

Clinical and Laboratory Predictors for Plaque Erosion in Patients With Acute Coronary Syndromes

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Background—Plaque erosion is responsible for 25% to 40% of patients with acute coronary syndromes (ACS). Recent studies suggest that anti-thrombotic therapy without stenting may be an option for this subset of patients. Currently, however, an invasive procedure is required to make a diagnosis of plaque erosion. The aim of this study was to identify clinical or laboratory predictors of plaque erosion in patients with ACS to enable a diagnosis of erosion without additional invasive procedures.

Methods and Results—Patients with ACS who underwent optical coherence tomography imaging were selected from 11 institutions in 6 countries. The patients were classified into plaque rupture, plaque erosion, or calcified plaque, and predictors were identified using multivariable logistic modeling. Among 1241 patients with ACS, 477 (38.4%) patients were found to have plaque erosion. Plaque erosion was more frequent in non-ST-segment elevation-ACS than in ST-segment-elevation myocardial infarction (47.9% versus 29.8%, $P=0.0002$). Multivariable logistic regression models showed 5 independent parameters associated with plaque erosion: age <68 years, anterior ischemia, no diabetes mellitus, hemoglobin >15.0 g/dL, and normal renal function. When all 5 parameters are present in a patient with non-ST-segment elevation-ACS, the probability of plaque erosion increased to 73.1%.

Conclusions—Clinical and laboratory parameters associated with plaque erosion are explored in this retrospective registry study. These parameters may be useful to identify the subset of ACS patients with plaque erosion and guide them to conservative management without invasive procedures. The results of this exploratory analysis need to be confirmed in large scale prospective clinical studies.

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Key Words: acute coronary syndrome • optical coherence tomography • plaque erosion

Plaque erosion is reported to be responsible for about 25% to 40% of patients with acute coronary syndromes (ACS).^{1–3} Current guidelines recommend early invasive

strategy for all ACS patients except for the low-risk subgroups^{4,5} and coronary stents are implanted in the majority of the cases. Recent studies reported that ACS

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Accompanying Data S1, Tables S1 through S5, and Figure S1 are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012322>

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Clinical Perspective

What Is New?

- Five parameters associated with plaque erosion have been identified: age <68 years, anterior ischemia, no diabetes mellitus, hemoglobin >15.0 g/dL, and normal renal function.
- These parameters indicate that plaque erosion may have different pathophysiology: “non-traditional” factors including abnormal local fluid dynamics, rather than the traditional vascular inflammation, may play an important role.

What Are the Clinical Implications?

- If these parameters are proven to be predictive of erosion in prospective studies, a subset of acute coronary syndromes patients with high probability of plaque erosion may be easily identified.
- This subset of patients may be managed conservatively with anti-thrombotic therapy without invasive procedures.

patients with plaque erosion might be treated conservatively without stenting.^{6–8} In these studies, a diagnosis of plaque erosion was made by intracoronary optical coherence tomography (OCT). If the patients with plaque erosion are identified by demographic information or by simple laboratory tests, invasive procedures and procedure-related complications may be avoided, and healthcare costs may be significantly reduced. However, demographic characteristics specific for the patients with plaque erosion are unknown. Although several groups published reports on plaque erosion,^{9–11} the study population in each report was too small or unbalanced to identify comprehensive characteristics associated with plaque erosion. The aim of the current study was to identify the predictors for plaque erosion in patients with ACS.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Participants

A new multi-center longitudinal international registry was created for this study from 11 institutions in 6 countries (Table S1) (Identification of Predictors for Coronary Plaque Erosion in Patients with Acute Coronary Syndrome study, <http://www.clinicaltrials.gov>: NCT03479723). Consecutive patients with ACS who had OCT imaging of the culprit lesion were eligible for the study. We included only patients who had undergone an OCT procedure, therefore this study was not

“all-comer” registry. ACS includes ST-segment-elevation myocardial infarction (STEMI) and non-ST-segment-elevation ACS (NSTEMI) which included non-ST-segment-elevation myocardial infarction (NSTEMI) and unstable angina pectoris. The data set consists of previously published^{1,2,9,10} (n=695) and unpublished (n=1004) patients. Among 1699 patients, 458 patients were excluded and 1241 patients were included in the final cross-sectional analysis (Figure S1). The protocol was approved by the institutional review board at each site and written informed consent was obtained from all patients before enrollment. The definitions are described in Data S1. Demographic data, medical history, laboratory data at admission, percutaneous coronary intervention procedure data, post-percutaneous coronary intervention biomarkers, and in-hospital death were collected. OCT imaging and angiographic imaging at index procedure were also collected. All images were de-identified, digitally stored, and sent to Massachusetts General Hospital (Boston, MA, USA), where analysis was performed.

OCT Image Acquisition

A frequency-domain OCT system (C7/C8 ILUMIEN OCT Intravascular Imaging Systems, St. Jude Medical, St. Paul, Minnesota) or a time-domain OCT system (M2/M3 Cardiology Imaging System, St. Jude Medical, Westford, Massachusetts) was used in this study. The detailed technique of intracoronary OCT imaging was described in the previous report.¹²

OCT Analysis

The methods of OCT analysis are summarized in Data S1. Underlying plaque type in the culprit lesion was categorized into 3 groups using the previously established OCT criteria; plaque rupture, plaque erosion, calcified plaque (Figure 1A through 1C). Plaque rupture was defined by the presence of fibrous cap discontinuity with a communication between the lumen and the inner core of plaque or with a cavity formation within the plaque (Figure 1A).^{13,14} Plaque erosion was identified by the presence of the attached thrombus overlying an intact and visualized plaque, luminal surface irregularity at the culprit lesion in the absence of thrombus, or attenuation of the underlying plaque by thrombus without superficial lipid or calcification immediately proximal or distal to the site of thrombus (Figure 1B).^{1,2,11} Calcified plaque was defined by the presence of superficial substantive calcium at the culprit site without evidence of ruptured lipid plaque (Figure 1C).^{1,2} Culprit lesions that did not satisfy these criteria were classified as others. Tissue characterization of underlying plaque was performed using the previously established criteria.^{15,16} Plaques were classified into 2 categories: (1) Fibrous plaque (homogeneous and high-backscattering

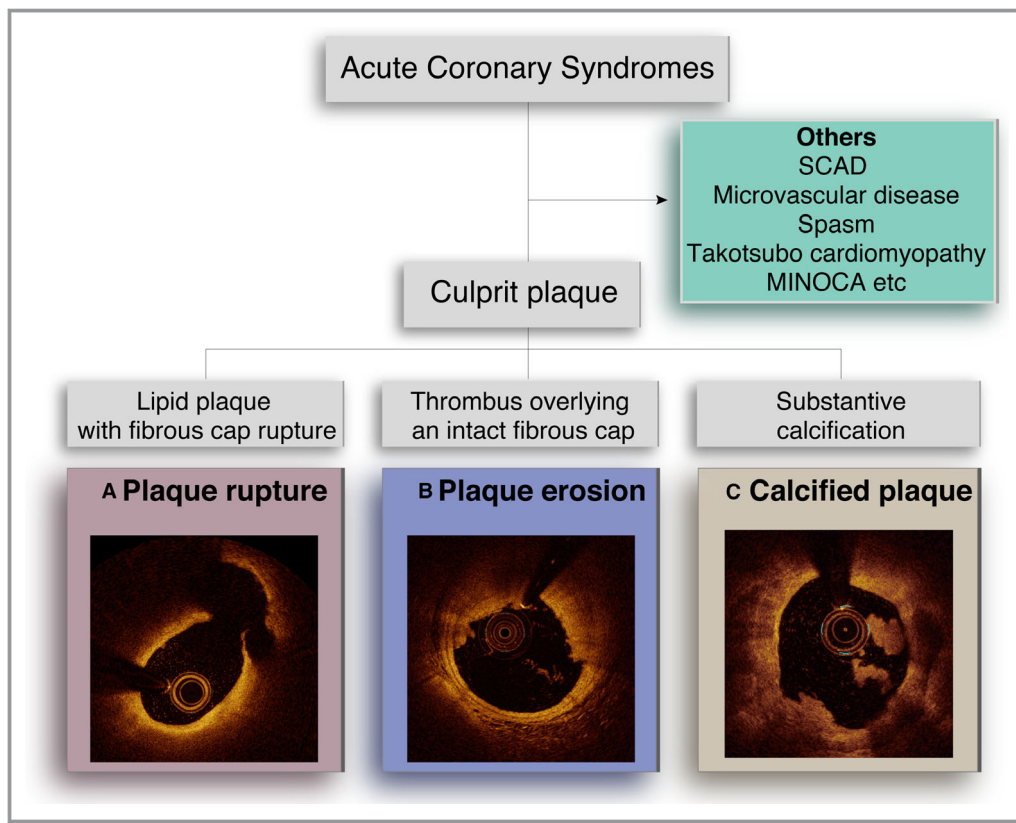


Figure 1. Optical coherence tomography images of 3 plaque pathologies. **A**, Plaque rupture was defined by the presence of fibrous cap discontinuity with a communication between the lumen and the inner core of a plaque or with a cavity formation within the plaque. **B**, Plaque erosion was defined as a culprit plaque with an intact fibrous cap with or without attached thrombus. **C**, Calcified plaque was defined by the presence of superficial substantive calcium at the culprit site without evidence of ruptured lipid plaque. Others include spontaneous coronary artery dissection, microvascular disease, spasm, Takotsubo cardiomyopathy, myocardial infarction with non-obstructive coronary arteries, etc. MINOCA indicates myocardial infarction with non-obstructive coronary arteries; SCAD, spontaneous coronary artery dissection.

region) or (2) Lipid plaque (low signal region with a diffuse border). Lipid-rich plaque was defined as a plaque with lipid arc $>90^\circ$. For each lipid plaque, the thinnest fibrous cap thickness and the maximal lipid arc were measured. A thin-cap fibroatheroma was defined as plaque with a lipid arc $>90^\circ$ and the thinnest part of the fibrous cap $<65\ \mu\text{m}$. Macrophage accumulations were defined as signal-rich, distinct, or confluent punctuate regions with heterogeneous backward shadows. Calcification was recorded as well-delineated, low backscattering heterogeneous regions. Minimal flow area was also measured for each lesion.

Angiographic Analysis

Coronary angiograms were analyzed with the Cardiovascular Angiography Analysis System (Pie Medical Imaging B.V., Maastricht, The Netherlands). The reference diameter, minimum lumen diameter, diameter stenosis, area stenosis, and lesion length were measured. Thrombolysis in Myocardial

Infarction flow grade was also evaluated for the culprit vessel.

Statistical Analysis

Categorical outcomes were presented as counts and proportions (%). Continuous outcomes were expressed as mean \pm SD. For overall between-group comparisons, 1-way analysis of variance or Kruskal–Wallis test was applied for continuous outcomes and Chi-square or Fisher exact test for categorical outcomes was applied. Then post-hoc comparisons with controlling type-1 error by using Bonferroni correction were performed if the overall test was significant with $P<0.05$. To identify the parameters associated with plaque erosion, univariable and multivariable logistic regression models were applied using variables that can be readily obtained in the emergency department (age, sex, medical history, medication at admission, location of ischemia, simple laboratory test (white blood cell count, hemoglobin, creatine

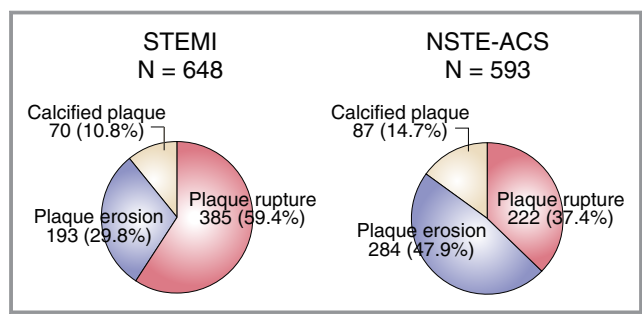


Figure 2. Prevalence of plaque rupture, erosion, and calcified plaque in ST-segment-elevation myocardial infarction and non-ST-segment-elevation acute coronary syndrome. Among 1241 patients, 648 presented with ST-segment-elevation myocardial infarction and 593 with non-ST-segment-elevation acute coronary syndrome. The prevalence of plaque rupture, plaque erosion, and calcified plaque was 59.4%, 29.8%, and 10.8% in ST-segment-elevation myocardial infarction; 37.4%, 47.9%, and 14.7% in non-ST-segment-elevation acute coronary syndrome. The prevalence of plaque erosion was significantly higher in non-ST-segment-elevation acute coronary syndrome than in ST-segment-elevation myocardial infarction patients (47.9% vs 29.8%, $P=0.0002$). NSTEMI-ACS indicates non-ST-segment-elevation acute coronary syndrome; STEMI, ST-segment-elevation myocardial infarction.

phosphokinase) and renal function (normal renal function was defined as no history of chronic kidney disease and estimated glomerular filtration rate (eGFR) >60 mL/min at admission). Age and hemoglobin cut-off were determined using Youden index. Variables with a $P<0.10$ in the univariate test were entered into the multivariable modeling. All statistical analyses were performed using JMP PRO 13.0 (SAS Institute Inc, Cary, NC).

Results

Among 1241 patients, 607 patients (48.9%) were classified as plaque rupture, 477 patients (38.4%) as plaque erosion, and 157 patients (12.7%) as calcified plaque. In 648 STEMI patients, 385 (59.4%) patients had plaque rupture and 193 (29.8%) patients had plaque erosion. In 593 NSTEMI-ACS patients, 222 (37.4%) patients had plaque rupture and 284 (47.9%) patients had plaque erosion. Inter-observer and intra-observer variability were assessed by the evaluation of all images by 2 independent observers and by the same observer at 2 separate time points, respectively. The intra-observer Kappa coefficients for plaque rupture, plaque erosion, and calcified plaque were 0.902, 0.922, 0.934, respectively. The inter-observer Kappa coefficients for plaque rupture, plaque erosion, and calcified plaque were 0.878, 0.895, 0.935, respectively. Plaque erosion was significantly more frequent in NSTEMI-ACS than in STEMI (47.9% versus 29.8%, $P<0.0002$) (Figure 2).

Patients Characteristics

Baseline characteristics of each group are summarized in Table 1 and Table S2. Compared with the non-erosion group, the plaque erosion group was younger and more frequently presented with NSTEMI-ACS. Hypertension, diabetes mellitus, and chronic kidney disease were significantly less frequent in the plaque erosion group. The plaque erosion group also had higher levels of hemoglobin, lower levels of inflammatory markers (high-sensitivity C-reactive protein and white blood cell count), and a better lipid profile. The calcified plaque group was older and had a higher prevalence of hypertension, diabetes mellitus, and chronic kidney disease, compared with the other groups. The patients in the calcified plaque group were on more medications on admission. Plaque erosion was located more frequently in the left anterior descending artery than in the right coronary artery (56.6% versus 28.5%), whereas plaque rupture was located equally in the left anterior descending and the right coronary artery (45.8% versus 40.5%). Angiographic and OCT analysis consistently showed plaque erosion patients had less complex and less vulnerable lesions, compared with patients with non-erosion.

Procedural detail, clinical course, and in-hospital outcome are shown in Table S3. Thrombectomy and stenting were more frequently performed in the plaque rupture group than in the plaque erosion group. There was no significant difference in in-hospital outcome between the plaque erosion and the non-erosion group except lower level of post-procedure peak creatine phosphokinase in the erosion group (1264 ± 1901 versus 1973 ± 2332 , $P<0.001$).

STEMI and NSTEMI-ACS in Plaque Erosion

When the erosion patients were divided based on clinical presentation, those with STEMI were more frequently smokers, had higher levels of serum low-density lipoproteins, and were on fewer medications (aspirin, P2Y12 inhibitors, statin, angiotensin-converting enzyme inhibitor/ARB, β -blocker) on admission than those with NSTEMI-ACS (Table S4).

Predictors of Plaque Erosion

Age cut-off <68 years, hemoglobin cut-off <15.0 g/dL were determined to maximize the area under the receiver operating characteristic (ROC) curve. As shown in Table 2, age <68 years (odds ratio [OR]: 1.56, 95% CI: 1.16–2.09, $P=0.003$), anterior ischemia (OR: 1.41, 95% CI: 1.06–1.86, $P=0.02$), no diabetes mellitus (OR: 1.47, 95% CI: 1.08–2.01, $P=0.01$), hemoglobin >15.0 g/dL (OR: 1.48, 95% CI: 1.09–2.01, $P=0.01$), and normal renal function (OR: 1.97, 95% CI: 1.32–2.95, $P=0.0009$) were found to be the independent

Table 1. Patient Characteristics

	Plaque Rupture (n=607)	Plaque Erosion (n=477)	Calcified Plaque (n=157)	P Value	P Value*		
					PR vs PE	PE vs CP	PR vs CP
Age, y	65.3±11.9	62.8±12.3	69.9±9.2	<0.0001	0.0009	<0.001	<0.0001
Men	478 (78.8)	380 (79.7)	121 (77.1)	0.78			
Presentation				<0.0001	<0.0001	0.36	<0.0001
STEMI	385 (63.4)	193 (40.5)	70 (44.6)				
NSTE-ACS	222 (36.6)	284 (59.5)	87 (55.4)				
Hypertension	401 (66.1)	283 (59.3)	123 (78.3)	<0.0001	0.03	<0.0001	0.003
Dyslipidemia	442 (72.8)	329 (69.0)	114 (72.6)	0.35			
Diabetes mellitus	201 (33.1)	130 (27.3)	64 (40.8)	0.004	0.04	0.001	0.07
Current smoker	254 (42.0)	196 (41.4)	39 (25.0)	0.0003	0.86	0.0002	0.0001
Past smoker	106 (17.5)	106 (22.4)	52 (33.3)	<0.0001	0.05	0.006	<0.0001
Current+past smoker	360 (59.5)	302 (63.9)	91 (58.3)	0.27
Previous MI	45 (7.4)	30 (6.3)	19 (12.1)	0.06			
Previous PCI	56 (9.2)	40 (8.4)	23 (14.7)	0.06			
Family history	88 (14.5)	85 (17.8)	32 (20.4)	0.13			
CKD	113 (18.6)	52 (10.9)	51 (32.5)	<0.0001	0.0004	<0.0001	0.0002
Laboratory data							
WBC, / μ L	9675±3386	9076±3270	8717±3500	0.001	0.004	0.26	0.001
Hemoglobin, g/dL	14.0±1.8	14.2±1.7	13.3±2.2	<0.0001	0.03	<0.0001	0.003
LDL-C, mg/dL	128±42	121±41	108±41	<0.0001	0.005	0.001	<0.0001
Creatinine, mg/dL	0.97±0.79	0.90±0.72	1.65±2.41	<0.0001	0.16	0.0003	0.0008
hs-CRP, mg/dL	0.84±2.25	0.45±0.95	0.92±1.95	0.003	0.0004	0.003	0.05
CPK, IU/L	518±928	371±652	438±935	0.03	0.004	0.47	0.13
Medication at admission							
Aspirin	92 (19.7)	75 (20.3)	54 (37.2)	<0.0001	0.84	<0.0001	<0.0001
P2Y12 inhibitor	38 (8.1)	41 (11.1)	27 (18.5)	0.002	0.14	0.03	0.0003
Statin	115 (24.6)	82 (22.2)	59 (40.7)	<0.0001	0.41	<0.0001	0.0002
ACE-I/ARB	134 (28.6)	105 (28.3)	70 (48.0)	<0.0001	0.92	<0.0001	<0.0001
β -blocker	63 (13.5)	60 (16.2)	39 (26.7)	0.0008	0.27	0.006	0.0002
Angiographic data							
Lesion location				0.0002	0.0002	0.77	0.007
LAD	278 (45.8)	270 (56.6)	93 (59.2)				
LCX	83 (13.7)	71 (14.9)	20 (12.7)				
RCA	246 (40.5)	136 (28.5)	44 (28.0)				
QCA							
RVD, mm	2.97±0.70	2.86±0.70	2.87±0.74	0.04	0.02	0.70	0.02
MLD, mm	0.51±0.59	0.68±0.66	0.73±0.68	<0.0001	<0.0001	0.48	0.0005
Diameter stenosis (%)	83.2±18.4	77.0±20.2	75.4±20.8	<0.0001	<0.0001	0.43	<0.0001
Lesion length, mm	16.1±7.8	15.1±6.5	17.8±8.5	0.0004	0.02	0.0005	0.02
TIMI flow grade 0 to 1	242 (39.9)	119 (25.0)	37 (23.6)	<0.0001	<0.0001	0.73	0.0002
Multivessel disease	232 (39.1)	149 (32.5)	78 (52.0)	<0.0001	0.03	<0.0001	0.004

Continued

Table 1. Continued

	Plaque Rupture (n=607)	Plaque Erosion (n=477)	Calcified Plaque (n=157)	P Value	P Value*		
					PR vs PE	PE vs CP	PR vs CP
Type B2/C lesion	483 (79.6)	286 (60.0)	122 (77.7)	<0.0001	<0.0001	<0.0001	0.61
OCT findings							
Lipid-rich plaque	554 (91.3)	178 (37.3)	24 (15.3)	<0.0001	<0.0001	<0.0001	<0.0001
TCFA	373 (61.5)	33 (6.9)	5 (3.2)	<0.0001	<0.0001	0.09	<0.0001
Macrophage	486 (80.1)	263 (55.1)	43 (27.4)	<0.0001	<0.0001	<0.0001	<0.0001
Calcification	231 (38.1)	160 (33.5)	158 (100)	<0.0001	0.12	<0.0001	<0.0001
Minimum flow area, mm ²	1.38±1.01	1.43±1.34	1.78±1.43	<0.0001	0.51	<0.0001	<0.0001
Minimum FCT, μ m	69±33	121±65	115±81	<0.0001	<0.0001	0.18	0.0007
Max lipid arc, degree	308±64	276±80	273±78	<0.0001	<0.0001	0.84	0.03

ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; CKD, chronic kidney disease; CP, calcified plaque; CPK, creatine phosphokinase; FCT, fibrous cap thickness; hs-CRP, high-sensitivity C-reactive protein; LAD, left anterior descending artery; LCX, left circumflex artery; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; MLD, minimum lumen diameter; NSTEMI-ACS, non-ST-segment-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; PE, plaque erosion; QCA, quantitative coronary angiography; PR, plaque rupture; RCA, right coronary artery; RVD, reference vessel diameter; STEMI, ST-segment-elevation myocardial infarction; TCFA, thin-cap fibroatheroma; TIMI, Thrombolysis in Myocardial Infarction; WBC, white blood cell count.

* $P<0.017$ was considered significant.

parameters associated with plaque erosion. When all 5 parameters are present in a patient with NSTEMI-ACS, the probability of plaque erosion increased to 73.1% (Figure 3). When all 5 conditions were present in NSTEMI-ACS patients, the odds ratio of plaque erosion was 3.40 (95% CI: 1.39–8.29, $P=0.007$). A 1000 bootstrap-samples based estimation for the probability of plaque erosion was conducted. The estimated probabilities are within the initial estimates (Table S5).

Discussion

This is an international collaborative work that includes >1200 patients with both STEMI and NSTEMI-ACS from 11 institutions in 6 countries to identify parameters associated with plaque erosion. Plaque erosion was more frequent in NSTEMI-ACS than in STEMI. Five parameters associated with

plaque erosion are identified: (1) Age <68 years, (2) anterior ischemia, (3) no diabetes mellitus, (4) hemoglobin >15.0 g/dL, and (5) normal renal function. When all these 5 conditions are present in a patient with NSTEMI-ACS, the probability of plaque erosion increases up to 73%.

Traditional Coronary Risk Factors in Plaque Erosion

Some of the conventional risk factors for coronary artery disease (older age, diabetes mellitus, dyslipidemia, chronic kidney disease, hypertension) were less frequent in plaque erosion, while younger age, no diabetes mellitus, and normal renal function were associated with plaque erosion in the current study. In addition, high-sensitivity C-reactive protein and white blood cell count were also significantly lower in

Table 2. Clinical and Laboratory Predictors of Plaque Erosion

Variables	Unadjusted			Adjusted		
	OR	95% CI	P Value	OR	95% CI	P Value
Age <68 y	1.65	1.31 to 2.08	<0.0001	1.56	1.16 to 2.09	0.003
Anterior ischemia	1.38	1.10 to 1.74	0.006	1.41	1.06 to 1.86	0.02
No DM	1.42	1.10 to 1.82	0.006	1.47	1.08 to 2.01	0.01
Hemoglobin >15.0 g/dL	1.67	1.25 to 2.34	0.0006	1.48	1.09 to 2.01	0.01
Normal renal function	2.23	1.60 to 3.13	<0.0001	1.97	1.32 to 2.95	0.0009
No hypertension	1.50	1.18 to 1.90	0.0009	1.26	0.94 to 1.68	0.13
Statin	0.72	0.53 to 0.97	0.03	1.21	0.88 to 1.69	0.24

DM indicates diabetes mellitus; OR, odds ratio.

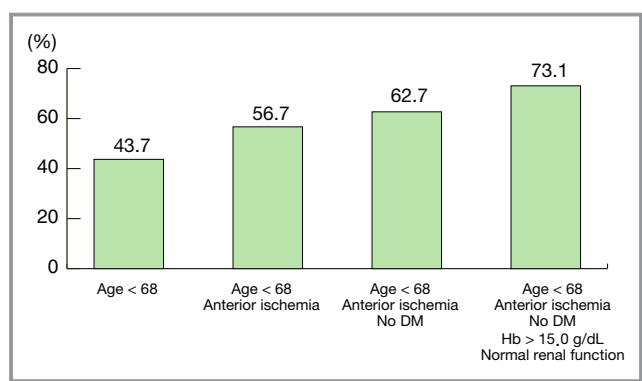


Figure 3. Probability of plaque erosion. When all 5 parameters are present in a patient with non-ST-segment-elevation acute coronary syndrome, the probability of plaque erosion increased to 73.1%. When a patient with non-ST-segment-elevation acute coronary syndrome has all 5 parameters, the odd ratio increases to 3.40. DM indicates diabetes mellitus.

the erosion patients. OCT analysis also demonstrated significantly lower levels of plaque vulnerability (lipid-rich plaque, thin-cap fibroatheroma, and macrophage). Taken together, all these data suggest that plaque erosion has a distinctly different pathobiology compared with plaque rupture. Previous pathology studies reported that the characteristics of plaque erosion, which include thrombus over less atherosclerotic and less vulnerable lesions without disruption of plaque structure and absence of endothelial cell layer.^{3,17,18} However, the underlying mechanism of local thrombosis remains unclear. A “2-hit scheme” was proposed for the pathogenesis of plaque erosion.^{19,20} The “first-hit” is chronic endothelial activation, propensity to slough, and impaired ability to repair the damaged endothelium. Disturbed flow was suspected to be the etiology, leading to activation of endothelial Toll-like receptor 2. The “second-hit” is recruitment of neutrophils via Toll-like receptor 2 and subsequent formation of neutrophil extracellular traps, as well as local production of chemo-attractants, thrombin, and fibrin, which further entrap platelets and lead to thrombus formation. This process is independent from pan-vascular chronic inflammation that lead to atherosclerosis, therefore plaque erosion can occur in younger patients with less atherosclerosis.

Local Fluid Dynamics in Plaque Erosion

Interestingly, high hemoglobin level was found to be a strong factor associated with plaque erosion. The changes of hemoglobin level over time were not collected. Therefore, a causal relationship cannot be established. However, several studies reported hemoconcentration was the risk factor for myocardial infarction.²¹ Hemoconcentration can increase blood viscosity, resulting in elevation of local endothelial

shear stress. High shear condition activates both platelets and coagulation factors.^{22,23} It was recently reported that high endothelial shear stress was associated with the thrombus in plaque erosion patients.²⁴ Therefore, high hemoglobin levels attributable to several systemic condition may contribute to formation of occlusive thrombus in plaque erosion. In addition, plaque erosion was more frequently observed in the left anterior descending artery with anterior ischemia than in the right coronary artery or circumflex. The left anterior descending artery has more side branches than other vessels. The presence of side branches affects the conditions of local flow dynamics and distribution of endothelial shear stress,²⁵ which may play a key role in pathogenesis of erosion.

STEMI and NSTEMI-ACS in Plaque Erosion

In the current study, 41% of plaque erosion patients presented with STEMI and the remaining 59% of patients presented with NSTEMI-ACS. Because of relatively preserved vascular structure, plaque erosion may be prone to develop non-occlusive thrombus or occlusive thrombus that may be easily embolized distally. Several differences were noted between these 2 groups: the erosion patients with STEMI were more frequently smokers, had higher levels of serum low-density lipoproteins, and took fewer medications on admission than those with NSTEMI-ACS (Table S4). The medications might have protected these patients from persistent occlusive thrombus formation. In addition, the smoking rate was significantly higher in plaque erosion patients with STEMI. Several previous studies reported that plaque erosion is associated with smoking.^{11,17,18} Smoking promotes activation of both platelets and clotting factors.^{26,27} In addition, smoking causes endothelial damage²⁸ as well as activation of Rho-kinase,²⁹ which leads to vascular hyperconstriction or vasospasm.

Clinical Significance of Predictors of Plaque Erosion

This study included only patients who had OCT imaging, therefore the result might not represent a general ACS population. Taken together, however, the current study suggests that, contrary to atherosclerotic lesions with underlying chronic inflammatory processes, plaque erosion might be the result of a combination of several “non-traditional” factors including endothelial, vasomotion, fluid dynamic, and systemic effects (Figure 4). Thus, the optimal management for plaque erosion might be different from the traditional treatment of plaque rupture. In the EROSION (Effective Anti-Thrombotic Therapy Without Stenting: Intravascular Optical Coherence Tomography-Based Management in

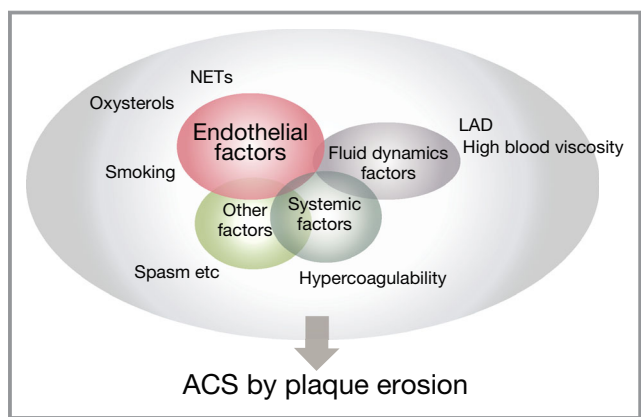


Figure 4. Pathogenesis of plaque erosion. Plaque erosion might be the result of a combination of several “non-traditional” factors; endothelial factors, vasomotion factors, fluid dynamics factors, and systemic factors. ACS indicates acute coronary syndromes; LAD, left anterior descending artery; NETs, neutrophil extracellular traps.

Plaque Erosion) study, we demonstrated the feasibility and safety of anti-thrombotic therapy without stenting in patients with ACS caused by plaque erosion.⁶ We also reported a further decrease in thrombus volume between 1 month and 1 year, and a majority of patients with plaque erosion who were managed with aspirin and ticagrelor without stenting remained free of major adverse cardiac events up to 1 year.³⁰ These results suggest that a tailored approach based on the underlying pathobiology of ACS may be warranted. Ultimately, whereas emergency invasive procedure with primary percutaneous coronary intervention is the standard of care for the patients with STEMI, those with NSTEMI-ACS can often be stabilized with anti-thrombotic therapy. Identification of a subset of NSTEMI-ACS patients with high probability of plaque erosion may facilitate an early triage of the patients and provide an opportunity for tailored therapy.

A different approach will be needed not only for the management after ACS, but also for prevention. In the EROSION study, all patients were treated with dual anti-platelet therapy for 1 year.^{30,31} Anti-thrombotic therapy should be the mainstay for plaque erosion patients without stenting. However, optimal duration/choice of medications remains unknown. The restoration of endothelial function should also be considered. Cessation of smoking could be particularly important.

Study Limitations

This study has several limitations. First, only patients who had undergone an OCT procedure were included, and the decision to perform OCT was left at the discretion of each operator. Therefore, true denominator is unknown and the inherent selection bias cannot be excluded. However, investigators in

participating institutions have extensive experience with OCT and OCT is routinely being performed in almost all comers. Second, since this was not a prospective study, there is the possibility of unmeasured confounders. Third, although data were collected from 11 institutions including 3 in Europe and 1 in the United States, the majority of patients were Asians. Fourth, no biomarkers were measured. If biomarkers specific for plaque erosion are discovered, it may significantly increase the accuracy of non-invasive diagnosis of plaque erosion. Fifth, it can indeed be difficult to make a diagnosis of plaque erosion in the presence of large thrombus burden. Aspiration thrombectomy was allowed, but the cases with balloon angioplasty were excluded to avoid iatrogenic damage to the vessel wall including plaque rupture. The majority of plaque ruptures are associated with superficial lipid and an emptied cavity. Those cases with large residual thrombus after thrombectomy or the cases with unclear diagnosis were excluded.

Conclusions

Plaque erosion was more frequent in NSTEMI-ACS than in STEMI. Five parameters associated with plaque erosion have been identified; younger age, anterior ischemia, no diabetes mellitus, normal renal function, and higher hemoglobin levels. These parameters might be useful for identification of patients with plaque erosion for possible tailored therapy based on underlying pathobiology of ACS. The results of this exploratory analysis need to be confirmed in large scale prospective clinical studies.

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Disclosures

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Supplemental Material

Data S1.

Supplemental Methods

Definitions

Acute coronary syndrome (ACS) includes ST-segment-elevation myocardial infarction (STEMI), non-ST-segment-elevation myocardial infarction (NSTEMI), and unstable angina pectoris (UAP). Non-ST-segment-elevation ACS (NSTEMI and UAP). STEMI is defined as continuous chest pain that lasts > 30 min., arrival at the hospital within 12 hours from the onset of symptoms, ST-segment-elevation > 0.1 mV in ≥ 2 contiguous leads or new left bundle-branch block on the 12-lead electrocardiogram (ECG), and elevated cardiac markers (creatinine kinase-myocardial band or troponin T/I). NSTEMI is defined as ischemic symptoms in the absence of ST-segment elevation on the ECG with elevated cardiac markers. UAP is defined as having newly developed/accelerating chest symptoms on exertion or rest angina within 2 weeks. Chronic kidney disease (CKD) is defined as eGFR < 60ml/min/1.73m² for ≥ 3 months. Normal renal function is defined as no history of CKD and eGFR > 60ml/min at admission. The culprit lesion was determined based on angiographic findings, ECG changes, and/or left ventricular wall motion abnormalities. Anterior ischemia is defined as culprit lesion located in left anterior descending artery.

OCT image analysis

<Tissue characterization of underlying plaque>

Tissue characterization of underlying plaque was performed using the previously established criteria^{1,2}. Plaques were classified into 2 categories: (1) Fibrous Plaque (homogeneous and high-backscattering region) or (2) Lipid Plaque (low signal region with a diffuse border). Lipid-rich plaque was defined as a plaque with lipid arc > 90 degrees. For each lipid plaque, the thinnest fibrous cap thickness and the maximal arc of lipid were measured. A thin-cap fibroatheroma (TCFA) was defined as plaque with a lipid arc >90 degrees and the thinnest part of the fibrous cap < 65 μ m. Macrophage accumulations were defined as signal-rich, distinct or confluent punctuate regions with heterogeneous backward shadows. Calcification was recorded as well-delineated, low backscattering heterogeneous regions. Minimal flow area was also measured for each lesion.

Table S1. Participating sites.

Participating sites	Country	Number of patients
Tsuchiura Kyodo General Hospital	Japan	318
Nara Medical University Hospital	Japan	257
The Chinese University of Hong Kong	Hong Kong	193
Nippon Medical Chiba Hokusoh Hospital	Japan	188
Massachusetts General Hospital	US	181
Catholic University of the Sacred Heart	Italy	148
Hirosaki University Hospital	Japan	130
University of Giessen	Germany	83
University Hospitals Leuven	Belgium	74
Kameda Medical Center	Japan	64
Kitasato University Hospital	Japan	63
Total		1699

Table S2. Patient characteristics (Erosion vs Non-erosion).

	Plaque erosion N=477	Non-erosion N=764	P
Age, years	62.8 ± 12.3	66.2 ± 11.5	< 0.001
Male	380 (79.7)	599 (78.4)	0.60
Presentation			< 0.001
STEMI	193 (40.5)	455 (59.5)	
NSTEMI-ACS	284 (59.5)	309 (40.5)	
Hypertension	283 (59.3)	524 (68.6)	< 0.001
Dyslipidemia	329 (69.0)	556 (72.8)	0.15
Diabetes Mellitus	130 (27.3)	265 (34.7)	0.006
Current smoker	196 (41.4)	293 (38.5)	0.31
Past smoker	106 (22.4)	158 (20.8)	0.49
Current + past smoker	302 (63.9)	451 (59.3)	0.11
Previous MI	30 (6.3)	64 (8.4)	0.18
Previous PCI	40 (8.4)	79 (10.3)	0.26
Family history of CAD	85 (17.8)	120 (15.7)	0.33
CKD	52 (10.9)	164 (21.5)	< 0.001
Laboratory data			
WBC, /μL	9076 ± 3270	9493 ± 3426	0.02
Hb, g/dL	14.2 ± 1.7	13.8 ± 1.9	0.002
LDL, mg/dL	121 ± 41	124 ± 43	0.26
Creatine, mg/dL	0.90 ± 0.72	1.11 ± 1.32	0.008
hs-CRP, mg/dL	0.45 ± 0.95	0.86 ± 2.20	0.01
CPK, IU/L	371 ± 652	504 ± 929	0.001
Medication at admission			
Aspirin	75 (20.3)	146 (23.9)	0.19
P2Y12 inhibitor	41 (11.1)	65 (10.5)	0.80
Statin	82 (22.2)	174 (28.4)	0.03
ACE-I/ARB	105 (28.3)	204 (33.2)	0.11
β-blocker	60 (16.2)	102 (16.6)	0.86

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CAD = coronary artery disease; CKD = chronic kidney disease; CPK = creatine phosphokinase; Hb = hemoglobin; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; NSTEMI-ACS = non-ST-segment-elevation myocardial acute coronary syndrome; PCI = percutaneous coronary intervention; STEMI = ST-segment-elevation myocardial infarction; WBC = white blood cell count.

Table S3. Procedure detail, post procedure biomarker, in-hospital outcome.

	Plaque rupture N=607	Plaque erosion N=477	Calcified plaque N=157	p All	p		
					PR vs PE	PE vs CP	PR vs CP
Procedure detail							
Thrombectomy	307 (64.9)	151 (41.8)	50 (43.5)	< 0.001	< 0.001	0.76	< 0.001
Stenting	593 (97.7)	441 (92.5)	155 (98.7)	< 0.001	< 0.001	0.004	0.42
Number of stent(s)	1.2 ± 0.5	1.1 ± 0.6	1.3 ± 0.6	0.01	0.15	0.04	0.02
Stent diameter, mm	3.2 ± 0.5	3.1 ± 0.4	3.0 ± 0.4	0.004	0.08	0.06	0.002
Total stent length, mm	28.0 ± 14.1	27.2 ± 15.1	30.0 ± 15.1	0.25			
Post procedure							
Peak CPK, IU/L	2078 ± 2396	1264 ± 1901	1527 ± 1987	< 0.001	< 0.001	0.12	0.002
In-hospital death							
	9 (1.5)	3 (0.6)	0	0.15			

CPK = creatine phosphokinase.

Table S4. Patient characteristics (STEMI vs NSTEMI-ACS in erosion patients).

	STEMI in erosion N=193	NSTEMI-ACS in erosion N=284	p
Age, years	62.5 ± 11.7	63.0 ± 12.8	0.62
Male	159 (82.4)	221 (77.8)	0.22
Hypertension	104 (53.9)	179 (63.0)	0.05
Dyslipidemia	139 (72.0)	190 (66.9)	0.24
Diabetes Mellitus	47 (24.4)	83 (29.2)	0.24
Current smoker	83 (43.7)	113 (39.9)	0.42
Past smoker	54 (28.4)	52 (18.4)	0.01
Current + past smoker	137 (72.1)	165 (58.3)	0.002
Previous MI	7 (3.6)	23 (8.1)	0.05
Previous PCI	7 (3.6)	33 (11.6)	0.002
Family history of CAD	36 (18.7)	49 (17.3)	0.70
CKD	20 (10.4)	32 (11.3)	0.76
Laboratory data			
WBC, /μL	10250 ± 3486	8221 ± 2817	< 0.001
Hb, g/dL	14.4 ± 1.8	14.1 ± 1.6	0.13
LDL-C, mg/dL	127 ± 39	117 ± 42	0.01
Creatinine, mg/dL	0.91 ± 0.67	0.90 ± 0.76	0.82
hs-CRP, mg/dL	0.32 ± 0.57	0.54 ± 1.15	0.01
CPK, IU/L	572 ± 878	219 ± 328	< 0.001
Medication at admission			
Aspirin	21 (11.9)	54 (28.0)	< 0.001
P2Y12 inhibitor	9 (5.1)	32 (16.5)	< 0.001
Statin	20 (11.3)	62 (32.1)	< 0.001
ACE-I/ARB	41 (23.2)	64 (33.0)	0.04
β-blocker	17 (9.6)	43 (22.3)	0.002

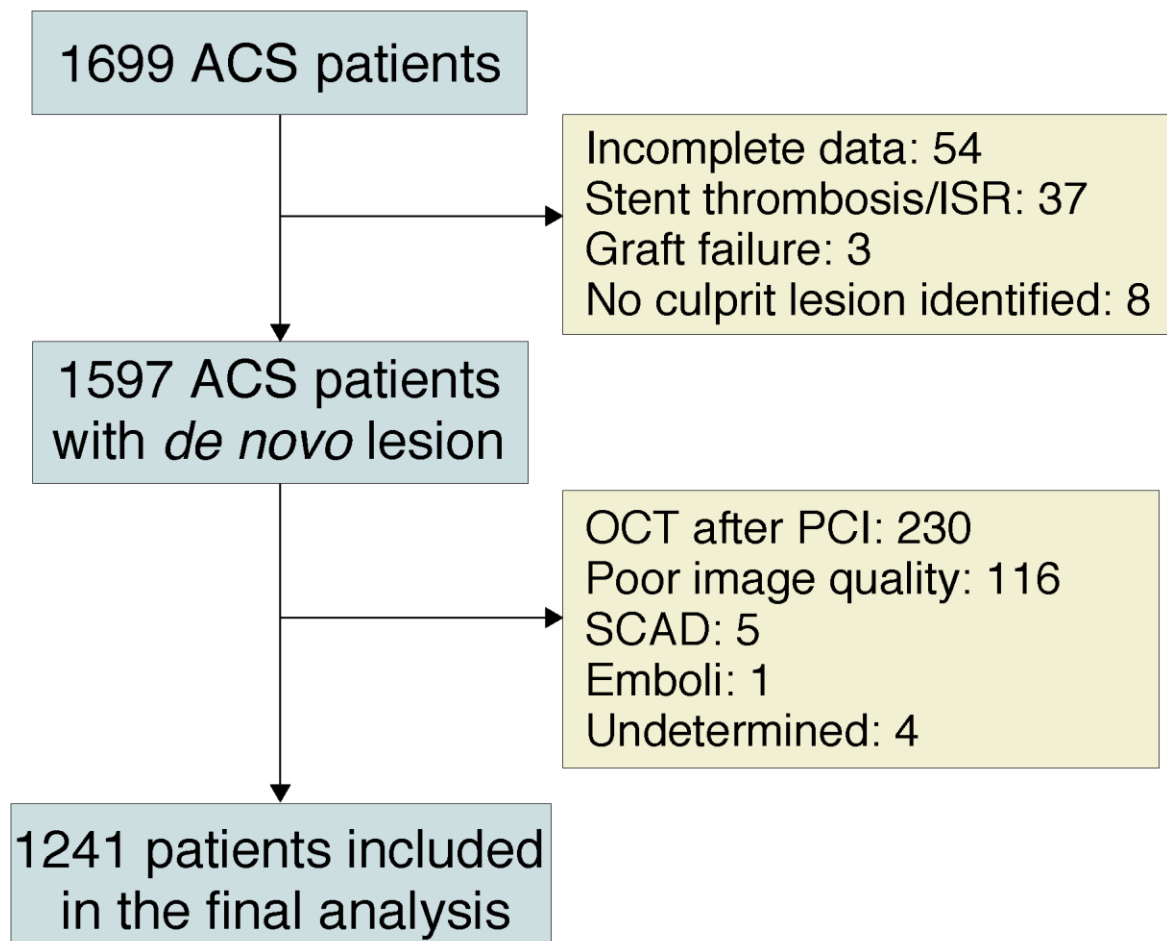
ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CAD = coronary artery disease; CPK = creatine phosphokinase; Hb = hemoglobin; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; NSTEMI-ACS = non-ST-segment-elevation myocardial acute coronary syndrome; PCI = percutaneous coronary intervention; STEMI = ST-segment-elevation myocardial infarction; WBC = white blood cell count.

Table S5. Estimation for the probability of plaque erosion.

		Predicted Percentage of plaque erosion (%)	Standard error	95%CI	
				lower	upper
Present all 5 factors	Plaque erosion	73.1	8.8	53.8	88.5
	Others	26.9	8.8	11.5	46.2
Present 3 factors (Age, Anterior ischemia, NoDM)	Plaque erosion	62.7	4.5	54	72.2
	Others	37.3	4.5	27.8	46
Present 2 factors (Age, Anterior ischemia)	Plaque erosion	56.7	3.6	49.7	63.5
	Others	43.3	3.6	36.5	50.3

CI= confidence interval; DM = diabetic mellitus;

Figure S1. Study flowchart.



Among 1699 ACS patients, 458 patients were excluded, and 1241 patients were included in the final analysis. ACS = acute coronary syndromes; ISR = in-stent restenosis; OCT = optical coherence tomography; PCI = percutaneous coronary intervention; SCAD = spontaneous coronary artery dissection.

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