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Multiple Plaque Rupture and C-Reactive Protein in Acute Myocardial Infarction

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OBJECTIVES This study sought to investigate the relationship between multiple plaque ruptures, C-reactive protein (CRP), and clinical prognosis in acute myocardial infarction (AMI).

BACKGROUND Several studies have demonstrated that ruptured or vulnerable plaques exist not only at the culprit lesion but also in the whole coronary artery in some acute coronary syndrome (ACS) patients. Recent studies have reported that a ruptured plaque at the culprit lesion is associated with elevated CRP, which indicates a poor prognosis in patients with ACS.

METHODS We performed intravascular ultrasound in 45 infarct-related arteries and another 84 major coronary arteries in 45 first AMI patients.

RESULTS Plaque rupture was observed in 21 patients (47%) at the culprit site. Intravascular ultrasound revealed 17 additional plaque ruptures at remote sites in 11 patients (24%). Patients with multiple risk factors were more frequently found in our multiple-plaque rupture patients compared with single-plaque rupture or nonrupture patients (82% vs. 40% vs. 29%, $p = 0.01$). High-sensitive CRP levels had a positive correlation with the number of plaque ruptures ($p < 0.01$). All culprit lesions were successfully treated by percutaneous coronary intervention. Patients with multiple plaque rupture showed significantly poor prognosis compared with others ($p = 0.01$).

CONCLUSIONS Multiple plaque rupture is associated with systemic inflammation, and patients with multiple plaque rupture can be expected to show a poor prognosis. Our results suggest that AMI treatment should focus not only on stabilization of the culprit site but also a systemic approach to systemic stabilization of the arteries. (J Am Coll Cardiol 2005;45:1594–9)
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A number of pathologic studies have suggested that plaque rupture and subsequent thrombosis are major causes of acute coronary syndrome (ACS) (1). Some studies have documented that ruptured plaque and/or vulnerable plaque exists not only at the culprit lesion but also in a pan-coronary artery setting in ACS patients (2–4). We have recently reported that pre-intervention intravascular ultrasound (IVUS) can identify lesion morphology, including the features of plaque rupture, in acute myocardial infarction (AMI) (5–7) and that ruptured plaque at the culprit lesion is associated with elevated C-reactive protein (CRP) (8).

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Elevation of CRP levels is associated with a poor prognosis and is a predictor of future risk of AMI (9–15). To the best of our knowledge, however, few studies have addressed the relationship between multiple-plaque rupture, CRP, and prognosis in AMI. In this study, our aim was to investigate the relationship between multiple-plaque rupture, as observed under IVUS, CRP, and prognosis in AMI.

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METHODS

Patient population. Between December 2002 and July 2003, we attempted to perform IVUS in the entire coronary trees of 45 patients with a first AMI (with or without ST-segment elevation). Infarct-related arteries were observed using IVUS before any percutaneous coronary intervention (PCI) within 6 h from the onset of symptoms, and the remaining coronary vasculature was examined within one month. No patients received any thrombolytic therapy. Diagnosis of AMI was done according to a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction (16). The infarct-related arteries or culprit lesions were identified using a combination of electrocardiographic findings, left ventricular wall motion abnormalities on echocardiography, scintigraphic findings, and angiographic findings. We excluded from our population patients with coronary artery bypass failure ($n = 1$) or subjects who required emergent coronary artery bypass graft surgery ($n = 2$), patients with subacute thrombosis or restenosis after PCI ($n = 2$), and patients in whom adequate IVUS images of the culprit site could not be obtained ($n = 1$). Patients in whom the culprit lesion could not be identified by angiograms were also excluded ($n = 1$). We further excluded patients with active inflammatory disease ($n = 1$) and postoperative status ($n = 1$). The protocol for the study was approved by the ethics committee of the Baba

Abbreviations and Acronyms

ACS = acute coronary syndrome
AMI = acute myocardial infarction
hs-CRP = high-sensitivity C-reactive protein
IVUS = intravascular ultrasound
PCI = percutaneous coronary intervention

Memorial Hospital. We also obtained written, informed consent from all participants before initial coronary angiography.

Study protocol. First, blood samples were taken from a peripheral vessel in the emergency room before the administration of any medical agents. In all patients, coronary angiography was performed using a 6-F Judkins-type catheter via the femoral approach. All patients received an intravenous bolus injection of 10,000 IU heparin and intracoronary isosorbide dinitrate (2 mg) before angiography. All patients were evaluated with pre-intervention IVUS. The IVUS catheter (3.2-F Ultra Cross, or Atlantis, Boston Scientific, Massachusetts) was carefully advanced distal to the culprit lesion under fluoroscopic guidance. It was then pulled back automatically from the distal portion at 0.5 mm/s, facilitating observation of the lesion. The IVUS images were recorded on S-VHS videotape for off-line analysis. While pulling back the catheter, we manually infused a contrast medium suitable for IVUS imaging (6), while carefully observing the lesion. Coronary angiography and IVUS were performed again one month after onset.

CRP analysis. The blood samples were centrifuged, and serum was removed and stored at −80°C until an assay could be performed. High-sensitivity C-reactive protein (hs-CRP) was analyzed using a commercially available testing kit (N-Latex CRP II, Dade Behring Marburg Gmbh, Marburg, Germany). Measurements of hs-CRP were repeated one month after the onset of AMI.

Analysis of IVUS images. The morphologic features detected in our IVUS images were interpreted by two independent experienced observers (D.F. and K.S.) unfamiliar with the clinical data. Evaluation of lesion morphology and other measurements during IVUS were done according to the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (17). Fissure was defined as an abrupt, focal, superficial break in the linear continuity of the plaque, extending in a radial direction. Dissection was defined as rupture of the plaque creating one or more neolumina. A lipid pool-like image was defined as a pooling of low-echoic material or echolucent material covered with a high-echoic layer (7). Computer planimetry (TapeMeasure, Indec Systems, Capitola, California) was used to measure the culprit lesion site, including the morphometric parameters and external elastic membrane cross-sectional area (EEM-CSA). The incidence of lesion EEM-CSA larger than the proximal reference EEM-CSA was defined as positive remodeling. We defined IVUS plaque rupture lesions as follows: 1) lesions with fissure/dissection; or 2) lesions without fissure/dissection but in which injection of saline or contrast medium confirmed a communication between the plaque and coronary artery lumen (8).

Angiographic analysis. Coronary angiograms were reviewed separately by two independent observers (Y.N. and T.S.) unaware of the IVUS findings. Perfusion degree was evaluated according to Thrombolysis In Myocardial Infarction (TIMI) criteria (18), and collaterals were graded according to the Rentrop classification (19), with good collateral flow defined as grade 2 or 3. Angiographic thrombus was defined as a filling defect seen in multiple projections surrounded by contrast in the absence of calcification and >10 mm in length. Definition of complex lesions were followed a previous report (20).

Clinical follow-up. The medication protocol was left to the discretion of the individual cardiologist. All patients were reviewed monthly at the outpatient clinic of the Baba Memorial Hospital. Data were collected prospectively from hospital charts. The primary end point was major cardiac adverse events, defined as cardiac death, recurrent or new-onset ACS, coronary artery bypass graft surgery, and target lesion revascularization.

Statistical analysis. Results are expressed as the mean value ± SD for continuous variables. Qualitative data are presented as numbers (%). Statistical analysis was done with commercially available software (StatView, SAS Institute, Cary, North Carolina). Continuous variables were compared using the Student *t* test or analysis of variance. Scheffe's method was used for multiple comparisons, and the chi-square test for categorical data. The IVUS measurements were done only at the culprit site in this study. Spearman's rank correlation test was used in analysis for the correlation between numbers of plaque ruptures and serum CRP levels. Clinical outcomes in multiple-plaque rupture patients, single-plaque rupture patients, and nonplaque rupture patients were examined by Kaplan-Meier curves and the log-rank test. A p value <0.05 was considered statistically significant.

RESULTS

Plaque rupture identified by IVUS. Intravascular ultrasound was conducted in all 45 culprit coronary arteries and the other 84 major coronary arteries without serious complications. For simply anatomic reasons (four small vessels or two tortuous arteries), IVUS could not be used successfully in six coronary arteries in six patients (13%). Plaque rupture was observed in 21 patients (47%) at the culprit site in the acute phase of AMI. Intravascular ultrasound revealed 17 occult plaque ruptures at remote sites in 11 patients (24%). These 11 patients also presented plaque rupture at the culprit site. Other plaque ruptures in remote sites of the infarct-related artery were found in 6 (13%) of

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Table 1. Pre-Intervention Intravascular Ultrasound Findings of Culprit Lesions

	Multiple-Plaque Rupture (n = 11)	Single-Plaque Rupture (n = 10)	Nonplaque Rupture (n = 24)	p Value
IVUS images				
Eccentric	8 (73%)	8 (80%)	10 (42%)	0.06
Fissure/dissection	10 (91%)	6 (67%)	0	
Lipid pool-like image	6 (55%)	7 (70%)	0	<0.001
Superficial calcium	5 (45%)	5 (50%)	10 (42%)	0.9
Deep calcification	5 (45%)	2 (20%)	10 (42%)	0.41
Positive remodeling	5 (49%)	3 (30%)	8 (33%)	0.72
Distal reference EEM CSA (mm^2)	15.3 ± 5.0	17.3 ± 6.1	12.7 ± 4.0*	0.03
Distal reference lumen CSA (mm^2)	7.2 ± 2.4	8.1 ± 4.0	5.9 ± 2.7	0.13
Lesion EEM CSA (mm^2)	18.2 ± 6.3	17.4 ± 5.0	13.4 ± 4.1†	0.02
Lesion lumen CSA (mm^2)	2.2 ± 1.1	2.5 ± 2.1	2.0 ± 2.1	0.59
Proximal reference EEM CSA (mm^2)	18.9 ± 6.7	20.5 ± 5.7	14.8 ± 4.6†	0.01
Proximal reference lumen CSA (mm^2)	8.9 ± 3.1	11.3 ± 5.4	6.6 ± 2.4*	<0.01

*$p < 0.01$ vs. single-plaque rupture. †$p < 0.05$ vs. others. These p values resulted from Scheffe's method of multiple comparisons. Data are presented as the mean value ± SD or number (%) of patients.
CSA = cross-sectional area; EEM = external elastic membrane; IVUS = intravascular ultrasound.

these 11 patients. This means that multiple-plaque ruptures were found in 11 patients (multiple-plaque rupture group); a single-plaque rupture at the culprit site was found in 10 patients (single-plaque rupture group); and no plaque ruptures were found in 24 patients (nonplaque rupture group). The other IVUS findings are summarized in Table 1. A representative case of multiple-plaque rupture is shown in Figure 1.

Patient characteristics and angiographic results. The patient characteristics for each group are summarized in Table 2. Half of our patients presented with ST-segment elevation MI. Patients with multiple-plaque rupture had more of a history of diabetes mellitus or multiple coronary risk factors, as compared with the single-plaque rupture or nonplaque rupture group. Angiographic results have been summarized in Table 3. The multiple-plaque rupture group presented with more complex lesions in both the infarct-related artery and other coronary arteries, as compared with other groups. No distal protection device was used in this study.

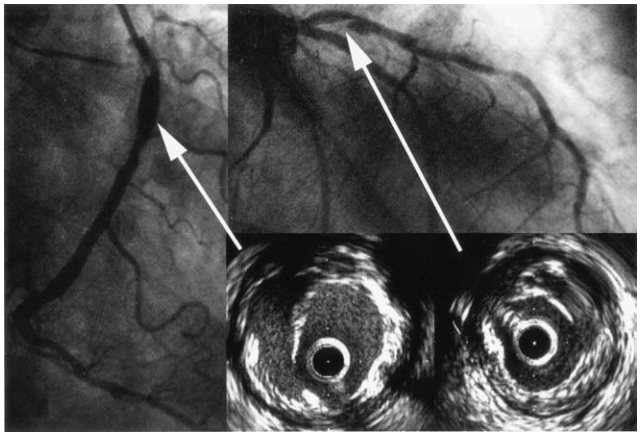

Figure 1. A representative case of multiple plaque rupture. Plaque rupture were observed in the proximal left descending coronary artery and mid portion of the right coronary artery.

Results of CRP levels. Patients with plaque rupture at the culprit site presented with higher hs-CRP levels, as compared with patients without plaque ruptures (3.1 ± 0.5 mg/l vs. 1.9 ± 0.4 mg/l, $p = 0.04$). At one month from onset, the number of plaque ruptures showed a positive correlation with hs-CRP levels ($p < 0.01$) (Fig. 2).

Clinical outcomes. The mean clinical follow-up period was 23 ± 11 months. During follow-up, all patients received aspirin, 42 patients (93%) received ticlopidine, 9 patients (20%) received beta-blockers, and 11 patients (24%) received statins. There were no significant differences in the use of these three drugs in the three groups. There were no cardiac events during the in-hospital period. After discharge, there was one death and four cases (8.9%) of recurrent ACS. All four patients were from the multiple-plaque rupture group (one case from a remote site in the infarct-related artery and three from a non–infarct-related artery), and no mortality or ACS was observed in other groups. Repeat PCI at the culprit lesion was performed in one patient in the multiple-plaque rupture group, two in the single-plaque rupture group, and two in the nonplaque rupture group. Therefore, a total of nine patients (20%) with recurrent ischemia required repeat PCI. The Kaplan-Meier curve showed that the multiple-plaque rupture group was associated with poor clinical outcomes, as compared with the other groups at two years ($p = 0.01$) (Fig. 3).

DISCUSSION

Multiple-plaque rupture, hs-CRP, and prognosis. Our results in this study demonstrate that some patients with AMI have multiple-plaque ruptures, which may be associated with systemic inflammation and adverse clinical outcomes. These observations support the concept that plaque instability not only is a localized vascular event but also reflects a more generalized inflammatory response throughout the coronary tree.

Table 2. Patient Characteristics

	Multiple-Plaque Rupture (n = 11)	Single-Plaque Rupture (n = 10)	Nonplaque Rupture (n = 24)	p Value
Age (yrs)	66 ± 10	61 ± 11	66 ± 9.0	0.43
Men	9 (82%)	9 (90%)	18 (75%)	0.57
Coronary risk factors				
Systemic hypertension	9 (82%)	4 (40%)	12 (50%)	0.10
Diabetes mellitus	8 (73%)	3 (30%)	6 (25%)	0.02
Smoking	7 (64%)	7 (70%)	14 (58%)	0.81
Hypercholesterolemia (>220 mg/dl)	5 (45%)	5 (50%)	10 (42%)	0.90
Obesity (body mass index >25 kg/m^2)	4 (36%)	3 (30%)	3 (13%)	0.23
Risk factor ≥3	9 (82%)	4 (40%)	7 (29%)	0.01
ST-segment elevation MI	6 (55%)	5 (50%)	13 (54%)	0.97

Data are presented as the mean value ± SD or number (%) of patients.
MI = myocardial infarction.

We have previously reported that the presence of ruptured plaque at the culprit site is only related to elevated CRP in patients with AMI (8). In this study, we again found that patients with plaque rupture at the culprit site showed higher hs-CRP levels in the acute phase of AMI. Recently, Hong et al. (21) also found an association between elevated CRP levels and the presence of plaque rupture in their own triple-vessel IVUS study. They concluded that an elevated CRP level is an independent clinical predictor of plaque rupture in AMI patients. Plaque rupture occurs most frequently at the point where the fibrous cap is thinnest and most heavily infiltrated by macrophage foam cells. These rupture-related macrophages are activated, which indicates ongoing inflammation at the site of plaque disruption. Macrophages are capable of degrading the extracellular matrix by the process of phagocytosis or by secreting proteolytic enzymes, such as plasminogen activators and the family of matrix metalloproteinases that may weaken the fibrous cap, thereby predisposing it to rupture (22).

Our results suggest that hs-CRP may reflect activity in these inflammation processes, leading to plaque rupture in all coronary arteries. Burke et al. (23) have reported that CRP may correlate with the number of thin-capped atheromas, which can be considered as vulnerable plaques, using immunohistochemical staining for CRP, in patients who had a sudden death associated with severe coronary artery disease. In an angiographic study, Zairis et al. (24) also reported that CRP was associated with multiple complex lesions. We found that hs-CRP correlates directly with the number of plaque ruptures in the human body.

Furthermore, recent studies have suggested that CRP may play a direct role in promoting inflammatory atherosclerosis (25,26). One recent study of a human CRP-transgenic mouse reported that human CRP may evoke rapid and frequent arterial thrombosis (27). Our results also suggest CRP is not only a marker of systemic vascular inflammation but also plays an important key role in plaque disruption and subsequent thrombosis.

Our patients with multiple-plaque ruptures also presented more frequently with multiple risk factors. An epidemiologic study reported that the extent of lesion development increases markedly with multiple coronary risk factors in children and young adults (28). We speculate that there were various systemic interactions over a long duration behind multiple-plaque ruptures.

Goldstein et al. (20) reported that multiple complex plaques, one of the angiographic features of plaque rupture (29), were associated with a poor prognosis. In their report, recurrent ACS and recurrent ischemia were observed in 9% and 24% of all patients, respectively, within one year. This is very similar to our 8.9% and 20% rates. In this study, patients with multiple-plaque ruptures also showed a sig-

Table 3. Angiographic Findings

	Multiple-Plaque Rupture (n = 11)	Single-Plaque Rupture (n = 10)	Nonplaque Rupture (n = 24)	p Value
Infarct-related artery				
Left anterior descending artery	4 (36%)	4 (40%)	11 (46%)	0.97
Left circumflex artery	2 (18%)	2 (20%)	3 (13%)	
Right coronary artery	5 (45%)	4 (40%)	10 (42%)	
TIMI flow grade 0 on initial angiogram	5 (45%)	4 (40%)	9 (38%)	0.77
Good collateral flow	4 (36%)	2 (20%)	3 (13%)	0.26
Multivessel disease	5 (45%)	3 (30%)	12 (50%)	0.56
Complex lesions at remote site	9 (82%)	1 (10%)	4 (17%)	<0.01
Final stent use	9 (82%)	10 (100%)	20 (83%)	0.37

Data are presented as the mean value ± SD or number (%) of patients.
TIMI = Thrombolysis In Myocardial Infarction.

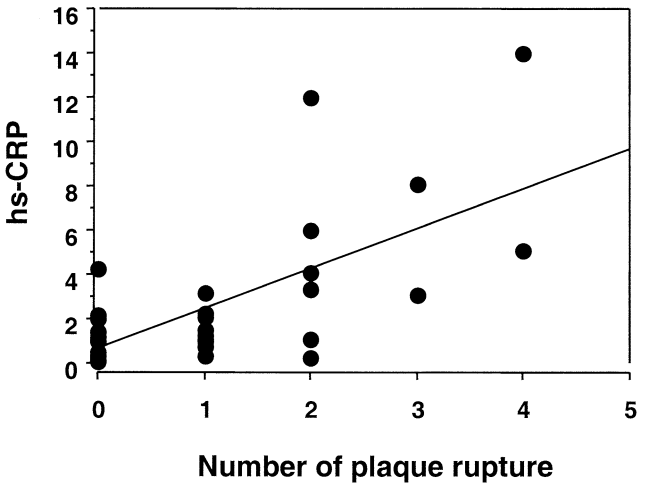

Figure 2. Relationship between the number of plaque ruptures and high sensitivity C-reactive protein (hs-CRP) levels. At one month from onset, the number of plaque ruptures showed a positive correlation with hs-CRP levels ($r = 0.68$, $p < 0.01$).

nificantly poorer prognosis compared with others, as did all of our recurrent ACS patients in the multiple-plaque rupture group. Our results may explain why hs-CRP has a strong predictive value for cardiovascular events (30).

Frequency of multiple-plaque rupture. Previous IVUS studies have reported the frequency of multiple-plaque rupture in ACS, but the frequency of plaque rupture reported is in sharp contrast. Rioufol et al. (3) reported that multiple-plaque ruptures were seen in 79% of all patients. Another group recently reported that additional plaque ruptures were found in only 6% of patients in the infarct-related artery and 7% in the non–infarct-related artery (31). Kotani et al. (4) reported that another plaque rupture was found in 15.8 % of cases in the infarct-related artery and multiple-plaque rupture in only 10.5% of patients, although it should be stressed that they did not perform IVUS in all

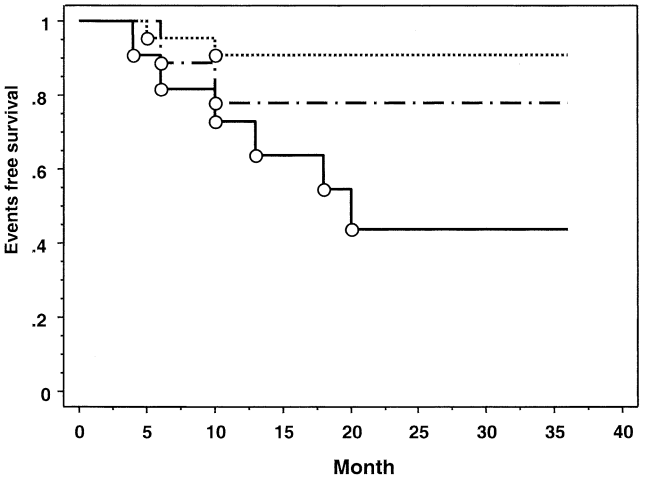

Figure 3. Event-free survival curve. The Kaplan-Meier curve showed that the multiple-plaque rupture group was associated with poor clinical outcomes as compared with the other groups at two years ($p = 0.01$). **Solid line** = multiple-plaque rupture; **dashed line** = single rupture; **dotted line** = nonrupture.

coronary trees. Schoenhagen et al. (32) reported that 19% of patients with AMI presented with other ruptured plaque in the infarct-related artery. In our study, additional plaque ruptures at remote sites in the infarct-related arteries were observed in 13% of patients. We consider that this frequency of additional plaque ruptures in infarct-related arteries is similar to those of Kotani et al. (4) and Schoenhagen et al. (32). One further piece of support comes from the recent triple-vessel IVUS study by Hong et al. (21), which reported multiple-plaque rupture in 20% of AMI patients, which is very similar to our own 24%.

The diagnosis of plaque rupture at the culprit site by IVUS may be strongly influenced by the presence, nature, and size of a coronary thrombus. We reported previously that thrombus imaging might be affected by the time from symptom onset to imaging (5). Low-echoic thrombus images that usually make IVUS assessments difficult increase in accordance with the time from symptom onset to imaging.

Rioufol et al. (3) used IVUS at 2.3 ± 1.5 weeks after the onset of ACS and Kotani et al. (4) at 4 ± 2 days. In our study, however, we did IVUS in the super-acute phase of MI. Furthermore, the use of adequate IVUS contrast is necessary to obtain good quality images. Another explanation was patient selection. One of the inclusion criteria in the Rioufol et al. (3) report was that all three epicardial coronary arteries were suitable for IVUS. A coronary artery suitable for IVUS is one without a bend and a large vessel. Rioufol et al. (3) also did not include patients in the acute phase of AMI or in the critical stage of unstable angina. We consecutively enrolled AMI patients and tried to perform IVUS. Despite all this, 71% of patients presented with multi-vessel disease in the Rioufol et al. (3) study, but only 44% in our study. A pathologic study suggested that healed plaque rupture might promote coronary stenosis (33). We therefore speculated that the higher the number of stenotic lesions, the greater association with more healed plaque ruptures.

Study limitations. There is said to be a number of limitations associated with the present study. The study population was relatively small, and small or tortuous arteries were not explored by IVUS. Not all plaque-rupture cases may present with fissure/dissection, or plaques with communications to the lumen when observed under pre-intervention IVUS. Lesions with small, ruptured plaques may be misread as nonruptured plaques. Our study may therefore contain some ruptured lesions misclassified as nonruptured lesions. Also, an occluded artery is devoid of pressure and undergoes elastic recoil with a marked reduction in all dimensional measurements. Therefore, positive remodeling and its assessment can be substantially influenced by either the presence of physiologic pressure in the artery or its absence. Because patients in this study had already presented with plaque rupture, it cannot be ascertained whether the CRP elevations are the result or the cause of the plaque rupture.

Clinical implications. Although a single lesion is clinically critical at the moment of ACS and is treated by catheter intervention, some patients have other plaque rupture or

ruptures in remote sites and are associated with a poor prognosis. We should therefore consider treatment and strategy for ACS to be stabilization not only of the culprit site but also of the whole coronary tree by a systemic approach (i.e., multiple risk factor intervention) (34).

Statins were used in 24% of patients in this study. Aggressive systemic therapy might have reduced recurrent events. Also, there are some possibilities that local treatments of one or two additional sites, in addition to the culprit site, might be needed, because systemic therapy is not all effective in reducing future events, and it might require several months to exert its beneficial effects. Although CRP is a nonspecific acute-phase reactant, our results may contribute to identifying high-risk patients in the setting of AMI.

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