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Computed Tomographic Angiography Characteristics of Atherosclerotic Plaques Subsequently Resulting in Acute Coronary Syndrome

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Objectives In a computed tomographic (CT) angiography study, we identified the characteristics of atherosclerotic lesions that were associated with subsequent development of acute coronary syndrome (ACS).

Background The CT characteristics of culprit lesions in ACS include positive vessel remodeling (PR) and low-attenuation plaques (LAP). These 2 features have been observed in the lesions that have already resulted in ACS, but their prospective relation to ACS has not been previously described.

Methods In 1,059 patients who underwent CT angiography, atherosclerotic lesions were analyzed for the presence of 2 features: PR and LAP. The remodeling index, and plaque and LAP areas and volumes were calculated. The plaque characteristics of lesions resulting in ACS during the follow-up of 27 ± 10 months were evaluated.

Results Of the 45 patients showing plaques with both PR and LAP (2-feature positive plaques), ACS developed in 10 (22.2%), compared with 1 (3.7%) of the 27 patients with plaques displaying either feature (1-feature positive plaques). In only 4 (0.5%) of the 820 patients with neither PR nor LAP (2-feature negative plaques) did ACS develop. None of the 167 patients with normal angiograms had acute coronary events ($p < 0.001$). ACS was independently predicted by PR and/or LAP (hazard ratio: 22.8, 95% confidence interval: 6.9 to 75.2, $p < 0.001$). Among 2- or 1-feature positive segments, those resulting in ACS demonstrated significantly larger remodeling index (126.7 ± 3.9% vs. 113.4 ± 1.6%, $p = 0.003$), plaque volume (134.9 ± 14.1 mm^3 vs. 57.8 ± 5.7 mm^3, $p < 0.001$), LAP volume (20.4 ± 3.4 mm^3 vs. 1.1 ± 1.4 mm^3, $p < 0.001$), and percent LAP/total plaque area (21.4 ± 3.7 mm^2 vs. 7.7 ± 1.5 mm^2, $p = 0.001$) compared with segments not resulting in ACS.

Conclusions The patients demonstrating positively remodeled coronary segments with low-attenuation plaques on CT angiography were at a higher risk of ACS developing over time when compared with patients having lesions without these characteristics. (J Am Coll Cardiol 2009;54:49–57) © 2009 by the American College of Cardiology Foundation

Computed tomographic (CT) angiography is a useful tool for assessing not only coronary artery stenoses (1–8), but also plaque characteristics (9–18). The atherosclerotic plaques that are causally related to acute coronary syndromes (ACS) reveal a variable extent of luminal narrowing but are almost always associated with expansive or positive vessel remodeling (PR) (16). The culprit lesions characteristically demonstrate low-attenuation plaques (LAP) (16). The noncalcified plaques (NCP) with <30 HU density identified by CT angiography correlate closely with intravascular ultrasound (IVUS)-verified low attenuation in coronary atherosclerotic plaques (15). Although these plaque characteristics on CT angiography have only been reported after the occurrence of acute events, it is conceivable that such characteristics in the absence of ACS would indicate plaque instability (17,20). We, therefore, analyzed CT angiographic findings in >1,000 subjects and classified atherosclerotic plaques in >10,000 coronary artery segments based on the presence of 2 features: PR and LAP. We monitored

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Abbreviations andAcronyms

ACS = acute coronary syndrome

CT = computed tomography

IVUS = intravascular ultrasound

LAP = low attenuation plaque(s)

NCP = noncalcified plaque(s)

PR = positive vessel remodeling

the outcomes for >2 years for development of acute coronary events and correlated them with qualitative and quantitative presence of plaque characteristics.

Methods

In all, 1,160 consecutive subjects (835 men and 325 women) who underwent coronary CT angiography for suspected or known coronary artery disease from February 2003 to May 2006 were included in this study. These patients were followed up for 12 to 50 months for the development of ACS. Of these, 101 patients were excluded from analyses because 64 patients underwent coronary artery bypass surgery, 3 patients died of noncardiac causes, and 4 patients were hospitalized for heart failure in the first 12 months; the follow-up was inadequate (<12 months) in 22 patients, and the culprit lesions could not be identified in 8 ACS patients. Hence, for the present study, all plaques were analyzed in 1,059 patients. The study end point was described as the occurrence of ACS, based on the definition set forth by the European Society of Cardiology and American College of Cardiology (21,22). ACS was defined as ischemic discomfort presenting with elevation of troponin level, and ischemic discomfort that was Canadian Cardiology Society class 3 or 4 without elevation of troponin level. The culprit lesion in ACS was determined based on invasive coronary angiography, echocardiography, and an electrocardiogram.

On CT images, coronary arteries were divided into 15 segments based on the recommendations of the American Heart Association (23). The segments treated previously by percutaneous coronary intervention (PCI) or those scheduled for PCI were excluded from the assessment. Therefore, all remaining 10,037 coronary artery segments with a diameter of >2 mm were evaluated for the presence of plaques. All plaques were characterized for the presence of vessel remodeling (positive, negative, or none), plaque consistency (low or intermediate attenuation, i.e., NCP <30 or 30 HU < NCP <150 HU, respectively) and disposition of coronary calcification (spotty or large). The characteristics of the plaques resulting in ACS were compared with those not resulting in a subsequent acute event. The magnitude of the whole plaque as well as the low-attenuation plaque and the extent of vascular remodeling were calculated. The study was approved by the Institutional Review Board and the ethics committees of Fujita Health University. The follow-up information was obtained from the hospital chart review; the patients' records are very complete because all patients are almost always followed up at the same hospital.

CT angiography, interpretation, and plaque characterization. The 64-slice CT (Aquilion 64, Toshiba Medical Systems, Otawara, Japan) was employed with a collimation of 64 × 0.5 mm, detector pitch of 9.8 to 11.2, pixel size of 0.39 × 0.39 mm, rotation time of 350, 375, or 400 ms, tube current of 400 or 450 mA, and voltage of 135 kV in 249 patients. For the contrast-enhanced scan, 60 ml of contrast media was injected at 4.0 ml/s followed by 20 ml at 2.0 ml/s. In the remaining 911 patients, 16-slice CT (Aquilion 16, Toshiba Medical Systems) was used with a collimation of 16 × 0.5 mm, detector pitch of 3.2 to 3.6, pixel size of 0.39 × 0.39 mm, rotation time of 400 ms, tube current of 360 mA, and voltage of 135 kV. For the contrast-enhanced scan, 60 ml of contrast media was injected at 3.0 ml/s followed by 40 ml at 1.5 ml/s. The start of contrast-enhanced scan was adapted to SureStart imaging (Toshiba Medical Systems) (24). All scans were performed during a single breath-hold. Patients received a beta-blocker 1 h before the CT scan if the heart rate was >60 beats/min. The raw data of the scans was reconstructed using algorithms optimized for retrograde ECG-gated multislice spiral reconstruction. The reconstructed image data of CT was transferred to a computer workstation for post-processing (ZIO M900, Amin/ZIO, Tokyo, Japan). For plaque detection, both cross-sectional and curved multiplanar reformation images were analyzed. The reconstructed image data of CT was also transferred to Sure Plaque software (Toshiba Medical Systems) to measure the plaque area and volume.

VESSEL REMODELING. Coronary arterial remodeling was defined as a change in the vessel diameter at the plaque site in comparison to the reference segment set proximal to the lesion in a normal-appearing vessel segment (reference diameter). Manual inspection, in both cross-section and longitudinal reconstruction, was used for defining the remodeling index (lesion diameter/reference diameter). The remodeling index was reported as positive remodeling when the diameter at the plaque site was at least 10% larger than the reference segment.

PLAQUE CONSISTENCY. We defined the plaque consistency based on our previously reported comparison of CT angiography and IVUS data (15). In that study, the HU attenuation of IVUS-verified lipid cores was 11 ± 12 HU (range −15 to +33 HU), fibrous plaques 78 ± 21 HU (range 32 to 130 HU), and calcified plaques 516 ± 198 HU (range 221 to 1,134 HU); the density of the lumen was 258 ± 43 HU (range 174 to 384 HU). Based on the distribution of HU in comparison to the IVUS-verified lipid cores, we proposed 30 HU as the cutoff point for the detection of lipid cores with a sensitivity and specificity of 91% and 100% (15,16). The IVUS-verified fibrous plaques were defined as 30 to 150 HU. As such, all NCP in the present study were classified into 2 categories: (NCP <30 HU) and intermediate attenuation plaques (30 HU < NCP <150 HU).

CALCIFICATION. Plaque calcification was classified as spotty or large. Spotty calcification was defined as <3 mm in size (25) on curved multiplanar reformation images and occupied only 1 side on cross-sectional images. Large calcification was defined as the calcification larger than spotty calcification.

In all, 10,037 coronary artery segments were evaluated for the presence of plaques in 1,059 patients. Each plaque in every coronary artery segment was analyzed for the 2 features, namely, PR and LAP. All patients and all coronary segments were then classified as 2-feature positive (PR and LAP) plaque, 1-feature positive (either PR or LAP) plaque, 2-feature negative (absence of both PR and LAP) plaque, or no plaques. All 2- and 1-feature positive plaques were further characterized for the extent of PR (remodeling index), total plaque volume, LAP plaque volume, maximum LAP area in the cross-sectional images, and percent maximum LAP area/plaque area. Plaque area and volume were measured semiautomatically using Sure Plaque software based on CT density. All scans were evaluated by 1 investigator (S.M.). All 1- or 2-feature positive plaques were reanalyzed by 2 investigators (S.M. and K.I.) together. They used automatic detection first, then corrected manually wherever needed, and agreed on the definition of outer border in each segment. Both investigators also confirmed the presence of LAP manually. The plaque characteristics of lesions resulting in ACS were compared with those not resulting in ACS.

Statistical analyses. The proportion of event-free patients was estimated by the Kaplan-Meier method and compared between plaque groups by use of the log-rank test. Categorical variables were expressed as percentages, and the Fisher exact test (or Student *t* test for age) was used for comparisons between those with and without ACS. Those variables significant at $p < 0.05$ or better were included in the multivariable Cox proportional hazards regression to evaluate for factors that were independently associated with the future development of ACS. Analysis of covariance (adjusted for age, hypertension, hyperlipidemia, and prior MI) was performed similarly to compare mean values of continuously measured plaque measures between those with and without ACS. Cutoff values for developing ACS for each plaque characteristic were determined based on receiver-operator characteristic (ROC) curves. The sensitivity, specificity, positive predictive value, and negative predictive value of various characteristics were also calculated. The chi-square test was used to compare the presence of ACS between those with and without spotty calcification in segments with PR and LAP. All p values were 2-sided, and a value of $p < 0.05$ was considered statistically significant. All analyses were performed with SPSS (SPSS Japan Inc., Tokyo, Japan).

Results

Patient-based analyses. In all, 1,059 subjects (age 64 ± 11 years; 780 male, 279 female) undergoing CT angiography for established or suspected coronary artery disease were followed up for at least 12 months (mean 27 ± 10 months; range 12 to 50 months). Of these, 351 patients had hypertension (33%), 337 hyperlipidemia (32%), and 175 had diabetes mellitus (17%); 208 (20%) subjects were active smokers, and 292 (28%) had a history of previous myocardial infarction (MI) (Table 1). Of 1,059 patients, 367 had a ≥75% stenotic lesion in at least 1 coronary vessel.

Of the 1,059 subjects, 15 had ACS during the follow-up; 9 of 1,059 (0.8%) had the acute event within the first 12 months. Follow-up data were available up to 24 months for 718 (68%) of the 1,059 subjects; 5 of these 718 (0.7%) had ACS during 12 to 24 months. During the follow-up of >25 months in 319 patients, ACS developed in 1 (0.3%). The assessment of CT angiography revealed that 45 patients had 2-feature positive plaques (plaques with both PR and LAP), 27 had 1-feature positive plaque (either PR or LAP), and 820 had 2-feature negative plaques (neither PR nor LAP); no plaques were detected in the remaining 167 subjects (Fig. 1). Of the 45 patients showing 2-feature positive plaques, 10 (22.2%) had ACS during follow-up, compared with 1 of the 27 patients with 1-feature positive plaques (3.7%; $p < 0.05$). Conversely, only 4 (0.49%) of the 820 patients with 2-feature negative plaques ($p < 0.001$) and none of the 167 patients with normal arteries had an acute event. A case example is presented in Figure 2. Comparisons of clinical factors of all subjects in whom ACS developed and did not develop are shown in Table 2; hypertension (66.7% vs. 32.7%, $p = 0.008$), hyperlipidemia (80.0% vs. 31.1%, $p < 0.001$), previous MI (66.7% vs. 27.0%, $p = 0.002$), and 2- or 1-feature positive plaques (73.3% vs. 5.8%, $p < 0.001$) were significantly different. From multivariable Cox regression analysis of these 4 selected variables in 1,059 patients, the presence of 2- or 1-feature positive plaques was the only significant independent predictor of ACS (hazard ratio: 22.8, 95% confidence interval: 6.9 to 75.2, $p < 0.001$) (Table 3). As such, there was a significantly higher likelihood of ACS in patients with 2- or 1-feature positive plaques compared with patients with 2-feature negative plaques or no plaques (22.2% vs. 3.7% vs. 0.49%, log-rank test $p < 0.001$) (Fig. 3). Clinical characteristics and risk factor profiles of 72 patients with 2- or

Table 1 Patient Characteristics

Variables	n (%)
Age, yrs	64 ± 11
Male	780 (74)
Hypertension	351 (33)
Hyperlipidemia	337 (32)
Diabetes mellitus	175 (17)
Obesity	173 (16)
Smoking	208 (20)
Previous myocardial infarction	292 (28)
1VD/2VD/3VD including LMCA*	250/96/21 (24/9/2)

*Lesions with 75% stenosis, including percutaneous coronary intervention lesions.
LMCA = left main coronary artery; VD = vessel disease.

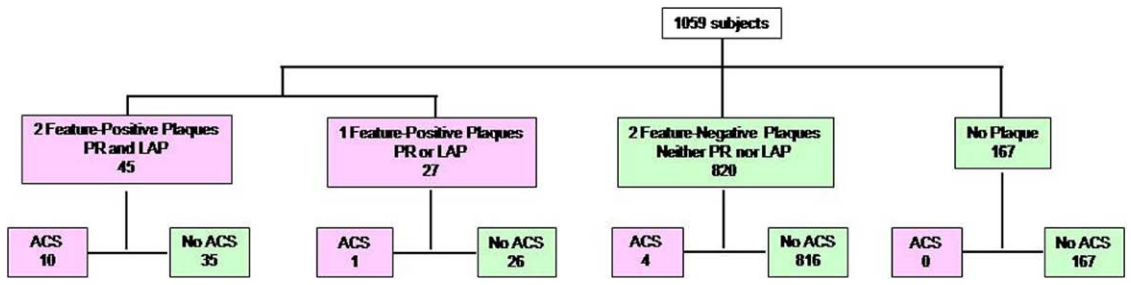

Figure 1 Acute Coronary Events in Patients on the Basis of Plaque Characteristics

Of the 45 patients showing 2-feature positive plaques, 10 (22.2%) developed acute coronary syndrome (ACS), whereas 1 of the 27 patients with 1-feature positive plaques had ACS (3.7%). Only 4 (0.5%) of the 820 patients with 2-feature negative lesions had an acute event, and none of the 167 patients with normal arteries developed ACS. LAP = low-attenuation plaque; PR = positive vessel remodeling.

1-feature positive plaques are shown in Table 4. There was no statistically significant difference in age, sex, presence of risk factors, previous MI or PCI, the coronary artery involved, and statin use after CT angiography, between patients having and not having ACS.

Segment-based analyses. Of the 10,688 segments (1,059 subjects) analyzed, 651 segments were excluded because they either contained target lesions for scheduled PCI or they were previously subjected to PCI (Fig. 4). Therefore, 10,037 segments were analyzed, wherein unstable plaques were suspected in 74 segments: 45 segments (from 45 patients) contained 2-feature positive plaques and 29 segments (from 27 patients) contained 1-feature positive plaques. In 2,853 of 10,037 segments, 2-feature negative plaques were observed, and no plaques were seen in the remaining 7,110 coronary artery segments. Of the 74 plaques classified as either 2- or 1-feature positive, 6 resulted in ACS in the first 12 months after CT examination, and an additional 5 resulted in ACS in 13 to 24 months. In 11 of these 2- or 1-feature positive plaques in patients who subsequently had ACS, the culprit lesion showed 50% stenosis in 7 and 25% stenosis in 4 lesions.

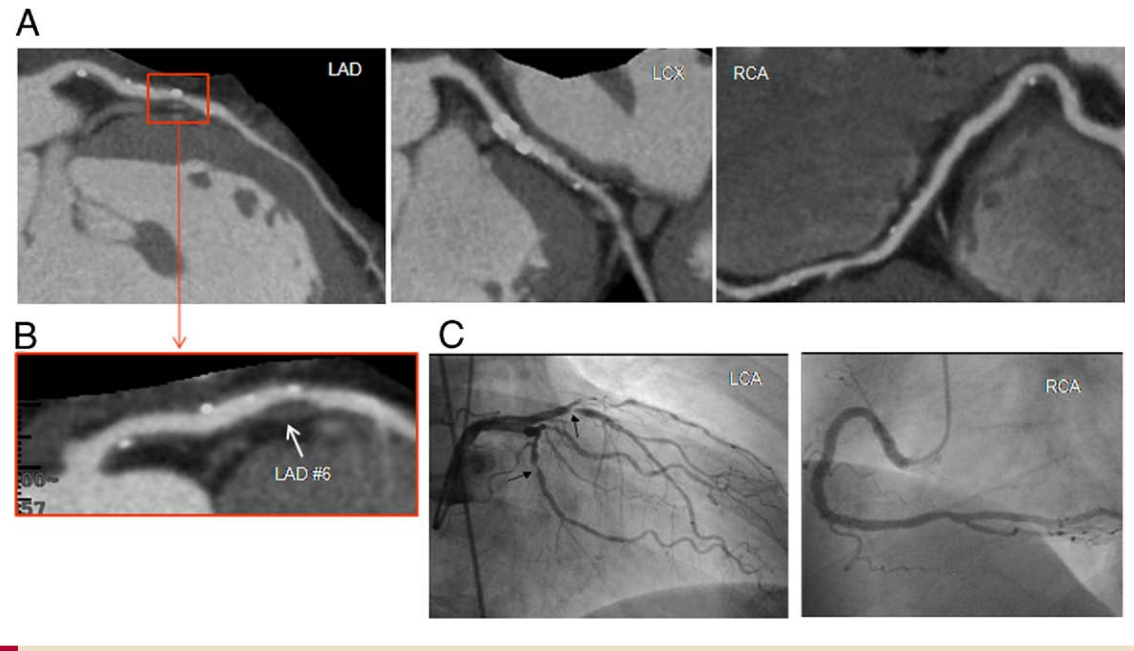

Figure 2 Example of a Patient With ACS 6 Months After CT Angiography

(A) Curved multiplanar reformation images of left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA). **(B)** Positive remodeling, low-attenuation plaque, and spotty calcification were detected in LAD #6 on coronary computed tomography (CT) angiography. **(C)** Acute coronary syndrome (ACS) occurred 6 months after CT angiography. LAD #6 was determined as the culprit lesion based on invasive coronary angiogram findings. Please note the location of the lesion proximal to the first septal branch, both in CT angiography before the event and coronary angiogram after the event when the patient was brought to the catheterization laboratory for percutaneous coronary intervention. LCA = left coronary artery.

Table 2 Comparison of Clinical Profile of All Subjects Who Did and Did Not Develop ACS

	ACS n = 15 (1.4%)	No ACS n = 1,044 (98.6%)	p Value
Age, yrs	67.7 ± 8.3	63.7 ± 10.5	0.14
Male	13 (87.7%)	767 (73.5%)	0.22
Hypertension	10 (66.7%)	341 (32.7%)	0.008
Hyperlipidemia	12 (80.0%)	325 (31.1%)	<0.001
Diabetes mellitus	4 (26.7%)	171 (16.4%)	0.32
Smoking*	5 (33.3%)	203 (19.4%)	0.21
Obesity (BMI >25 kg/m^2)	2 (13.3%)	171 (16.4%)	0.74
Previous MI	10 (66.7%)	282 (27.0%)	0.002
2- or 1-feature positive plaques	11 (73.3%)	61 (5.8%)	<0.001

*Current versus former and never.
ACS = acute coronary syndrome; BMI = body mass index; MI = myocardial infarction.

The metrics of either 2- or 1-feature positive plaques that led to ACS were different from those of the plaques that did not lead to ACS (Table 5). The remodeling index (126.7 ± 3.9% vs. 113.4 ± 1.6%, p = 0.003), total plaque volume (134.9 ± 14.1 mm^3 vs. 57.8 ± 5.6 mm^3, p < 0.001), maximum LAP area (3.2 ± 0.5 mm^2 vs. 0.5 ± 0.2 mm^2, p < 0.001), and maximum LAP area/plaque area in cross-sectional images (21.4 ± 3.7% vs. 7.7 ± 1.5%, p = 0.001) were significantly larger in plaques resulting in ACS compared with those that did not. Furthermore, the 2- or 1-feature positive plaques that resulted in ACS within 12 months were compared with plaques that did not result in ACS within 12 months (Table 5). The CT characteristics of the plaques resulting in ACS earlier were more striking. There were significant differences in the remodeling index (131.1 ± 5.1% vs. 120.8 ± 5.9% vs. 113.4 ± 51.6%, p = 0.005), total plaque volume (166.5 ± 17.8 mm^3 vs. 92.8 ± 20.4 mm^3 vs. 58.1 ± 5.5 mm^3, p < 0.001), maximum LAP area (4.7 ± 0.5 mm^2 vs. 1.2 ± 0.6 mm^2 vs. 0.5 ± 0.2 mm^2, p < 0.001), and maximum LAP area/plaque area in cross-sectional images (31.5 ± 4.5% vs. 8.1 ± 5.2% vs. 7.8 ± 1.4%, p < 0.001) between those associated with subsequent ACS in ≤12 months, ACS in 13 to 24 months, and those not associated with ACS in 24 months, respectively. Cutoff values for developing ACS in each plaque characteristics were determined based on ROC curve analyses (Fig. 5). The sensitivity, specificity, positive predictive value, and negative predictive value of various characteristics independently are provided in the Figure 5.

Role of spotty calcification. Our previous study of plaque characterization in patients presenting after ACS had demonstrated a modest association with spotty calcification (16).

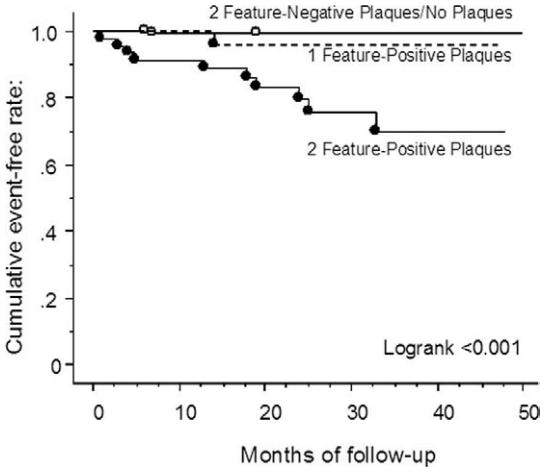

Figure 3 Kaplan-Meier Curve for Development of ACS on the Basis of Plaque Characteristics

Patient stratification according to the presence of 2- and 1-feature positive, and 2-feature negative plaques/no plaques. The y-axis represents cumulative event-free rate (log-rank test, p < 0.001). ACS = acute coronary syndrome.

Presence of spotty calcification in positively remodeled LAP that resulted in ACS (27%) was twofold more frequent than the vulnerable plaques that did not lead to ACS (13%); however, this difference was not statistically significant (p = 0.31) owing to the small number of plaques associated with ACS.

Discussion

The present study. Our study was designed to evaluate the role of CT plaque characterization for predicting acute coronary events in >1,000 subjects with established or suspected coronary artery disease who were followed up for an average of 27 months. On the basis of the previous information (16) about the plaques associated with culprit lesions in ACS, plaque vulnerability was assessed by the presence of 2 features: positive vessel remodeling at the lesion site, and LAP. Of 45 patients carrying a 2-feature positive plaque (PR and LAP), 10 had acute coronary events within the next 2 years, offering a >22% risk. In patients with 2-feature negative plaques (showing neither PR nor LAP), <0.5% patients had acute events. In addition, 1-feature positive plaques had a higher likelihood of resulting in acute events compared with 2-feature negative lesions. It seems logical to propose that 2-feature positive

Table 3 Multivariate Cox Regression Analysis for Development of Acute Coronary Syndrome

Variables	ß	SE	p Value	Hazard Ratio	95% Confidence Interval
Hypertension	0.687	0.575	0.233	1.99	0.64–6.14
Hyperlipidemia	1.293	0.679	0.057	3.65	0.96–13.79
Previous myocardial infarction	0.806	0.575	0.154	2.24	0.74–6.79
2- or 1-feature positive plaques	3.126	0.609	<0.001	22.79	6.91–75.17

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Table 4 Comparison of Clinical Profile of Subjects With 2- or 1-Feature Positive Plaques in Whom ACS Did and Did Not Develop

	ACS n = 11 (15%)	No ACS n = 61 (85%)	p Value
Age, yrs	66.3 ± 8.2	65.8 ± 9.5	0.84
Male	11 (100%)	51 (83.6%)	0.34
Hypertension	8 (62.5%)	31 (50.8%)	0.21
Hyperlipidemia	9 (75.0%)	36 (59.0%)	0.19
Diabetes mellitus	2 (25.0%)	18 (29.5%)	0.72
Smoking*	4 (25.0%)	19 (31.1%)	0.74
Obesity (BMI >25 kg/m^2)	1 (12.5%)	8 (13.1%)	0.99
Previous MI	8 (72.7%)	32 (52.5%)	0.33
Previous PCI	8 (72.7%)	32 (52.5%)	0.33
Statin use after CTA	6 (62.5%)	41 (67.2%)	0.50

*Current versus former and never.

CTA = computed tomography angiography; PCI = percutaneous coronary intervention; other abbreviations as in Table 2.

lesions can be considered potentially vulnerable, and 2-feature negative plaques potentially stable.

Our data suggest that once a patient is identified to be at high risk of having an adverse cardiac event on the basis of traditional clinical, biochemical, and biomarker risk profiles, imaging may help identify those at greater risk of acute coronary events. Of interest, only 2-feature positive plaques resulted in acute events that were significantly positively remodeled, and had larger plaque volumes and LAP volumes. Furthermore, the plaque volumes and LAP volumes were substantially greater in the plaques that led to acute events within the first year of follow-up. All acute events in 2- or 1-feature positive plaques occurred within the first 2 years of follow-up. Although the number of subjects with 3- and 4-year follow-up is significantly smaller, it seems logical that the natural history of the plaques after the CT examination (possibly because of pharmacological intervention and life-style modification taking effect) is altered significantly, and the initial scan results may not remain necessarily discriminatory thereafter.

CT characteristics confirm histopathological information. Plaque rupture is a substrate for ACS in up to 75% patients presenting with ACS, and pathological characteristics of plaques vulnerable to rupture are well established (19,20). These plaques are typically voluminous, contain large necrotic cores, and induce expansive remodeling of the vascular segment; these plaques are covered by thin and inflamed fibrous caps. The larger the plaque extent and necrotic core size, the higher is the likelihood of vulnerability of the plaque to rupture (19,26).

Whereas 80% of ruptured plaques occupy at least one-half of the vessel area in a cross section, >40% of ruptured plaques involve more than three-fourths of the cross-sectional vascular area. The plaques that are vulnerable to rupture also demonstrate large plaque areas, but the dimensions are somewhat smaller than the ruptured plaques, suggesting that the larger the plaque size, the more vulnerable is the lesion. The CT characteristics as observed in this study also reflect similar findings. Of the 74 plaques that were considered to be unstable, the plaque size was significantly larger in plaques that caused the events compared

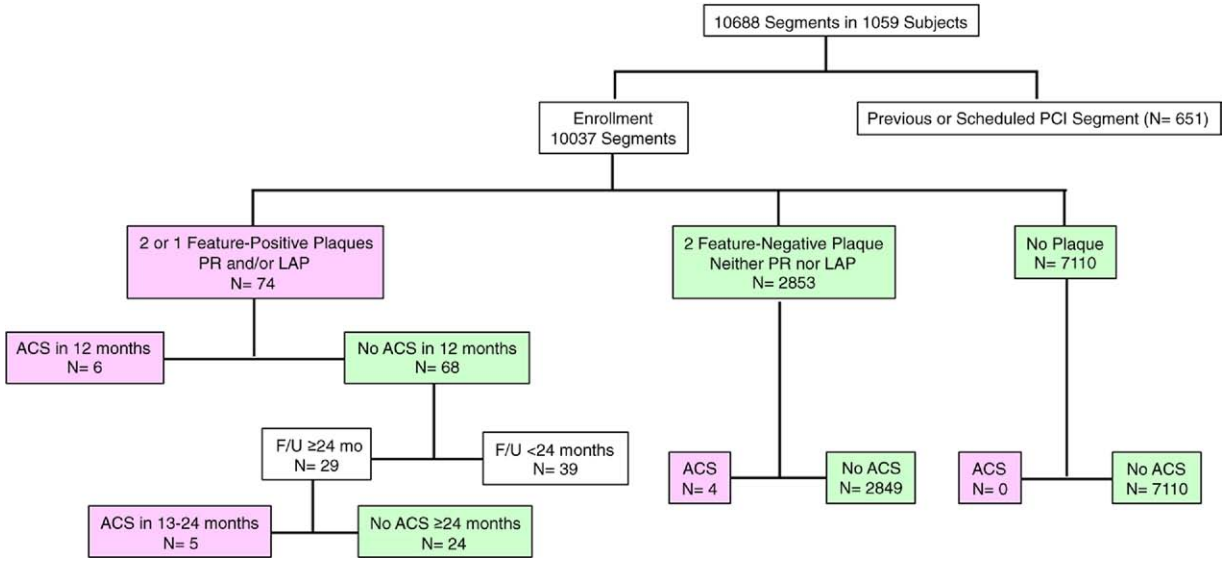

Figure 4 Plaque Characteristics and Incidence of ACS by Segment-Based Analysis

2- and 1-feature positive plaques were identified in 74 segments, 2-feature negative plaques were observed in 2,853 of 10,037 segments, and no plaques were seen in 7,110 segments. Of 74 segments with 2- and 1-feature positive plaques, 6 (8.1%) resulted in acute coronary syndrome (ACS) in the first 12 months after computed tomography examination, and an additional 5 (17.2%) of 29 plaques resulted in ACS in 13 to 24 months. F/U = follow-up; LAP = low-attenuation plaque; PCI = percutaneous coronary intervention; PR = positive vessel remodeling.

Table 5 Comparison of CT Characteristics of 2- or 1-Feature Positive Plaques That Did or Did Not Develop ACS

	2-Feature Positive Plaques			1-Feature Positive Plaques			
	ACS (n = 11)	No ACS (n = 63)	p Value	ACS 0–12 Months (n = 11)	ACS 13–24 Months (n = 5)	No ACS in 24 Months (n = 24)	p Value
Remodeling index (%)			0.003				0.005
Mean ± SE	126.7 ± 3.9	113.4 ± 1.6		131.2 ± 5.1	120.8 ± 5.9	113.4 ± 1.6	
95% confidence interval	(118.9 to 134.5)	(110.2 to 116.6)		(120.9 to 141.4)	(109.1 to 132.6)	(110.3 to 116.6)	
Total plaque volume (mm^3)			<0.001				<0.001
Mean ± SE	134.9 ± 14.1	57.8 ± 5.7		166.5 ± 17.8	92.8 ± 20.4	58.1 ± 5.5	
95% confidence interval	(106.8 to 162.9)	(46.3 to 69.2)		(131.1 to 201.9)	(52.1 to 133.6)	(47.1 to 69.1)	
LAP volume (mm^3)			<0.001				<0.001
Mean ± SE	20.4 ± 3.4	1.1 ± 1.4		30.5 ± 4.1	6.9 ± 4.8	1.2 ± 1.3	
95% confidence interval	(13.58 to 27.21)	(−1.7 to 3.9)		(22.3 to 38.8)	(−2.6 to 16.4)	(−1.3 to 3.8)	
Maximum LAP area (mm^2)			<0.001				<0.001
Mean ± SE	3.2 ± 0.5	0.5 ± 0.2		4.7 ± 0.5	1.2 ± 0.6	0.5 ± 0.2	
95% confidence interval	(2.3 to 4.1)	(0.2 to 0.9)		(3.6 to 5.7)	(−6.6 to 2.4)	(0.2 to 0.9)	
Maximum LAP area/plaque area (%)			0.001				<0.001
Mean ± SE	21.4 ± 3.7	7.7 ± 1.5		31.5 ± 4.5	8.1 ± 5.2	7.8 ± 1.4	
95% confidence interval	(14.1 to 28.7)	(4.7 to 10.6)		(22.5 to 40.4)	(−2.2 to 18.4)	(5.0 to 10.5)	

Analysis of covariance adjusted for age, hypertension, hyperlipidemia, and prior MI. p values represent comparison across groups.
LAP = low-attenuation plaque; NCP = noncalcified plaque; other abbreviations as in Table 2.

with plaques that did not lead to acute events in follow-up. The plaques were even larger in patients who had ACS in the first year of follow-up. Although plaque volume is often enormous in unstable plaques, plaque burden may not necessarily compromise the lumen diameter significantly, and sparing of the lumen occurs because of a positive or outward vessel remodeling (27,28). Therefore, angiographic encroachment of the lumen has often been reported as <50% in ACS (29). Conversely, stable plaques or ACS associated with plaque erosion do not show expansive remodeling (30,31). In the present study, the vessel segments containing the ACS culprit lesions demonstrated greater remodeling compared with vulnerable plaques that were not associated with subsequent ACS in the follow-up period.

Not only are plaques that are vulnerable to rupture larger in volume, these plaques also harbor large necrotic cores. The necrotic core in a vulnerable plaque often occupies 25% of the plaque area (32); they are 2 to 22 mm long (median 8 mm), and in up to 75% plaques are spread over 120° or more of vascular circumference (20,26). The LAP areas, which are expected to represent necrotic cores, were significantly larger in the plaques associated with ACS compared with the unstable plaques that did not. Similarly, LAP areas were significantly larger in the plaques that resulted in ACS in the first year after CT examination. In fact, >21% of the plaque area demonstrated low attenuation and confirmed the morphologic observations described in autopsy data (32). The CT information from the present study is also similar to the descriptions available from an IVUS study (33), wherein the plaques leading to an acute coronary event subsequently exhibited a large eccentric plaque containing an echolucent zone by IVUS.

Clinical implications. Traditionally, the risk of acute coronary events is calculated on the basis of clinical and biochemical characteristics (34,35). Such risk scores have been refined by the use of circulating biomarkers (36). Asymptomatic patients who are at a high-intermediate or high risk of having ACS, namely, >10% over 10 years, are subjected to intense global risk factor reduction by behavioral modification and pharmacologic intervention. It has been hypothesized that noninvasive imaging modalities such as CT angiography or positron emission tomography may further stratify high-risk patients to a very high-risk group (34). Localization of plaques showing both PR and LAP (2-feature positive plaque) may portend a higher likelihood of the future development of ACS for the next 2 years. Whether these findings extend to the larger group of asymptomatic intermediate- and/or high-risk patients would require a larger multicenter study.

Although CT angiography may be significantly more predictive of coronary disease compared with the Framingham risk score (37), and a positive scan may identify significantly increased risk for all cause death (38), current appropriateness guidelines do not recommend screening with CT angiography (39). It is partly because of radiation dose, use of contrast media, cost effectiveness, and a lack of evidence. All patients with subsequent ACS in the present study had culprit lesions that were <75% stenotic at the time of CT angiography. Such subjects who are likely to be asymptomatic may not be candidates for CT angiography by the American Heart Association/American College of Cardiology criteria (Class III, Level of Evidence: C). Recent advances in CT technology employing a larger number of slices (8,40), prospective ECG-gating scan (41), or dual-source CT (42) offer a promise of substantial reduction in radiation burden, which may facilitate application of CT

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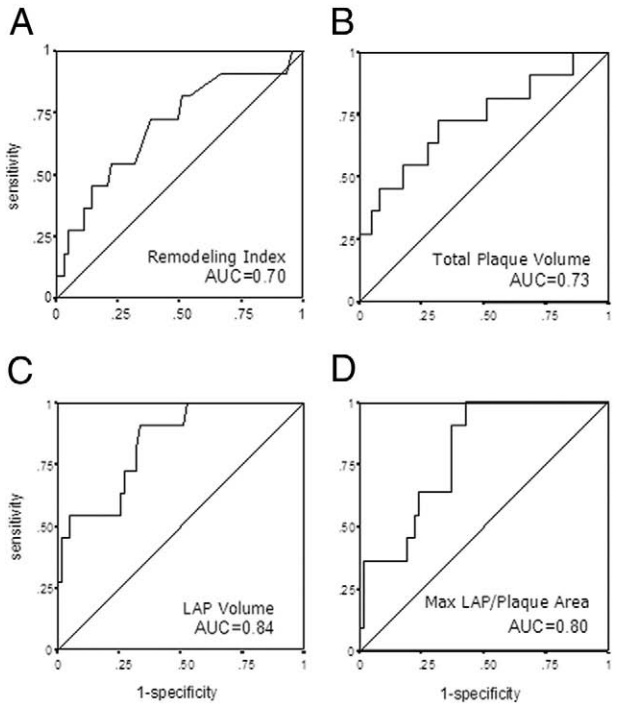

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	Cutoff Value	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Remodeling Index (%)	116.5	72.7	61.9	25.0	69.0
Total Plaque Volume (mm³)	63.13	72.7	68.3	28.6	93.5
LAP Volume (mm³)	0.99	90.0	66.7	32.3	97.7
Max LAP Area/ Plaque Area (%)	11.39	63.6	76.2	31.8	92.3

Figure 5 **ROC Curve and Cutoff Values for Various Plaque Characteristics for Developing ACS**

Receiver-operator characteristic (ROC) curves for **(A)** remodeling index, **(B)** total plaque volume, **(C)** low-attenuation plaque (LAP) volume, and **(D)** maximum LAP area/plaque area. **(E)** Cutoff values of various plaque characteristics and their diagnostic accuracy in subsequent acute coronary syndrome (ACS). AUC = area under the curve; NPV = negative predictive value; PPV = positive predictive value; Sens = sensitivity; Spec = specificity.

angiography for screening purposes. The guidelines recommend continuous research in cardiac CT imaging to determine the potential of noncatheter-based modalities to detect, characterize, and measure atherosclerotic plaque burden, and monitor change in plaque burden over time or in response to therapeutic intervention (Class I, Level of Evidence: C).

Study limitations. The foremost limitation of the study is the proposal of the cutoff value of <30 HU for the LAP. This value was defined on the basis of our IVUS-CT angiography comparison study (15). However, many centers use <50 HU as the cutoff level for the soft plaques. The CT plaque density is likely to be affected by various factors such as the lumen density of contrast (43,44) and the tube voltage. We used a tube voltage of 135 kV, unlike the most practices in which CT studies are performed at 120 kV or some in which dual energy scanning is performed (45–47). As such, a better definition of LAP will need to be established. Second, although this study includes a large cohort of patients, the number of clinical events is small and follow-up limited to ≈2 years. For clarification of the short- and long-term prognostic role of CT angiography, and for wider applicability in the high-risk asymptomatic patients, a larger number of events from longer-term follow-up and/or study of a greater number of subjects would be required. Nonetheless, these data form an important foundation for developing imaging-based prevention studies. It is likely that imaging biomarkers may be able to help improve risk stratification based on clinical and biochemical profiles.

Conclusions

The present CT angiography study demonstrates that coronary plaques that are likely to result in subsequent ACS during follow-up are often voluminous and contain large areas of low attenuation. These coronary plaques are associated with positive vascular remodeling. Although larger and longer follow-up studies will be necessary for establishing the role of CT angiography in high-risk asymptomatic subjects, these CT characteristics confirm previously reported pathologic features of unstable plaques.

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