was complete for 98.7% of the patients, which is very high compared with the 91% in the COURAGE trial, and the difference between the PCI+MT and initial MT groups was significant.

Conclusions

In patients with low-risk CAD, PCI+MT treatment may improve long-term prognosis more effectively than initial MT treatment.

Acknowledgments

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Key Words: angina pectoris ■ randomized trial ■ long-term prognosis.

APPENDIX

For a complete list of investigators and institutions, please see the online version of this article.