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Number of Yellow Plaques Detected in a Coronary Artery Is Associated With Future Risk of Acute Coronary Syndrome

Detection of Vulnerable Patients by Angioscopy

Tomohito Ohtani, MD, Yasunori Ueda, MD, PHD, FACC, FESC, Isamu Mizote, MD, Jota Oyabu, MD, Katsuki Okada, MD, Atsushi Hirayama, MD, PHD, FACC, Kazuhisa Kodama, MD, PHD, FACC

Osaka, Japan

OBJECTIVES We sought to test whether the risk of acute coronary syndrome (ACS) can be estimated by angioscopy.

BACKGROUND Disruption of vulnerable plaque and subsequent thrombosis is regarded as a major mechanism of ACS. Although yellow plaques are supposedly vulnerable, the association between angioscopically determined extent of coronary atherosclerosis and risk of ACS events has not been reported.

METHODS Patients (n = 552) who received catheterization and angioscopic examination for the diagnosis of coronary artery diseases were prospectively included and followed up for new onset of ACS events. Yellow color intensities of all detected yellow plaques were graded as 1, 2, or 3 according to the standard colors. Number of yellow plaques (NYP) in a coronary artery and maximum color grade of detected yellow plaques (maxYP) were determined. Association between the incidence of ACS events and angioscopic findings were analyzed.

RESULTS Follow-up interval was 57.3 ± 22.1 months. Acute coronary syndrome events were detected in 39 patients (7.1%). Although maxYP was not statistically different (2.0 ± 0.7 vs. 1.8 ± 0.9; p = 0.18), NYP was higher in the patients with an ACS event than those without the event (3.1 ± 1.8 vs. 2.2 ± 1.5; p = 0.008). Patients with NYP ≥2 and those with NYP ≥5 had 2.2- and 3.8-fold higher event rates, respectively, than those with NYP 0 or 1 (9.0% and 15.6%, respectively, vs. 4.1%; p = 0.02). Multivariate logistic regression analysis revealed NYP and multivessel disease as the independent risk factors of ACS events.

CONCLUSIONS Patients with multiple yellow plaques per vessel have a higher risk of suffering ACS events than those with NYP 0 or 1. Angioscopy would be useful to detect vulnerable patients. (J Am Coll Cardiol 2006;47:2194–200) © 2006 by the American College of Cardiology Foundation

Pathologic and angioscopic studies (1–5) have revealed that disruption of lipid-rich yellow plaques and subsequent thrombosis play a major role both in the development of acute coronary syndrome (ACS) and in the asymptomatic progression of coronary artery diseases. Yellow color intensity of plaques, which can be evaluated by angioscopy, is known to be determined by the thickness of fibrous cap, and is associated with plaque vulnerability (6,7). Although it is of great interest to find out from the whole coronary artery trees the "vulnerable plaques" that will cause ACS in the near future, angioscopy or any other invasive examination would not be practically useful for this purpose. However, we thought it would be beneficial to identify "vulnerable patients" using angioscopic findings. We previously proposed the hypothesis (8) on the process of yellow plaque formation and development of ACS. According to this hypothesis, patients with more yellow plaques of higher yellow color intensity would have a higher risk of suffering ACS. We have been prospectively following all patients who received angioscopic examination in our hospital since 1996 to find out if the risk of suffering an ACS event can be estimated by the angioscopic findings. Here we analyzed the follow-up data to October 2004 of the patients who received angioscopic examination from July 1996 to July 2002.

METHODS

Study patients and protocol. Patients who received catheterization and successful angioscopic examination for the diagnosis of coronary artery diseases were prospectively followed for ACS events since 1996. Although we included all the patients who received successful angioscopic examination for the first time, angioscopic examination was performed for the following reasons: 1) to identify and evaluate the culprit lesions in ACS patients; 2) to evaluate the stabilization/healing of the disrupted culprit plaques in the follow-up of ACS patients; 3) to evaluate the percutaneous coronary intervention (PCI) target lesions in patients with stable effort angina or silent myocardial ischemia; 4) to evaluate the stabilization/healing of the PCI site in the follow-up of patients with stable effort angina or silent myocardial ischemia; and 5) to examine in the

From the Cardiovascular Division, Osaka Police Hospital, Osaka, Japan. Drs. Ohtani and Ueda contributed equally to this paper.

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Abbreviations and Acronyms

ACS = acute coronary syndrome
maxYP = maximum color grade of detected yellow plaques
NYP = number of yellow plaques
PCI = percutaneous coronary intervention

suspected ACS patient without significant coronary stenosis if the patient has disrupted yellow plaque and thrombus formation. Acute coronary syndrome events as the end point of this study were defined as sudden cardiac death, acute myocardial infarction, and unstable angina that occurred after the initial catheterization. Sudden cardiac death included all death if a noncardiac cause was not identified. Acute myocardial infarction and unstable angina was defined as worsening or newly onset effort angina or chest pain at rest whose cause was identified as the newly developed occlusion or stenosis of coronary artery that required PCI or coronary artery bypass graft. Differentiation of acute myocardial infarction from unstable angina was previously done by the elevation of creatine kinase-MB and recently by the elevation of troponin T. We made efforts so that we would not miss any ACS event by performing coronary angiography in all possible ACS patients. Acute coronary syndrome due to restenosis or reocclusion of PCI site was excluded from the event. Therefore, the best efforts were made to detect all coronary events caused by abrupt progression of de novo lesions probably owing to plaque rupture and thrombosis. Treatment strategies of patients were decided without knowing the results of angioscopic examinations. A well-trained research nurse assessed the patients' characteristics using a structured questionnaire. Hypertensive patients in this study were defined as those with blood pressure ≥140/90 mm Hg or those already taking antihypertensive drugs. Hypercholesterolemic patients in this study were defined as those with fasting serum total cholesterol ≥220 mg/dl or those already taking lipid-lowering drugs. Diabetic patients were defined as those with fasting blood glucose ≥126 mg/dl or those already receiving drug therapy for diabetes mellitus. Patients were regarded as taking each drug (aspirin or statin) if the drug was administered at any time during the follow-up interval. Informed written consent was obtained from all patients. The protocol was approved by the Osaka Police Hospital Ethical Committee. For this report, patients who received angioscopic examination from July 1996 to July 2002 were included, and the ACS events documented to October 2004 were analyzed. Among 581 patients included for this study, 552 (95%) patients were successfully followed up. We examined if the baseline extent of coronary atherosclerosis evaluated by angioscopy would be associated with the incidence of ACS events during the follow-up interval.

Catheterization and angioscopic examination. Catheterization was performed by femoral approach using a 6- to 8-F sheath and catheters. Intravenous heparin (100 U/kg) was administered at the beginning of catheterization. A coronary angiogram was recorded by the Advantx medical system (General Electric, Milwaukee, Wisconsin). The culprit vessel with angiographically significant (>50%) stenosis was examined by angioscopy. In the patients without angiographically significant stenosis, the suspected culprit vessel that had mild or no coronary stenosis (<50%) or the vessel in which vasospasm was induced by acetylcholine stress test was examined by angioscopy. Angioscopic observation was performed from the distal segment to the ostium of the vessel as far as the vessel diameter was >2 mm. Angioscopic examination was performed before and after PCI, if needed, so that we could observe the whole target vessel fully. The angioscope MC-800E (Nihon Kohden, Tokyo, Japan) and the optic fiber AS-003 (Nihon Kohden) were used. The angioscopic observations were made while blood was cleared away from view by the injection of 3% dextran-40 as previously reported (3). The images of angioscopy were recorded on S-VHS and digital videotapes.

Evaluation of angioscopic images. Number of yellow plaques in the observed coronary artery and the yellow color intensity of those yellow plaques were evaluated. Yellow plaque was defined simply as the yellow area on the luminal surface, which may have a smooth or irregular surface with or without protrusion into the lumen. Yellow color of those plaques was graded as 1 (light yellow), 2 (yellow), or 3 (intense yellow) according to the standard colors as previously reported (7,9). If no yellow plaque was detected, the color grade was determined as 0 (white). The extent of coronary atherosclerosis was evaluated for each patient by the maximum yellow color grade (maxYP) and the number of yellow plaques (NYP). We made efforts not to miss white area in the yellow area, however narrow it might be; and if white area was detected in the midst of yellow area, we counted the yellow areas as separate yellow plaques. Thus, the sizes of yellow plaques were not so different (about 3 to 9 mm in length) in our study population. Angioscopic images were interpreted by two specialists in angioscopy, and in case of disagreement a third reviewer determined the evaluation. There were no cases where three reviewers judged different color grades, meaning at least two of them agreed on the judgment. Interobserver and intraobserver reproducibility for the interpretation of plaque color was 85% and 87%, respectively.

Statistics. Continuous data were presented as mean values ± SD. The incidence of ACS events was compared between groups by chi-squared test and estimated with the Kaplan-Meier method. A log rank test was used to compare the incidence of ACS events between groups. Data of patients' characteristics were compared between groups by the Student *t* test or chi-square test, and their influence on the incidence of ACS events was examined by multivariate logistic regression analysis. A p value of <0.05 was regarded as statistically significant.

RESULTS

Patients' characteristics. Among 552 patients included, ACS events were detected in 39 patients during the

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follow-up interval of 57.3 ± 22.1 months. Although one patient died from noncardiac cause, cardiac sudden death was not detected. Nonfatal acute myocardial infarction occurred in 17 patients and unstable angina in 22 patients. Patients' characteristics were compared between patients with and without an ACS event (Table 1). Prevalence of hypertension, hypercholesterolemia, diabetes mellitus, or current smoking was not different between the groups. Prevalence of multivessel disease was significantly higher in the patients with an ACS event. Although maxYP was not statistically different, NYP was higher in the patients with ACS event than those without the event. Patients' characteristics of those who suffered ACS event are further presented in Table 2. There was no significant difference in the time from angioscopic examination to ACS event between the patients with NYP 0 or 1 and those with NYP ≥2 (32.3 ± 27.4 months vs. 28.4 ± 23.4 months; p = 0.71). There was no significant difference in the time from angioscopic examination to an ACS event between the patients who had >50% stenosis and those who had ≤50% stenosis in the future ACS culprit at baseline angiography (34.5 ± 27.2 months vs. 27.6 ± 23.8 months; p = 0.45). Figure 1 shows the distribution of maxYP and NYP. Multiple yellow plaques (NYP ≥2) were observed in 335 patients (60%), and ≥5 yellow plaques were observed in 45 patients (8%). A representative case with no yellow plaque and that with multiple yellow plaques were presented in Figure 2. The culprit lesion of ACS event had been observed by angioscopy at baseline only in four patients (10.3%). The yellow color grade of those lesions was 0 in no patient, 1 in one (25%) patient, 2 in two (50%) patients, and 3 in one (25%) patient. A case among them was presented in Figure 3.

Table 1. Patient Characteristics

	Event Free (n = 513)	ACS Event (n = 39)	p Value
Age, yrs	59.9 ± 10.2	59.7 ± 8.4	0.92
Male gender, n (%)	411 (80)	32 (84)	0.54
Diagnosis at baseline, n (%)			
Acute MI	267 (52)	21 (54)	0.83
On PCI	155 (30)	13 (33)	
At FU*	112 (22)	8 (21)	
Unstable angina	90 (18)	8 (21)	0.64
On PCI	76 (15)	8 (21)	
At FU*	14 (3)	0 (0)	
Stable effort angina	68 (13)	5 (13)	0.94
On PCI	53 (10)	5 (13)	
At FU*	15 (3)	0 (0)	
Silent myocardial ischemia	62 (12)	4 (10)	0.74
On PCI	57 (11)	3 (7)	
At FU*	5 (1)	1 (3)	
No coronary stenosis >50%	26 (5)	1 (3)	0.49
PCI performed at baseline, n (%)	341 (67)	29 (74)	0.31
Angioscopically examined vessel, n (%)			
LAD	272 (53)	18 (46)	0.41
LCX	77 (15)	8 (21)	0.38
RCA	164 (32)	13 (33)	0.84
Prior MI, n (%)	217 (42)	17 (44)	0.87
No. of diseased vessel,† n (%)			
3	52 (10)	8 (21)	0.04
2	118 (23)	13 (33)	0.14
1	317 (62)	17 (44)	0.03
0	26 (5)	1 (3)	0.48
Multivessel disease,‡ n (%)	170 (33)	21 (54)	0.01
Coronary risk factors, n (%)			
Hypertension	268 (52)	23 (59)	0.41
Hypercholesterolemia	288 (56)	23 (59)	0.74
Diabetes mellitus	163 (31)	14 (36)	0.59
Current smoking	230 (44)	21 (54)	0.31
Medications, n (%)			
Aspirin	479 (93)	37 (95)	0.95
Statin	331 (65)	21 (54)	0.23
Angioscopic findings			
maxYP	1.8 ± 0.9	2.0 ± 0.7	0.18
NYP	2.2 ± 1.5	3.1 ± 1.8	0.008

Data are presented as n (%) or mean ± SD. *Planned follow-up at 1 or 6 months after PCI. †Number of vessels with >75% diameter stenosis by angiography. ‡Multivessel disease was defined as having ≥2 coronary vessels with >75% diameter stenosis by angiography.

ACS = acute coronary syndrome; FU = follow-up; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; maxYP = maximum yellow color grade; MI = myocardial infarction; NYP = number of yellow plaques; PCI = percutaneous coronary intervention; RCA = right coronary artery.

Table 2. Patient Characteristics of Those Who Suffered an ACS Event

n	39
Time from angioscopic examination to ACS event, months (mean ± SD)	29.3 ± 24.1
Type of ACS event, n (%)	
Acute MI	17 (44)
Unstable angina	22 (56)
Culprit vessel of ACS event, n (%)	
LAD	14 (36)
LCX	12 (31)
RCA	12 (31)
LMCA	1 (2)
Diameter stenosis of ACS culprit at baseline, n (%)	
≤50%	27 (69)
>50%	12 (31)
ACS culprit observed by angioscopy at baseline, n (%)	4 (10)

LMCA = left main coronary artery; other abbreviations as in Table 1.

Risk of ACS event. According to the results of multivariate logistic regression analysis (Table 3), multivessel disease and NYP were the independent risk factors of an ACS event. Presence of multiple yellow plaques was associated with incidence of an ACS event (log-rank 5.53; p = 0.02) (Fig. 4). Patients with multiple yellow plaques (NYP ≥2) had a 2.2-fold higher incidence of an ACS event than those with fewer (NYP 0 or 1) yellow plaques (9.0% [30 of 335] vs. 4.1% [9 of 217]; p = 0.02). Furthermore, patients with ≥5 yellow plaques had an extremely higher (3.8-fold) incidence of an ACS event than those who had no or a single yellow plaque (15.6% [7 of 45] vs. 4.1% [9 of 217]; p = 0.01). The use of a statin did not have significant influence on the risk of ACS events by logistic regression analysis in the present study. However, the use of a statin was associated with a lower incidence of an ACS event among patients with multiple yellow plaques (13.8% [15 of 108] vs. 6.6% [15 of 227]; p = 0.02), although it was not

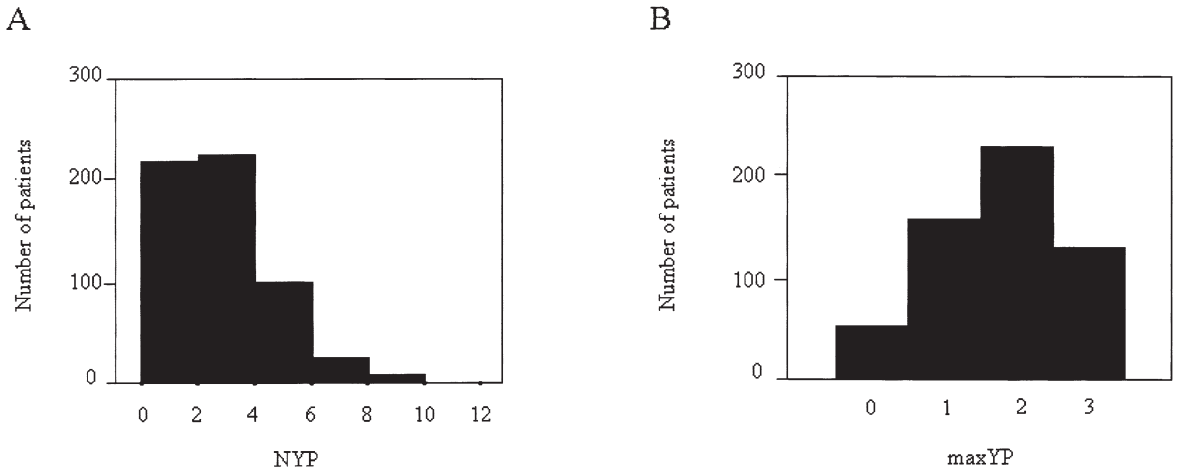

Figure 1. Distributions of number of yellow plaques (NYP) **(A)** and maximum color grade of yellow plaques (maxYP) **(B)**. Patients with NYP ≥2 and those with NYP ≥5 comprised 60% and 9% of study patients, respectively.

among patients with fewer yellow plaques (3.4% [3 of 86] vs. 4.6% [6 of 131]; p = 0.41).

DISCUSSION

We have demonstrated in the present study that the number of yellow plaques in a coronary artery and multivessel disease are independent risk factors of an ACS event. Patients with ≥2 yellow plaques and those with ≥5 yellow plaques had a 2.2- and 3.8-fold higher incidence of an ACS event, respectively, than those with no or a single yellow plaque. Therefore, angioscopy may be useful to find patients at high risk of an ACS event (i.e., vulnerable patients). This would be the first report, to our knowledge, that reveals the association between the presence of multiple yellow plaques determined by angioscopy and the future incidence of pure ACS events, excluding the events caused by restenosis/reocclusion among patients with wide spectrum of coronary artery diseases.

Classic coronary risk factors and plaque formation. Hypertension, hypercholesterolemia, diabetes mellitus, and current smoking are known (10–13) to enlarge lipid-rich coronary plaques and increase their vulnerability. However, those classic coronary risk factors were not selected as independent risk factors of an ACS event in the present

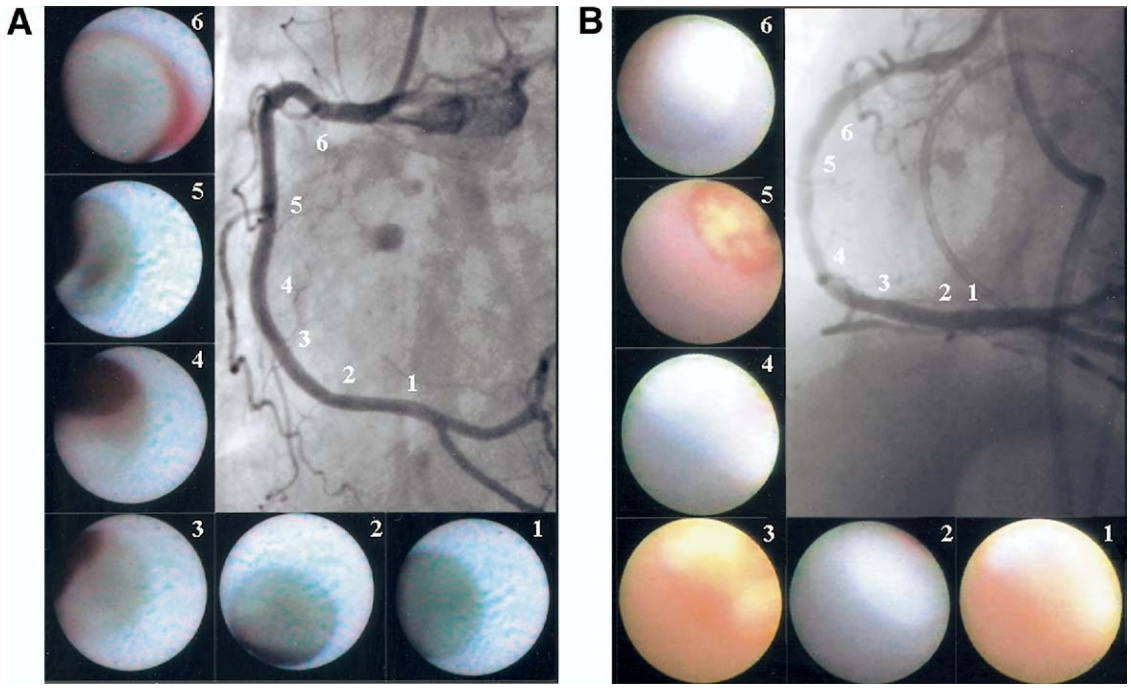

Figure 2. A representative case with no yellow plaque **(A)** and a representative case with multiple yellow plaques **(B)**. **(A)** No yellow plaque was detected in the right coronary artery: number of yellow plaques (NYP) 0, maximum color grade of yellow plaques (maxYP) 0. **(B)** Three yellow plaques were detected in the right coronary artery: NYP 3, maxYP 3.

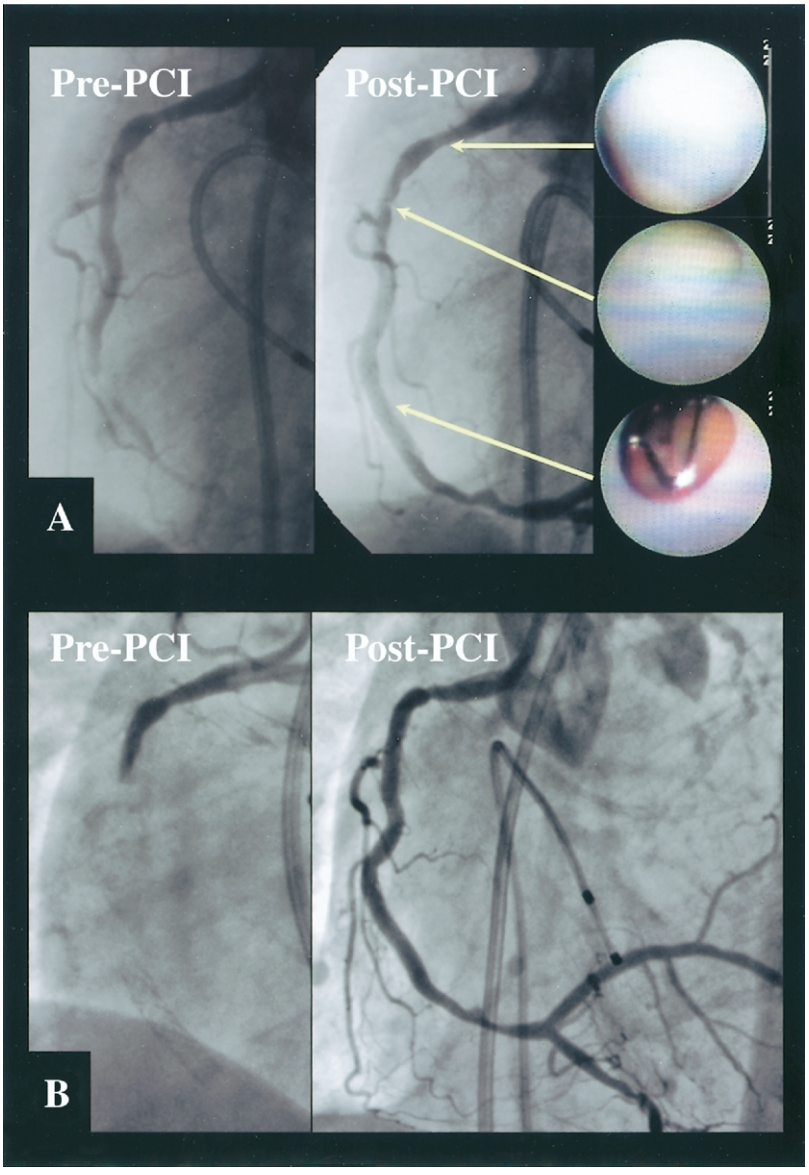

Figure 3. A case in which culprit vessel of acute coronary syndrome event had been observed by angioscopy at baseline. The patient was a 48-year-old man. **(A)** Initial clinical presentation when angioscopy was performed was inferior acute myocardial infarction. The culprit lesion was in the distal right coronary artery. **(B)** The second event was also inferior acute myocardial infarction, 51 months later. The culprit lesion was in the proximal right coronary artery where yellow plaque had been detected. PCI = percutaneous coronary intervention.

study. Because yellow plaques are regarded as the direct cause of an ACS event (14), classic coronary risk factors may work as a risk for an ACS event mainly through the formation of yellow plaques.

Multiple plaques and ACS events. Several reports have revealed multiple vulnerable plaques in the patients with coronary heart disease and have been associated with the risk of ACS events. Presence of plaque ruptures remote from the culprit lesion has been shown in autopsy studies (15,16), angiography studies (17), and intravascular ultrasound (IVUS) studies (18–21). The presence of multiple complex lesions in the patients with ACS has been associated with a high incidence of subsequent cardiac events unrelated to the initial event (17), although the ruptured plaque detected by IVUS has not been associated with clinical events under statin treatment (21). Yellow plaques are more often accompanied by thrombus and regarded as more vulnerable than white plaques, as we have previously reported (7). Waxman et al. (22) have demonstrated that yellow plaques are associated with the risk of adverse outcomes after balloon angioplasty. These reports are consistent with our result that patients with multiple yellow plaques have higher risk of ACS event.

Extent of plaque formation in culprit and nonculprit vessels. The process of plaque formation is now regarded as a pan-coronary process occurring widely in three coronary vessels. Three-vessel IVUS study revealed multiple plaque ruptures in nonculprit segments of culprit and nonculprit vessels (19,20). We have previously reported using angioscopy that number of yellow plaques in a coronary artery is

Table 3. Independent Risk Factors of ACS Event by Multivariate Logistic Regression Analysis

	Adjusted Hazard Risk* (95% CI)	p Value
NYP	1.23 (1.03–1.45)	0.02
Multivessel disease†	2.21 (1.10–4.46)	0.03
Statin use	0.38 (0.12–1.19)	0.10

*Adjusted for male gender, age, ACS at baseline, prior myocardial infarction, hypertension, diabetes mellitus, hypercholesterolemia, current smoking, aspirin use. †Multivessel disease was defined as having ≥2 coronary vessels with >75% diameter stenosis by angiography.

ACS = acute coronary syndrome; CI = confidence interval; NYP = number of yellow plaques.

not different between infarct-related and infarct-nonrelated coronary arteries, suggesting that formation of yellow plaques may progress equally in three major coronary arteries (23). Therefore, the extent of coronary atherosclerosis and the risk of future ACS events may be evaluated by observing any one of three coronary arteries.

Angioscopically determined extent of coronary atherosclerosis. The extent of plaque formation would be measured by the area and the vulnerability of yellow plaques. Because vulnerability of yellow plaques could be measured by their yellow color intensity (7), we used the maximum yellow color grade as the marker of plaque vulnerability. Because we could not measure the total area of yellow plaques by angioscopy, we used the number of yellow plaques as the marker of plaque area. One of the reasons why maxYP was not proved to be a significant risk in the present study may be that it would reflect only the probability of the plaque to rupture but not necessarily the probability of the plaque to cause ACS. It will be difficult to find the specific plaque that has a high probability of causing ACS, because silent plaque ruptures are often observed by angioscopy or IVUS and because we do not know the time course of plaque formation and rupture. Because the time course of yellow plaque formation and disruption is unknown, it is possible that coronary segments that will cause a future ACS event may not have yellow plaque at baseline. Most yellow plaques observed at baseline may not cause an ACS event even if they disrupted (silent plaque rupture); in contrast, yellow plaques that caused an ACS event might be formed after the time of baseline angioscopic observation. We had the information on the baseline angioscopic appearance of the segments that caused an ACS event later only in four patients. However, we revealed in the present study that vulnerable patients could be detected by the number of yellow plaques in a coronary artery evaluated by angioscopy. The vulnerability of yellow plaques may change within a shorter period than the number of yellow plaques changes; therefore, the number of yellow plaques rather than the vulnerability of those plaques may better reflect the risk of an ACS event. The most important observation in our study is that imaging analysis would predict future risk for cardiovascular events by the overall number of lesions rather than by identifying the most vulnerable lesions.

Prevention of ACS events by lipid-lowering therapy with statins. Although lipid-lowering therapy with statins was reported effective to prevent secondary cardiac events (24–26), it was not selected by multivariate logistic regression analysis in this study as a factor that had significant influence on the incidence of an ACS event. A possible reason may be that our study population was small and was not randomized for the use of statins. Actually, the percentage of statin use increased at follow-up compared with the point of enrollment. However, among patients with multiple yellow plaques, statin use was significantly associated with a low incidence of ACS events, whereas among patients with no or a single yellow plaque it was not. Therefore, statin treatment may be more effective in the patients with multiple yellow plaques. The mechanism of statin-induced plaque stabilization (27,28) is thought to be a change in plaque composition from large lipid core with thin fibrous cap to small lipid core with thick fibrous cap. Angioscopic study (29) also revealed that statin treatment reduced yellow color intensity of coronary plaques. Therefore, angioscopy may be useful to select patients who will receive more benefit from statin treatment.

Clinical implications. We can evaluate the risk of an ACS event for each patient by angioscopy and change the therapy according to the evaluated risk; however, its application is limited to the relatively high-risk patients who receive catheterization. Furthermore, we may be able to use angioscopy to determine the surrogate end point in clinical trials to evaluate the effect of drugs that reduce the risk of ACS events through the regression of vulnerable plaques.

Study limitations. Because only the patients with successful angioscopic examination were included in this study, results might not apply to the patients who had coronary arteries not suitable for angioscopic examination (e.g., diffusely stenotic or tortuous coronary arteries). We may possibly underestimate the extent of plaque formation in the patients who have a few but

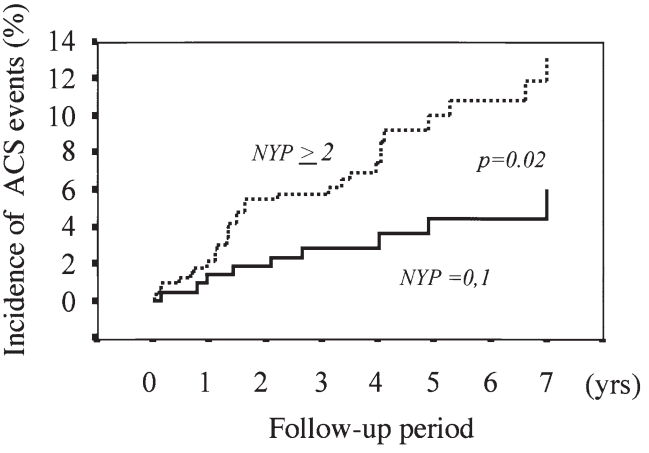

Figure 4. Incidence of acute coronary syndrome (ACS) events. The incidence of ACS events was estimated with the Kaplan-Meier method. Patients with multiple yellow plaques (number of yellow plaques [NYP] ≥2) had a significantly higher incidence (p = 0.02 by log rank test) of ACS events compared with those with fewer yellow plaques (NYP 0 or 1).

large yellow plaques; however, in the real world among the Japanese population, the size of yellow plaques was not very different (about 3 to 9 mm in length) in most patients. Furthermore, large yellow plaques were exclusively detected in the patients who had multiple yellow plaques (i.e., no patient had only one large yellow plaque). Therefore, the effect of this underestimation should be small. However, theoretically, this is an important limitation of angioscopic evaluation and should better be solved by developing a new analyzing method. The length of observed coronary artery by angioscopy was not measured. However, the number of yellow plaques per vessel may be better associated with the risk of the patient to suffer an ACS event than the number of yellow plaques per observed vessel length. Because this study was not designed to evaluate the effect of drug interventions, interpretation on the effect of statins should be limited. Although we observed only one of three coronary arteries at baseline, based on the fact that number of yellow plaques was not statistically different among three coronary arteries, the other two coronary arteries might not always have similar yellow plaques. Although the data on C-reactive protein was reported to be associated with the ACS risk, they were not available and were not included for analysis in the present study.

Conclusions. Patients with ≥2 yellow plaques and those with ≥5 yellow plaques have a 2.2- and 3.8-fold higher incidence of an ACS event, respectively, than those with a single or no yellow plaque in a coronary artery. Angioscopy would be useful for the detection of vulnerable patients who have a high risk of suffering ACS events.

Reprint requests and correspondence: Dr. Yasunori Ueda, Cardiovascular Division, Osaka Police Hospital, 10-31 Kitayama-cho, Tennoji-ku, Osaka, 543-0035 Japan. E-mail: ueda@oph.gr.jp.

REFERENCES

1. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (1). N Engl J Med 1992;326:242–50.
2. Waxman S, Mittleman MA, Zarich SW, et al. Angioscopic assessment of coronary lesions underlying thrombus. Am J Cardiol 1997; 79:1106–9.
3. Ueda Y, Asakura M, Hirayama A, Komamura K, Hori M, Kodama K. Intracoronary morphology of culprit lesions after reperfusion in acute myocardial infarction: serial angioscopic observations. J Am Coll Cardiol 1996;27:606–10.
4. Thieme T, Wernecke KD, Meyer R, et al. Angioscopic evaluation of atherosclerotic plaques: validation by histomorphologic analysis and association with stable and unstable coronary syndromes. J Am Coll Cardiol 1996;28:1–6.
5. Davies MJ. Stability and instability: two faces of coronary atherosclerosis. The Paul Dudley White Lecture 1995. Circulation 1996;94: 2013–20.
6. Kawasaki M, Takatsu H, Noda T, et al. In vivo quantitative tissue characterization of human coronary arterial plaques by use of integrated backscatter intravascular ultrasound and comparison with angioscopic findings. Circulation 2002;105:2487–92.
7. Ueda Y, Ohtani T, Shimizu M, Hirayama A, Kodama K. Assessment of plaque vulnerability by angioscopic classification of plaque color. Am Heart J 2004;148:333–5.
8. Ueda Y, Ohtani T, Shimizu M, Mizote I, Hirayama A, Kodama K. Coronary atherosclerosis and acute coronary syndrome: new insights from angioscopic viewpoints. Vasc Dis Prev 2004;1:53–7.
9. Ueda Y, Asakura M, Yamaguchi O, Hirayama A, Hori M, Kodama K. The healing process of infarct-related plaques. Insights from 18 months of serial angioscopic follow-up. J Am Coll Cardiol 2001;38:1916–22.
10. Virmani R, Burke A, Farb A. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. Eur Heart J 1998;19:678–80.
11. Meyer G, Merval R, Tedgui A. Effects of pressure-induced stretch and convection on low-density lipoprotein and albumin uptake in the rabbit aortic wall. Circ Res 1996;79:532–40.
12. Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. N Engl J Med 1997;336:1276–82.
13. Moreno PR, Murcia AM, Palacios IF, et al. Coronary composition and macrophage infiltration in atherectomy specimens from patients with diabetes mellitus. Circulation 2000;102:2180–4.
14. Fernandez-Ortiz A, Badimon JJ, Falk E, et al. Characterization of the relative thrombogenicity of atherosclerotic plaque components: implications for consequences of plaque rupture. J Am Coll Cardiol 1994;23:1562–9.
15. Falk E, Shah PK, Fuster V. Coronary plaque disruption. Circulation 1995;92:657–71.
16. Davies MJ, Thomas A. Thrombosis and acute coronary-artery lesions in sudden cardiac ischemic death. N Engl J Med 1984;310:1137–40.
17. Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neill WW. Multiple complex coronary plaques in patients with acute myocardial infarction. N Engl J Med 2000;343:915–22.
18. Schoenhagen P, Stone GW, Nissen SE, et al. Coronary plaque morphology and frequency of ulceration distant from culprit lesions in patients with unstable and stable presentation. Arterioscler Thromb Vasc Biol 2003;23:1895–900.
19. Rioufol G, Finet G, Ginon I, et al. Multiple atherosclerotic plaque rupture in acute coronary syndrome: a three-vessel intravascular ultrasound study. Circulation 2002;106:804–8.
20. Hong MK, Mintz GS, Lee CW, et al. Comparison of coronary plaque rupture between stable angina and acute myocardial infarction: a three-vessel intravascular ultrasound study in 235 patients. Circulation 2004;110:928–33.
21. Rioufol G, Gilard M, Finet G, Ginon I, Boschat J, Andre-Fouet X. Evolution of spontaneous atherosclerotic plaque rupture with medical therapy: long-term follow-up with intravascular ultrasound. Circulation 2004;110:2875–80.
22. Waxman S, Sassower MA, Mittleman MA, et al. Angioscopic predictors of early adverse outcome after coronary angioplasty in patients with unstable angina and non–Q-wave myocardial infarction. Circulation 1996;93:2106–13.
23. Asakura M, Ueda Y, Yamaguchi O, et al. Extensive development of vulnerable plaques as a pan-coronary process in patients with myocardial infarction: an angioscopic study. J Am Coll Cardiol 2001;37:1284–8.
24. 4S Group. Randomised trial of cholesterol lowering in 4,444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9.
25. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349–57.
26. Pitt B, Mancini GB, Ellis SG, Rosman HS, Park JS, McGovern ME. Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I): reduction in atherosclerosis progression and clinical events. PLAC I investigation. J Am Coll Cardiol 1995;26:1133–9.
27. Aikawa M, Rabkin E, Sugiyama S, et al. An HMG-CoA reductase inhibitor, cerivastatin, suppresses growth of macrophages expressing matrix metalloproteinases and tissue factor in vivo and in vitro. Circulation 2001;103:276–83.
28. Shimizu K, Aikawa M, Takayama K, Libby P, Mitchell RN. Direct antiinflammatory mechanisms contribute to attenuation of experimental allograft arteriosclerosis by statins. Circulation 2003;108:2113–20.
29. Takano M, Mizuno K, Yokoyama S, et al. Changes in coronary plaque color and morphology by lipid-lowering therapy with atorvastatin: serial evaluation by coronary angioscopy. J Am Coll Cardiol 2003;42: 680–6.