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Calcified Plaques in Patients With Acute Coronary Syndromes

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ABSTRACT

OBJECTIVES This study conducted detailed analysis of calcified culprit plaques in patients with acute coronary syndromes (ACS).

BACKGROUND Calcified plaques as an underlying pathology in patients with ACS have not been systematically studied.

METHODS From 1,241 patients presenting with ACS who had undergone pre-intervention optical coherence tomography imaging, 157 (12.7%) patients were found to have a calcified plaque at the culprit lesion. Calcified plaque was defined as a plaque with superficial calcification at the culprit site without evidence of ruptured lipid plaque.

RESULTS Three distinct types were identified: eruptive calcified nodules, superficial calcific sheet, and calcified protrusion (prevalence of 25.5%, 67.4%, and 7.1%, respectively). Eruptive calcified nodules were frequently located in the right coronary arteries (44.4%), whereas superficial calcific sheet was most frequently found in the left anterior descending coronary arteries (68.4%) ($p = 0.012$). Calcification index (mean calcification arc × calcification length) was greatest in eruptive calcified nodules, followed by superficial calcific sheet, and smallest in calcified protrusion (median 3,284.9 [interquartile range (IQR): 2,113.3 to 5,385.3] vs. 1,644.3 [IQR: 1,012.4 to 3,058.7] vs. 472.5 [IQR: 176.7 to 865.2]; $p < 0.001$). The superficial calcific sheet group had the highest peak post-intervention creatine kinase values among the groups (eruptive calcified nodules vs. superficial calcific sheet vs. calcified protrusion: 241 [IQR: 116 to 612] IU/l vs. 834 [IQR: 141 to 3,394] IU/l vs. 745 [IQR: 69 to 1,984] IU/l; $p = 0.032$).

CONCLUSIONS Three distinct types of calcified culprit plaques are identified in patients with ACS. Superficial calcific sheet, which is frequently located in the left anterior descending coronary artery, is the most prevalent type and is also associated with greatest post-intervention myocardial damage. (Identification of Predictors for Coronary Plaque Erosion in Patients With Acute Coronary Syndrome; NCT03479723) (J Am Coll Cardiol Intv 2019;12:531–40)

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CK = creatine kinase

IVUS = intravascular ultrasound

LAD = left anterior descending coronary artery

OCT = optical coherence tomography

PCI = percutaneous coronary intervention

RCA = right coronary artery

Acute coronary syndromes (ACS) arise from acute occlusive thrombosis of a coronary artery (1). The leading cause of acute occlusive coronary thrombosis is a rupture of a lipid plaque with subsequent release of thrombogenic substrate into the bloodstream, which triggers activation of platelets and a coagulation system (2). Ruptured lipid plaque is characterized by the presence of a large necrotic core with disruption of an overlying thin fibrous cap (1). In contrast, 2% to 7% of fatal acute coronary thrombosis is caused by calcified nodules (1,3). The definition of calcified nodule in pathology is a lesion with acute thrombi showing eruptive calcific nodules through a disrupted fibrous tissue with an underlying fibrocalcific plaque (1,3). However, in vivo data on calcified plaques at the culprit lesion responsible for ACS are limited.

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In this study, we aimed to conduct detailed analysis of calcified plaques in patients with ACS to study the prevalence, optical coherence tomography (OCT) findings, and clinical significance.

METHODS

STUDY POPULATION. This was a multicenter longitudinal international collaborative study of ACS patients enrolled from 11 sites across 6 countries (NCT03479723). Patients presenting with ACS who had undergone OCT imaging of the culprit lesion at index procedure were eligible for the study. Among 1,241 patients, 607 (48.9%) patients had a ruptured lipid plaque and 477 (38.4%) patients had plaque erosion at the culprit lesion (**Figure 1**). Consequently, we identified 157 (12.7%) patients who had a calcified plaque at the culprit lesion. Diagnosis of ACS included ST-segment elevation myocardial infarction and non-ST-segment elevation ACS, as previously described (4). The culprit lesion was identified based on angiographic findings, electrocardiogram changes, or left ventricular wall motion abnormalities. In patients with multiple stenoses, the culprit lesion was identified as the lesion having the most severe stenosis or with evidence of recent plaque disruption such as filling defect suggestive of thrombus on angiogram. Demographic, angiographic, and OCT findings of the culprit lesions, peak post-percutaneous coronary intervention (PCI) creatine kinase (CK) values, and in-hospital outcomes (death and target lesion revascularization) were evaluated. This study was approved by the Institutional Review Board at each participating site and written informed consent was obtained from all patients before enrollment.

CORONARY ANGIOGRAPHY ANALYSIS. Quantitative coronary angiography analysis was performed using CAAS 5.10.1 software (Pie Medical Imaging BV, Maastricht, the Netherlands). The minimal lumen diameter, reference vessel diameter, diameter stenosis, and length of the culprit lesions were measured (5). Coronary flow was assessed according to the Thrombolysis In Myocardial Infarction (TIMI) flow grade (6). Lesion complexity was assessed using the American College of Cardiology/American Heart Association classification (7). Thrombus was defined as an intraluminal filling defect or a haze seen in multiple angiographic projections (8). Calcification was identified as readily apparent radiopacities within the vascular wall at the site of the stenosis (9).

OCT IMAGE ACQUISITION AND ANALYSIS. OCT examination was performed using either a frequency-domain (C7/C8, OCT Intravascular Imaging System, St. Jude Medical, St. Paul, Minnesota) or time-domain (M2/M3 Cardiology Imaging Systems, LightLab Imaging Inc., Westford, Massachusetts) OCT system. All OCT images were submitted to the core laboratory at Massachusetts General Hospital and analyzed by 2 independent investigators (E.Y. and T.S.) who were blinded to clinical, angiographic, and laboratory data, using an offline review workstation (St. Jude Medical). Any discordance was resolved by consensus with a third reviewer. Plaque was identified as a segment with a loss of the normal 3-layered structure of the

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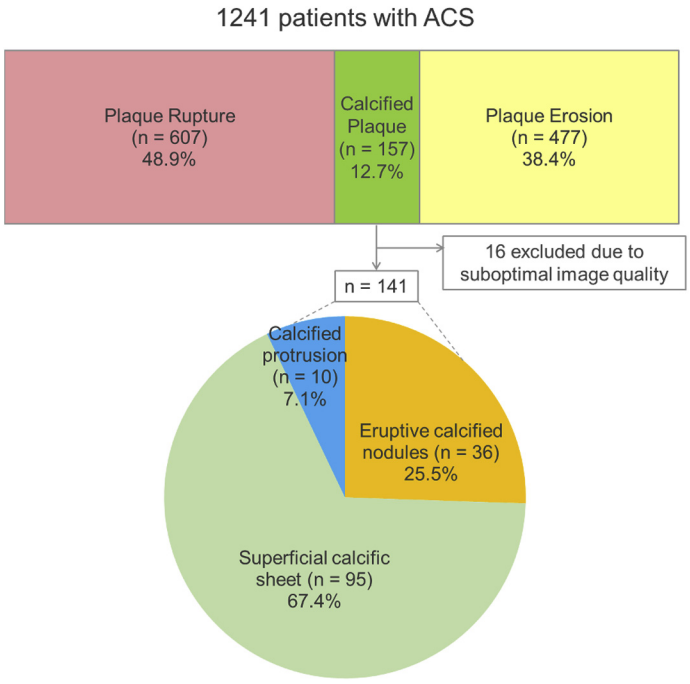
vessel wall (10). Proximal and distal references were identified as the sites with the largest lumen area proximal and distal to the plaque within a 10-mm segment, and mean reference lumen area was calculated (11). Minimal flow area was defined as the smallest flow area within the length of the plaque. Percent area stenosis was calculated as follows: [(mean reference lumen area - minimal flow area) / mean reference lumen area] × 100 (11). Calcification was identified by the presence of well-delineated low-backscattering heterogeneous regions (10). Calcified plaque was identified by the presence of superficial substantive calcification at the culprit site without evidence of ruptured lipid plaque. Calcified plaques were classified into 3 types: 1) eruptive calcified nodules; 2) superficial calcific sheet; and 3) calcified protrusion. Eruptive calcified nodules were defined by expulsion of small calcific nodules into the lumen (**Figures 2A and 2B**). Superficial calcific sheet, also called sheet calcium by pathologists, was defined by: 1) sheet-like superficial calcific plate without erupted nodules or protruding mass into the lumen; 2) minimal or no visible disruption of overlying fibrous tissue; and 3) minimal compromise of the lumen (**Figures 2C and 2D**). Calcified protrusion, also called protruding nodular calcification by pathologists, was defined by protruding calcific mass without eruptive nodules (**Figures 2E and 2F**). Quantitative analysis was performed at 1-mm intervals on cross-sectional OCT images. Calcification arc and calcification thickness were measured in each cross-sectional image. Calcification length was obtained on the longitudinal view. Calcification index was calculated as the product of mean calcification arc and calcification length (12). Thrombus was defined as an irregular mass with minimum diameter >250 μm attached to the luminal surface or floating within the lumen (11). Type of thrombus was determined by the predominance of either red thrombus (high backscattering with high signal attenuation) or white thrombus (homogenous backscattering with low signal attenuation) (10,13).

STATISTICAL ANALYSIS. All analyses were performed using SPSS Statistics 23.0 software (International Business Machines Corporation, Armonk, New York). Categorical data were expressed as absolute frequencies and percentages and compared using the chi-square test or Fisher exact test, as appropriate. Continuous variables were expressed as mean ± SD for normally distributed variables and as median (interquartile range) for non-normally distributed variables, and compared using the Student's *t*-test, 1-way analysis of variance, Mann-Whitney *U* test, or Kruskal-Wallis test, as appropriate. In case of significance, pairwise post hoc tests were performed with the Bonferroni correction. Intraobserver and interobserver differences were quantified using the kappa coefficient of agreement for the plaque classification. A p value <0.05 was considered statistically significant.

FIGURE 1 Prevalence of Subtypes of Calcified Plaques



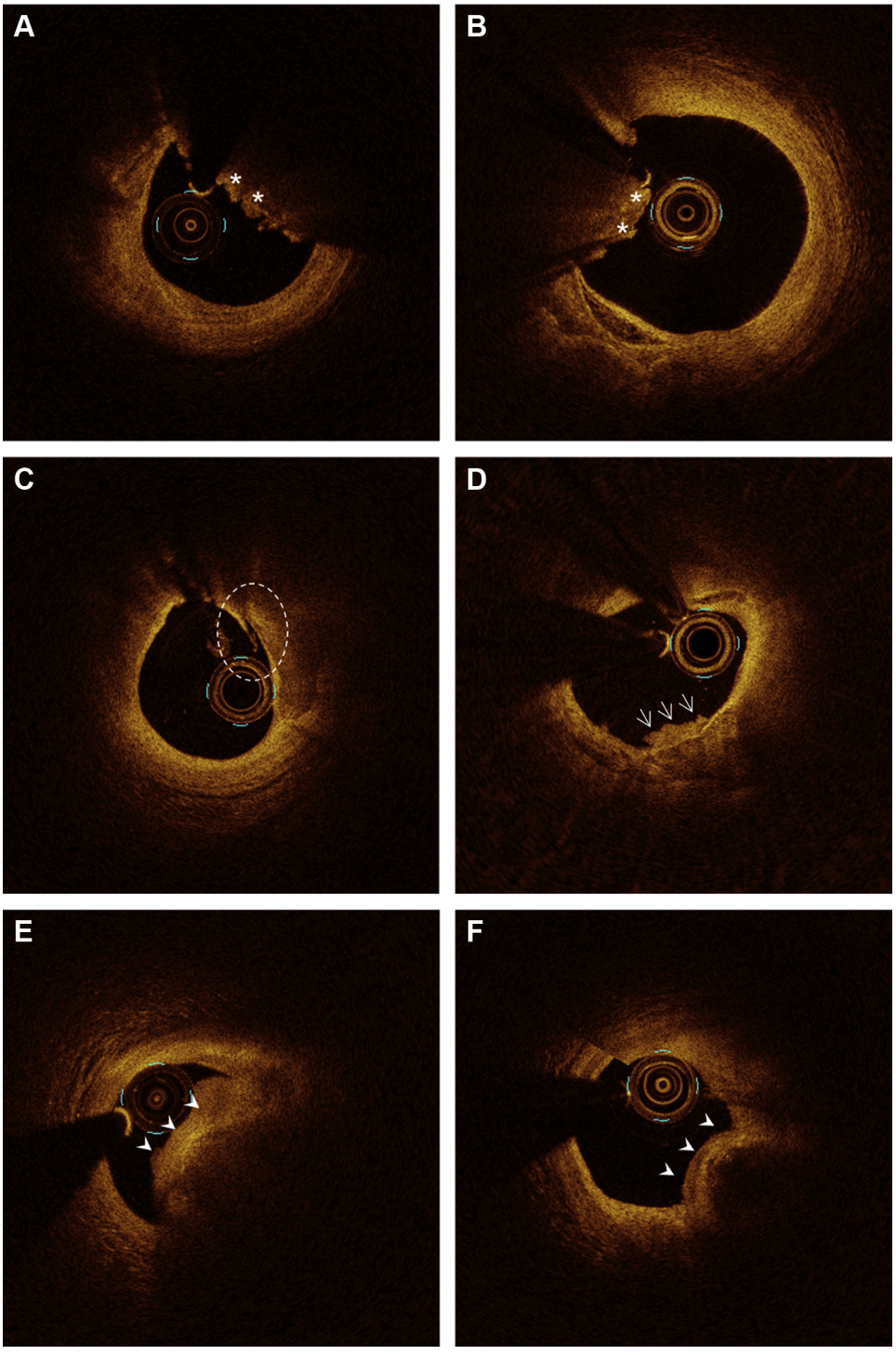
In 1,241 culprit lesions, calcified plaque was the underlying etiology in 12.7% of patients. Among the 3 subtypes of calcified plaque, superficial calcific sheet was the most common type, followed by eruptive calcified nodules and calcified protrusion. ACS = acute coronary syndrome(s).

RESULTS

PATIENT CHARACTERISTICS. Among 157 patients with calcified culprit plaque, 16 cases were excluded due to suboptimal image quality and 141 patients were included in the final analysis. Among them, 36 (25.5%) patients had eruptive calcified nodules, 95 (67.4%) patients had superficial calcific sheet, and 10 (7.1%) patients had calcified protrusion (**Figure 1**). Mean age was 69.1 years and 73.0% of patients were men. There were no significant differences in patient characteristics and laboratory findings among the groups (**Table 1**).

ANGIOGRAPHIC FINDINGS. Eruptive calcified nodules were most frequently located in the right coronary arteries (RCAs), whereas superficial calcific sheet

FIGURE 2 Representative Optical Coherence Tomography Images of Calcified Plaques at the Culprit Lesions



(A, B) Eruptive calcified nodules represent expulsion of a cluster of small calcific nodules into the lumen **(*)**. **(C, D)** Superficial calcific sheet represents sheet-like superficial calcific plate with minimal or no disruption of overlying fibrous tissue, and minimal compromise of the lumen, but without erupted nodules or protruding mass into the lumen. Calcific plate is accompanied by **(C)** disruption of fibrous tissue **(dashed circle)** or discontinuity of fibrous tissue, or by **(D)** intact but thin fibrous tissue **(arrows)**. **(E, F)** Calcified protrusion represents protruding calcific mass without small eruptive calcific nodules **(arrowheads)**.

was most frequently located in the left anterior descending coronary arteries (LADs) (Table 2). The prevalence of complex lesion and multivessel disease were not different among the groups. The superficial calcific sheet group had the worst pre-PCI coronary flow, smallest minimal lumen diameter, and greatest percent diameter stenosis.

OCT FINDINGS. OCT findings are shown in Table 3. Among 95 patients with superficial calcific sheet, 81 patients had minimally disrupted fibrous tissue and 14 patients had intact fibrous tissue. Calcium burden (calcification arc, thickness, length, and index) was greatest in the eruptive calcified nodule group, followed by the superficial calcific sheet group, and smallest in the calcified protrusion group. The superficial calcific sheet group had smallest minimal flow area and reference lumen area. White thrombus was predominant in the superficial calcific sheet group, in contrast to eruptive calcified nodules, which had predominantly red thrombus.

Excellent intraobserver and interobserver agreement was observed in the diagnosis of each subtype of calcified culprit plaque (kappa = 0.868 and 0.854, respectively).

IN-HOSPITAL OUTCOMES. In-hospital outcomes are shown in Table 4. Post-PCI coronary flow was comparable among the groups. The superficial calcific sheet group had highest peak post-PCI CK values. In-hospital cardiac event rate during initial hospitalization was low in all 3 groups.

TABLE 1 Patient Characteristics

	Eruptive Calcified Nodules (n = 36)	Superficial Calcific Sheet (n = 95)	Calcified Protrusion (n = 10)	p Value
Age, yrs	70.2 ± 11.1	69.0 ± 9.9	65.4 ± 6.0	0.414
Sex				0.523
Male	28 (77.8)	69 (72.6)	6 (60.0)	
Female	8 (22.2)	26 (27.4)	4 (40.0)	
Clinical presentation				0.263
STEMI	13 (36.1)	43 (45.3)	2 (20.0)	
NSTE-ACS	23 (63.9)	52 (54.7)	8 (80.0)	
Prior MI	6 (16.7)	11 (11.6)	0 (0.0)	0.428
Prior PCI	4 (11.1)	15 (15.8)	1 (10.0)	0.850
Hypertension	30 (83.3)	74 (77.9)	6 (60.0)	0.290
Dyslipidemia	20 (55.6)	65 (68.4)	7 (70.0)	0.375
Diabetes mellitus	17 (47.2)	36 (37.9)	5 (50.0)	0.537
Renal insufficiency	12 (33.3)	28 (29.5)	5 (50.0)	0.418
Family history of CAD	4 (11.1)	18 (18.9)	3 (30.0)	0.306
Current smoking	9 (25.0)	23 (24.2)	2 (20.0)	1.000
Creatinine, mg/dl	0.82 (0.69–1.26)	0.92 (0.76–1.10)	0.95 (0.89–1.39)	0.376
Low-density lipoprotein cholesterol, mg/dl	107.9 ± 40.5	109.3 ± 40.5	93.6 ± 28.8	0.696
High-density lipoprotein cholesterol, mg/dl	49.3 ± 13.2	48.1 ± 13.9	42.7 ± 3.2	0.596
Triglyceride, mg/dl	104.9 ± 61.3	135.6 ± 99.2	160.6 ± 110.6	0.197
HbA_{1c}, %	8.2 ± 3.7	7.0 ± 2.3	5.9 ± 0.7	0.080
WBC count/μl	7,400 (6,700–8,703)	9,000 (6,920–10,510)	8,200 (5,945–9,450)	0.283
Hemoglobin, g/dl	13.4 ± 2.0	13.4 ± 2.2	11.9 ± 1.6	0.127
Initial CK, IU/l	110 (76–238)	131 (83–443)	96 (50–459)	0.382

Values are mean ± SD, n (%), or median (interquartile range).

CAD = coronary artery disease; CK = creatine kinase; HbA_{1c} = glycosylated hemoglobin; MI = myocardial infarction; NSTE-ACS = non-ST-segment elevation acute coronary syndrome(s); PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; WBC = white blood cell.

DISCUSSION

This is the first report that demonstrates 3 distinct types of calcified plaques at the culprit lesion in patients presenting with ACS: eruptive calcified nodules, superficial calcific sheet, and calcified protrusion. The additional findings of this study include that: 1) superficial calcific sheet is the most common type; 2) eruptive calcified nodules are frequently located in the RCA, whereas superficial calcific sheet is most frequently found in the LAD; 3) the superficial calcific sheet group has a poor baseline TIMI flow and smallest luminal diameter; 4) the eruptive calcified nodule group has the largest calcium burden; 5) red thrombus is predominant in eruptive calcified nodules and white thrombus in superficial calcific sheet; and 6) post-PCI myocardial damage is greatest in the superficial calcific sheet group.

PREVALENCE OF CALCIFIED CULPRIT PLAQUES IN PATIENTS WITH ACS. Calcification is a signature of advanced atherosclerosis, and the presence and the extent of calcification is strongly associated with poor prognosis (14). Fibrocalcific plaques are mainly accompanied by calcific sheet (>3 mm), whereas fragmented calcification and microcalcification (0.5 to 15 μm) were frequently found in ruptured lipid plaques (15). Several imaging studies including computed tomography (16) and intravascular ultrasound (IVUS) (17) showed that spotty calcification was prevalent in the culprit lesions associated with ACS, although OCT studies reported conflicting results (12,18,19). Taken together, small calcium deposits may play a role in destabilization of lipid plaque, whereas extensive calcification may be a signature of advanced atherosclerosis and more likely to be associated with plaque stabilization. Nevertheless, calcified plaques are occasionally found in the absence of ruptured lipid core at the culprit lesion in patients with ACS. In this subset of patients, calcified plaques are likely to be responsible for ACS, but the pathogenesis and detailed information of calcified culprit plaque leading to ACS has not been fully investigated.

TABLE 2 Angiographic Findings

	Eruptive Calcified Nodules (n = 36)	Superficial Calcific Sheet (n = 95)	Calcified Protrusion (n = 10)	p Value
Culprit artery				0.012
Left anterior descending	15 (41.7)	65 (68.4)	4 (40.0)	
Left circumflex	5 (13.9)	12 (12.6)	3 (30.0)	
Right	16 (44.4)	18 (18.9)	3 (30.0)	
Initial TIMI flow grade 0–1	1 (2.8)	22 (23.2)	2 (20.0)	0.009
Thrombus	6 (16.7)	9 (9.5)	2 (20.0)	0.571
Moderate to heavy calcification	20 (55.6)	40 (42.1)	2 (20.0)	0.265
Type B2/C lesion	25 (69.4)	69 (72.6)	9 (90.0)	0.471
Multivessel disease	22 (61.1)	43 (45.2)	5 (50.0)	0.253
Quantitative coronary angiography analysis				
Minimal lumen diameter, mm	1.05 ± 0.82	0.63 ± 0.57	0.92 ± 0.51	0.003
Reference vessel diameter, mm	2.82 ± 0.65	2.77 ± 0.68	3.12 ± 1.22	0.387
Diameter stenosis, %	65.3 ± 21.8	77.3 ± 20.2	68.9 ± 13.9	0.012
Lesion length, mm	16.4 ± 7.0	19.0 ± 9.2	15.4 ± 6.0	0.203

Values are n (%) or mean ± SD.
TIMI = Thrombolysis In Myocardial Infarction.

A recent study reported the clinical characteristics of calcified nodules at the culprit lesion. However, in that study, both ACS and stable angina pectoris cases were combined (20). In our study, we included calcified plaque at the culprit lesion only in patients with ACS to investigate the role of calcified plaque in the development of ACS.

ERUPTIVE CALCIFIED NODULES. Previous pathology studies reported that 2% to 7% of fatal coronary thromboses were caused by calcified nodules (1,3). Several OCT studies also reported calcified nodules in 2% to 8% of patients with ACS (4,20,21). Our result demonstrating that eruptive calcified nodules were identified in 2.9% (n = 36 of 1,241) of the entire ACS cohort was in line with these studies. Calcified nodules are found predominantly in heavily calcified coronary arteries (1,3). Pathology studies surmise that eruption of calcific nodules causes disruption of the endothelium, leading to thrombus formation (1,3). Fracture of calcific sheet, turning into nodules, breaks through the overlying tissue into the lumen. A recent OCT study supports this concept by demonstrating that calcified nodules were most frequently found in the mid segment of the RCA and were associated with larger hinge movement on angiogram (20). RCAs are situated in the atrioventricular groove and known to have an increased risk for stent fracture (22). Continuous cyclic mechanical forces exerted on the segment of hinge movement over a prolonged period may cause weakening of calcified plaque, leading to fracture. Calcified nodules are commonly surrounded by fibrin, potentially arising from surrounding capillaries that are leaky or damaged (3). Eruptive nodules also cause local flow turbulence that activates procoagulant factors triggering thrombosis (23). In our study, eruptive calcified nodules were indeed associated with a higher prevalence of red thrombus.

SUPERFICIAL CALCIFIC SHEETS. In calcified culprit plaques, in the absence of typical calcified nodules, we observed the following 2 distinctly different patterns: superficial calcific sheets and calcified protrusions. In these 2 types, the underlying mechanism of thrombosis may be different from eruptive calcified nodules. The superficial calcific sheet group had the smallest minimal lumen area among the 3 groups. Luminal narrowing creates a local high endothelial shear stress environment that could lead to platelet aggregation and thrombosis (24). Alternatively, high local plaque structural stress at the junction of fibrous tissue with a rigid calcified plate within the intima could cause intimal tearing (25). Furthermore, because calcium contains collagenous matrix, exposure of collagen could also initiate platelet thrombus formation (26). Taken together, narrow lumen with high biomechanical stress as well as minimal disruption of fibrous tissue could initiate thrombosis. These processes may explain the higher frequency of platelet-rich white thrombus in this group. It should be noted, however, that there has been no pathology report that showed superficial calcific sheets as a cause of cardiac death. However, it may be related to selection bias of the pathology studies. An OCT study on superficial calcific sheet in a patient with ACS has been reported (27).

Spotty calcification is occasionally found in ruptured lipid plaques (18). However, the significance of spotty calcification in the pathogenesis of ACS was recently questioned (12). In the present study, patients who had a ruptured lipid plaque at the culprit lesion were not included in the analysis. All cases in the superficial calcific sheet group did not fulfill the previously reported definition of spotty calcification (12,19). A ruptured lipid plaque with spotty calcification is easily distinguished from a superficial calcific sheet, as the latter does not contain superficial lipid.

CALCIFIED PROTRUSIONS. OCT-derived calcified protrusions were least frequent among the 3 types. This type may correspond to protruding "nodular calcification" in pathology studies. Pathologists claim not to confuse nodular calcification with calcified nodules. The terminology "protruding nodular calcification" is sometimes used to refer a benign bystander protruding plaque with calcification. In a previous IVUS study, pathologically validated calcified nodules corresponded well to convex calcification and irregular luminal surface (28). Another study reported that IVUS-derived calcified nodules at the

TABLE 3 Culprit Plaque Characteristics on Optical Coherence Tomography

	Eruptive Calcified Nodules (n = 36)	Superficial Calcific Sheet (n = 95)	Calcified Protrusion (n = 10)	p Value: Eruptive Calcified Nodules vs. Superficial Calcific Sheet	p Value: Eruptive Calcified Nodules vs. Calcified Protrusion	p Value: Superficial Calcific Sheet vs. Calcified Protrusion
Maximal calcification arc, degree	306.3 (208.2–360.0)	231.7 (158.8–324.7)	88.5 (73.4–141.5)	0.029	<0.001	<0.001
Maximal calcification thickness, μm	1,015 (770–1,198)	930 (760–1,090)	710 (575–795)	0.211	0.001	0.005
Calcification length, mm	21.0 (17.0–33.8)	15.0 (10.0–18.0)	7.0 (3.5–12.0)	<0.001	<0.001	0.001
Calcification index	3,284.9 (2,113.3–5,385.3)	1,644.3 (1,012.4–3,058.7)	472.5 (176.7–865.2)	<0.001	<0.001	<0.001
Minimal flow area, mm^2	2.32 ± 1.79	1.46 ± 0.87	1.82 ± 1.41	0.001	0.740	1.000
Reference lumen area, mm^2	8.54 ± 4.08	6.22 ± 2.58	7.58 ± 2.86	<0.001	1.000	0.546
Area stenosis, %	72.0 ± 16.9	75.6 ± 11.8	75.6 ± 12.3	0.521	1.000	1.000
Thrombus				<0.001	0.016	0.261
White	5 (13.9)	63 (66.3)	5 (50.0)			
Red	30 (83.3)	17 (17.9)	4 (40.0)			
No	1 (2.8)	15 (15.8)	1 (10.0)			

Values are median (interquartile range), mean ± SD, or n (%).

nonculprit lesion were benign, with a very low incidence of future cardiac events (29). However, IVUS does not always accurately distinguish noneruptive protruding nodular calcifications from eruptive calcified nodules, or clearly visualize the plaque surface due to its limited resolution. OCT may be the only imaging modality capable of distinguishing protruding multiple small calcific nodules in the eruptive calcified nodule group from protuberant calcific mass without eruptive nodules in the calcified protrusion group. As shown in **Figure 2**, the leading edge of eruptive calcified nodules is often irregular due to a cluster of small calcific nodules, whereas calcified protrusions typically show smooth leading edge. In our results, calcified protrusions had the smallest calcium burden among the 3 groups and showed high signal attenuation on OCT which was similar to that of lipid pools. This finding implies that this group may have not reached the advanced stage of atherosclerosis or calcific sheet formation compared with the other 2 groups. Given that the necrotic core itself as well as the surrounding collagenous matrix becomes calcified in the atherosclerotic process (15), calcified protrusions may be related to a previously ruptured necrotic core. Eccentric protruding mass into the lumen could induce local flow disturbance and high endothelial shear stress, resulting in platelet aggregation and thrombus formation (23,24).

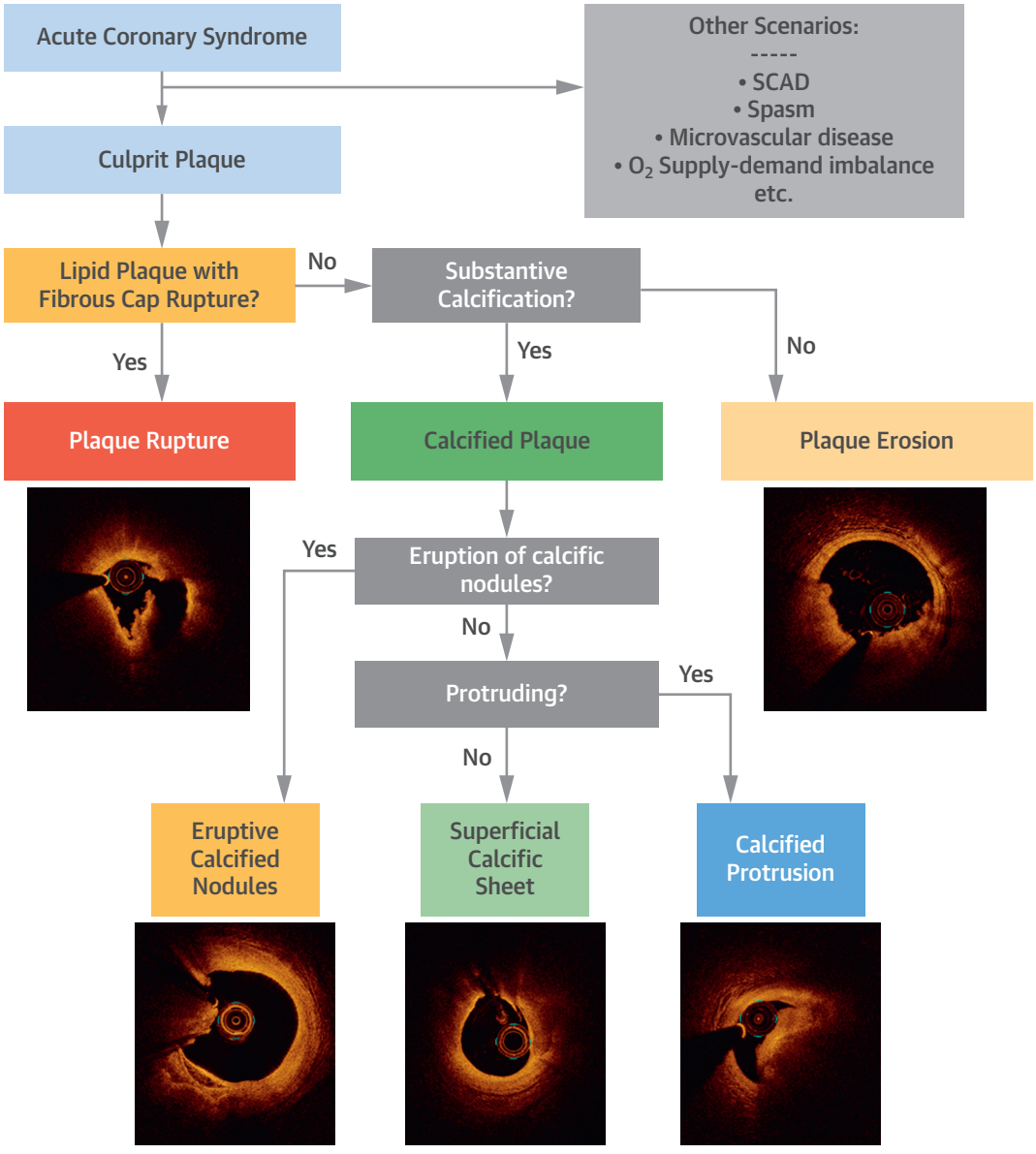
NEW CLASSIFICATION AND CLINICAL IMPLICATIONS. We previously reported an algorithm for in vivo plaque classification including calcified nodules as assessed by OCT in patients with ACS (4). In the referenced study, the number of patients with calcified culprit plaques was small and the understanding of calcified plaque was limited. As we have reviewed a larger number of cases, we came to acknowledge that a subset of patients had severe calcification at the culprit plaques with luminal thrombi without evidence of ruptured lipid plaque or typical eruptive calcified nodules.

TABLE 4 In-Hospital Outcomes

	Eruptive Calcified Nodules (n = 36)	Superficial Calcific Sheet (n = 95)	Calcified Protrusion (n = 10)	p Value: Eruptive Calcified Nodules vs. Superficial Calcific Sheet	p Value: Eruptive Calcified Nodules vs. Calcified Protrusion	p Value: Superficial Calcific Sheet vs. Calcified Protrusion
Final TIMI flow grade 0–2	1 (2.8)	2 (2.1)	1 (10.0)	1.000	0.391	0.262
Peak CK, IU/l	241 (116–612)	834 (141–3,394)	745 (69–1,984)	0.011	0.542	0.289
In-hospital outcome						
Death	0 (0.0)	0 (0.0)	0 (0.0)	1.000	1.000	1.000
Target lesion revascularization	0 (0.0)	1 (1.1)	0 (0.0)	1.000	1.000	1.000

Values are (%) or median (interquartile range).
Abbreviations as in **Tables 1 and 2**.

CENTRAL ILLUSTRATION **Optical Coherence Tomography Diagnostic Algorithm for Acute Coronary Syndromes**



Sugiyama, T. et al. J Am Coll Cardiol Intv. 2019;12(6):531–40.

The presence or absence of rupture of a lipid plaque is the most distinguishing finding. In plaques with the absence of ruptured lipid core, calcified plaques are characterized by the presence of substantive superficial calcification. Depending on the morphology of calcification, calcified culprit plaques are categorized into 3 groups. Plaque erosion is finally identified by the diagnosis of exclusion. SCAD = spontaneous coronary artery dissection.

The present study represents the first and largest series that describes the detailed OCT characteristics of calcified plaques. In this study, we revised the previous algorithm and classified calcified plaques into 3 types based on the pattern of calcification and the presence of disruption of fibrous tissue. We proposed to put these 3 subgroups under "calcified plaque" (Central Illustration). In understanding the underlying mechanism of ACS, the presence or absence of rupture of a lipid plaque is the key finding. In plaques without

evidence of ruptured lipid core, calcified plaques are characterized by the presence of substantive superficial calcification. Our study showed a higher prevalence of calcified culprit plaque (12.7%) compared with the previous studies (2% to 8%) (1,3,4,20,21). Our result was derived from a combination of the previously reported "calcified nodules," superficial calcific sheet, and calcified protrusion.

The association between calcification and prognosis is not fully understood. In our study, the superficial calcific sheet group had higher peak post-PCI CK elevation compared with the eruptive calcified nodule group. These findings imply that we may need to pay more attention to superficial calcific sheet subtype in the setting of PCI that may potentially result in greater myocardial damage. Furthermore, management of calcified plaques in patients with ACS is still challenging. In the superficial calcific sheet group, the presence of smaller minimal lumen area suggests that debulking or plaque modification such as rotational and orbital atherectomy may have a role. In contrast, the eruptive calcified nodule group may require fracture-resistant stents with constant hinge movement. The calcified protrusion group may result in stent malapposition. We believe that our updated OCT diagnosis algorithm and classification will help with understanding of the pathobiology of calcified culprit plaques and selecting efficient treatment strategy in patients with ACS.

STUDY LIMITATIONS. First, this is a retrospective observational study and therefore has intrinsic risk of selection bias. However, the data were prospectively collected at each participating site. All the investigators had extensive experience in OCT and pre-intervention OCT was routinely performed at those institutions in all ACS patients whenever it was feasible. Therefore, ACS cases with pre-intervention OCT were consecutively collected at all participating sites. Nevertheless, selection bias could not be totally excluded, as the study was not prospectively designed. Second, due to its shallow penetration, OCT could not always be useful to detect deep calcification. Because deep calcification may not affect the incidence of luminal thrombosis, we focused on superficial calcification in this study. When the trailing edge of calcium was not clearly visible at the thickest part, we measured the thickness of calcium at the thickest part where the trailing edge was detectable. In the cases with eruptive calcified nodules, maximal calcification arc was measured as a maximal part of circumferential calcification, but not limited to the erupted part. Therefore, calcification arc might have been overestimated in this group, as small calcified nodules erupted into the lumen might have been mixed with thrombus. Third, these OCT findings are not validated by histopathology data. A pathology validation case report demonstrated OCT-derived calcified nodules casting major dorsal shadow in the absence of red thrombus (30). When it was difficult to differentiate calcific nodules from red thrombus, we reviewed adjacent image frames to minimize the chance of misinterpretation. The presence or absence of endothelium and microcalcification cannot be imaged by the current OCT system despite its high resolution. Fourth, massive thrombus may sometimes obscure OCT images. Because the aim of this study was to evaluate the underlying plaque morphology, the use of aspiration thrombectomy before OCT imaging was allowed to obtain optimal OCT images of the culprit lesion. An extreme caution was exercised not to disrupt the underlying structure. Fifth, the culprit lesion in patients with ACS is usually easily identified. However, in patients with non-ST-segment elevation ACS who have multiple stenoses, it can sometimes be challenging to identify the culprit lesion. When it was not obvious, additional findings in OCT images were used to confirm the culprit lesion. Finally, this study, despite the largest series to date, did not evaluate clinical outcomes. Further studies to evaluate the best treatment options and long-term outcomes of each type of calcified culprit plaques are warranted.

CONCLUSIONS

In this study, we report the 3 distinct types of calcified plaques in patients with ACS and proposed a new in vivo OCT diagnosis algorithm, which will help us to better understand the pathobiology and to provide optimal care.

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PERSPECTIVES

WHAT IS KNOWN? Pathology studies showed that calcified nodule is responsible for 2% to 7% of sudden cardiac death. In vivo data on calcified plaques at the culprit lesion in patients with ACS are limited.

WHAT IS NEW? Three distinct types of calcified plaques are identified at the culprit lesion in patients with ACS: superficial calcific plate, eruptive calcified nodules, and calcified protrusion. Superficial calcific plate is frequently located in the LAD and is associated with white thrombus. Eruptive calcified nodules are most frequent in the RCA and are associated with red thrombus. A new OCT diagnosis algorithm and classification are proposed.

WHAT IS NEXT? These new findings may help to better understand the pathobiology of calcified culprit plaques, to guide for optimal treatment strategy and to predict outcomes after PCI in patients with ACS.

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