JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 64, NO. 7, 2014

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jacc.2014.05.039

High-Risk Plaque Detected on Coronary CT Angiography Predicts Acute Coronary Syndromes Independent of Significant Stenosis in Acute Chest Pain

Results From the ROMICAT-II Trial

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ABSTRACT

BACKGROUND It is not known whether high-risk plaque, as detected by coronary computed tomography angiography (CTA), permits improved early diagnosis of acute coronary syndromes (ACS) independently to the presence of significant coronary artery disease (CAD) in patients with acute chest pain.

OBJECTIVES The primary aim of this study was to determine whether high-risk plaque features, as detected by CTA in the emergency department (ED), may improve diagnostic certainty of ACS independently and incrementally to the presence of significant CAD and clinical risk assessment in patients with acute chest pain but without objective evidence of myocardial ischemia or myocardial infarction (MI).

METHODS We included patients randomized to the coronary CTA arm of the ROMICAT-II (Rule Out Myocardial Infarction/Ischemia Using Computer-Assisted Tomography II) trial. Readers assessed coronary CTA qualitatively for the presence of nonobstructive CAD (1% to 49% stenosis), significant CAD (≥50% or ≥70% stenosis), and the presence of at least 1 of the high-risk plaque features (positive remodeling, low <30 Hounsfield units plaque, napkin-ring sign, spotty calcium). In logistic regression analysis, we determined the association of high-risk plaque with ACS (MI or unstable angina pectoris) during the index hospitalization and whether this was independent of significant CAD and clinical risk assessment.

RESULTS Overall, 37 of 472 patients who underwent coronary CTA with diagnostic image quality (mean age 53.9 ± 8.0 years; 52.8% men) had ACS (7.8%; MI n = 5; unstable angina pectoris n = 32). CAD was present in 262 patients (55.5%; nonobstructive CAD in 217 patients [46.0%] and significant CAD with ≥50% stenosis in 45 patients [9.5%]). High-risk plaques were more frequent in patients with ACS and remained a significant predictor of ACS (odds ratio [OR]: 8.9; 95% CI: 1.8 to 43.3; p = 0.006) after adjustment for ≥50% stenosis (OR: 38.6; 95% CI: 14.2 to 104.7; p < 0.001) and clinical risk assessment (age, sex, number of cardiovascular risk factors). Similar results were observed after adjustment for ≥70% stenosis.

CONCLUSIONS In patients presenting to the ED with acute chest pain but negative initial electrocardiogram and troponin, presence of high-risk plaques on coronary CTA increased the likelihood of ACS independent of significant CAD and clinical risk assessment (age, sex, and number of cardiovascular risk factors). (Multicenter Study to Rule Out Myocardial Infarction by Cardiac Computed Tomography [ROMICAT-II]; NCT01084239) (J Am Coll Cardiol 2014;64:684–92) © 2014 by the American College of Cardiology Foundation.

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Coronary computed tomography angiography (CTA) is a viable alternative to functional testing with or without imaging in the evaluation of patients with acute chest pain in the emergency department (ED) (1–3). However, the related trials revealed uncertainty around management decisions in patients with significant coronary artery disease (CAD) by CTA because the positive predictive value of CTA for significant CAD remains moderate. Furthermore, the ROMICAT-I (Rule Out Myocardial Infarction/Ischemia Using Computer-Assisted Tomography I) trial demonstrated that the presence of stenosis >50% had limited diagnostic value for acute coronary syndromes (ACS) because only 46% of patients who had obstructive CAD by CTA had matching single-photon emission computed tomography (SPECT) perfusion abnormalities during stress testing (4). Therefore, the optimal management of patients with significant CAD on CTA in this setting remains uncertain.

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An opportunity for more efficient use of CTA in the management of patients with chest pain may arise from the ability of CTA to accurately assess plaque characteristics, such as positive remodeling, spotty calcium, low Hounsfield units (HU) attenuation, and napkin-ring sign (5–11). Similar characteristics have been demonstrated to represent high-risk plaque on histology (necrotic lipid-rich core, thin-cap fibroatheroma, positive remodeling, spotty calcium) (12,13) and intravascular imaging (positive remodeling, larger plaque volume, spotty calcium) (14,15). Furthermore, initial evidence from CTA studies has suggested that these features were associated with an increased risk for future cardiovascular events in patients with stable chest pain syndromes (16–18) However, there are limited data on the potential use of high-risk plaque on CTA in patients with acute chest pain (19,20).

This study's primary aim was to determine whether high-risk plaque features, as detected by CTA in the ED, may improve diagnostic certainty of ACS independently and incrementally to the presence of significant CAD and clinical risk assessment in patients with acute chest pain but without objective evidence of myocardial ischemia or myocardial infarction (MI).

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndromes
CAD = coronary artery disease
CTA = computed tomography angiography
ED = emergency department
HU = Hounsfield units
MI = myocardial infarction

METHODS

The study cohort consisted of patients who were randomized to the CTA arm of the ROMICAT-II trial and underwent CTA (Fig. 1). A detailed description of the patient population was reported (2). Between April 2010 and January 2012, 1,000 patients with chest pain, a clinical suspicion for ACS, and cardiovascular risk factors presenting to the ED of 9 U.S. hospitals were enrolled. All study participants provided written consent for participation in the ROMICAT-II trial. The local institutional review boards approved the study.

CTA images were acquired using either retrospectively electrocardiogram (ECG)-gated or prospectively ECG-triggered protocols. The investigators in the study used the scanners from 3 vendors (Siemens Healthcare, Erlangen, Germany; GE Healthcare, Waukesha, Wisconsin; or Toshiba America Medical Systems, Tustin, California) and different scanner generations (64, 128, and 256 row and dual source). The images were transferred to the core laboratory. Image analysis was performed on a cardiac workstation (TeraRecon, Foster City, California). Three readers with at least 5 years of experience and level III training in CTA analyzed the datasets. Each reader analyzed one-third of randomly assigned CTA datasets. Further, 30 randomly selected CTA datasets were analyzed by all 3 readers to determine interobserver agreement. The CTA analysis was performed per coronary segment using the model of the Society of Cardiovascular Computed Tomography (21). For each coronary segment, the reader determined whether the image quality was sufficient to evaluate

Tufts Medical Center, Boston, Massachusetts; and the **Knight Cardiovascular Institute, Oregon Health & Science University, Portland, Oregon. This work was supported by grants from the National Heart, Lung, and Blood Institute (NHLBI) (U01HL092040 and U01HL092022). Dr. Truong has received support from the National Institutes of Health/NHLBI (K23HL098370 and L30HL093896), St. Jude Medical, American College of Radiology Imaging Network, and Duke Clinical Research Institute. Dr. Nagurney has received research grants from Biosite/Allere, Brahms Limited/Thermo-Fisher, and Nanosphere for work on cardiac biomarkers. Dr. Udelson has received research grants from the NHLBI (U01HL092040 and U01HL092022). Dr. Ferencik has received support from the American Heart Association (13FTF16450001). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Manuscript received January 12, 2014; revised manuscript received March 26, 2014, accepted May 12, 2014.

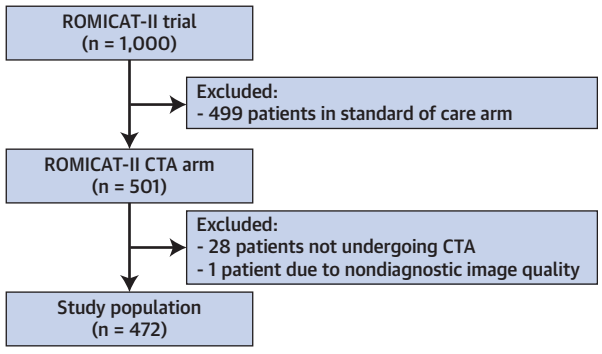


FIGURE 1 Study Population Enrollment, Exclusion, and Inclusion

The flow chart summarizes the selection of the patient population included in the analysis. CTA = computed tomography angiography; ROMICAT-II = Rule Out Myocardial Infarction/Ischemia Using Computer-Assisted Tomography II.

for the presence of stenosis and coronary plaque with confidence. Coronary segments that were assessed as nondiagnostic in image quality were treated as noninformative for the purpose of the analysis.

Each evaluable coronary segment was assessed for the presence of stenosis. The severity of stenosis was quantified by visual estimation and divided into 4 categories: 0% no stenosis, 1% to 49% mild stenosis, 50% to 70% moderate stenosis, and ≥70% severe stenosis/occlusion. For each evaluable coronary segment, we noted the presence of plaque. Noncalcified coronary plaque was defined as any discernible structure that could be assigned to the coronary artery wall, had a CT number below the contrast-enhanced coronary lumen but above the surrounding connective tissue, and could be identified in at least 2 independent planes (22). Any structure with a density of ≥130 HU that could be visualized separately from the contrast-enhanced coronary lumen, assigned to the coronary artery wall, and identified in at least 2 independent planes was defined as calcified atherosclerotic plaque (22). In each coronary segment with plaque, we performed further qualitative evaluation for the presence of high-risk plaque features, which were defined as positive remodeling, low CT number of plaque, napkin-ring sign, and spotty calcium (**Central Illustration**). Positive remodeling was assessed visually in multiplanar reformatted images reconstructed in long-axis and short-axis views of the vessel. Additional manual measurements of outer vessel diameter were performed at the readers' discretion, and a threshold of 1.1 was used to define positive remodeling (5,6). If low CT attenuation was visually noted in noncalcified plaque, readers placed 3 random region-of-interest measurements (approximately 0.5 to 1.0 mm^2) in the noncalcified low CT attenuation portion of the plaque. Low HU plaque was defined as the mean CT number within these 3 regions of interest <30 HU (7,16). The napkin-ring sign was defined as a ring-like peripheral higher attenuation of the noncalcified portion of the coronary plaque (20,23-25). Spotty calcium was defined as the presence of calcified plaque with a diameter <3 mm in any direction, length (extent in the longitudinal direction of the vessel) of the calcium less than 1.5 times the vessel diameter, and width (extent of the calcification perpendicular to the longitudinal direction of the vessel) of the calcification less than two-thirds of the vessel diameter (8,9,26). The patient was classified as having high-risk plaque features if at least 1 high-risk plaque feature was present.

The primary outcome of the study was an ACS event during the index hospitalization. ACS was defined as acute MI or unstable angina pectoris according to the American College of Cardiology/American Heart Association Guidelines (2,27). An independent clinical events committee predefined and adjudicated the endpoint. We excluded ACS (MI) during the index hospitalization in a patient with an anomalous right coronary artery from the main pulmonary artery, but with no evidence of coronary plaque or stenosis, who underwent reimplantation of the right coronary artery during the index hospitalization.

All statistical analyses were performed using Stata 13.1 (StataCorp LP, College Station, Texas). Continuous data are presented as mean ± SD. Comparisons between groups were performed with the use of an independent sample Student *t* test for continuous variables, Fisher exact test for categorical variables, and Wilcoxon rank-sum test for ordinal variables. To determine whether the presence of high-risk plaque was an independent predictor of ACS, we performed multivariable logistic regression analyses and adjusted for the presence of ≥50% stenosis, age, sex, and the number of cardiovascular risk factors (hypertension, dyslipidemia, diabetes mellitus, smoking status, and family history of premature CAD). We also performed the analyses with a definition of significant CAD as ≥70% stenosis or left main coronary stenosis ≥50%. To determine whether high-risk plaque was incremental to the presence of significant CAD and clinical risk assessment, we compared areas under the receiver-operating characteristics curve (AUC) using the DeLong algorithm (28). For all analyses, a 2-tailed p value <0.05 was required to reject the null hypothesis.

RESULTS

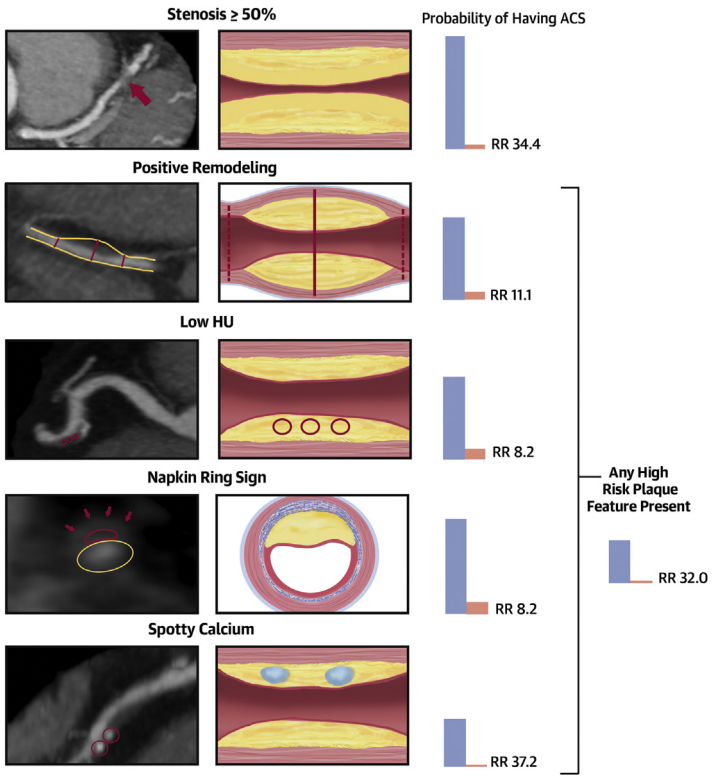
From 501 patients randomized to CTA, 473 underwent CTA. Reasons for not undergoing CTA were patient declined CTA (n = 9), safety concerns (n = 5), unavailability of CTA (n = 5), and technical difficulties (n = 9). One patient was excluded from further analysis due to nondiagnostic image quality in all coronary segments. CTA was performed using the scanners from 3 vendors (Siemens 58%, GE 34%, Toshiba 7%). Overall, 472 patients who underwent CTA with diagnostic image quality formed the study population (mean age 53.9 ± 8.0 years; 52.8% men). The prevalence of ACS was 7.8% (n = 37; MI n = 5; unstable angina pectoris n = 32). Patients with ACS had more cardiovascular risk factors and higher Thrombolysis in Myocardial Infarction scores (Table 1).

Overall, 202 of 6,855 coronary segments (2.9%) were nonevaluable, with at least 1 nonevaluable segment present in 71 of 472 patients (15.0%). The most common reason for nonevaluability was the presence of motion artifacts (n = 153), followed by coronary calcium (n = 31) and poor contrast-to-noise ratio (n = 17). Interobserver agreement among 3 readers in 30 patients was very good for the presence of coronary plaque (kappa = 0.77) and significant CAD (stenosis ≥50%; kappa = 0.80) and good for high-risk plaque (kappa = 0.69).

CAD, defined as the presence of any plaque, was detected in 262 patients (55.5%). Among 262 patients with coronary plaque, calcified plaques were present in 217 (82.2%) and noncalcified plaques in 199 (76.0%) patients. Nonobstructive CAD (1% to 49% stenosis) was detected in 217 of 472 patients (46.0%). Significant CAD (≥50% stenosis) was found in 45 of 472 patients (9.5%). Stenosis ≥70% or left main coronary stenosis ≥50% was detected in 24 patients (5.1%).

At least 1 high-risk plaque feature was present in 167 of 472 patients (35.4%), at least 2 high-risk plaque features were present in 56 patients (11.9%), and at least 3 high-risk plaque features were present in 35 patients (7.4%). The most common feature was spotty calcium (n = 151 [32.0%]) followed by positive remodeling (n = 55 [11.7%]), low HU plaque (n = 40 [8.5%]), and napkin-ring sign (n = 26 [5.5%]).

Among 45 patients with significant CAD (≥50% stenosis), at least 1, 2, and 3 or more high-risk plaque features were present in 41 (91.1%), 27 (60.0%), and 24 (53.3%) patients, respectively. The prevalence of the individual high-risk plaque features in patients with significant CAD was as follows: spotty calcium in 40 (88.9%), positive remodeling in 28 (62.2%), low HU plaque in 19 (42.2%), and napkin-ring sign in 16 (35.6%) patients. We observed a lower prevalence of high-risk plaque features in 217 patients with nonobstructive CAD (1% to 49% stenosis). At least 1, 2, and 3 high-risk plaque features were present in 125 (57.6%), 29 (13.4%), and 11 (5.1%) patients, respectively. The prevalence of the individual high-risk plaque features in patients with nonobstructive CAD was as follows: spotty calcium in 111 (51.2%), positive



CENTRAL ILLUSTRATION **Significant Stenosis and High-Risk Coronary Plaque Features and Their Association With the Probability of ACS During Index Hospitalization**

Stenosis ≥50%: severe stenosis of the mid left anterior descending coronary artery **(red arrow)**. Positive remodeling: Noncalcified plaque with positive remodeling in the distal right coronary artery. The **2 dotted red lines** demonstrate the vessel diameters at the proximal and distal references (both 1.8 mm), and the **solid red line** demonstrates the maximal vessel diameter in the mid portion of the plaque (2.7 mm). The remodeling index is 1.5. Low Hounsfield units (HU) plaque: partially calcified plaque in the mid right coronary artery with low <30 HU plaque. The **red circles** demonstrate the 3 regions of interest, with mean computed tomography (CT) numbers of 22 HU, 19 HU, and 20 HU. Napkin-ring sign: napkin-ring sign plaque in the mid left anterior descending coronary artery. Schematic cross-sectional view of the napkin-ring sign. The **red line** demonstrates the central low HU area of the plaque adjacent to the lumen **(yellow ellipse)** surrounded by a peripheral rim of the higher CT attenuation **(red arrows)**. Spotty calcium: partially calcified plaque in the mid right coronary artery with spotty calcification (diameter <3 mm in all directions; **red circles**). ACS = acute coronary syndromes; RR = relative risk.

TABLE 1 Clinical Characteristics of Study Patients Stratified According to the Diagnosis of ACS

	ACS (n = 37)	No ACS (n = 435)	p Value
Age, yrs	57.2 ± 8.3	53.6 ± 7.9	0.015
Women	6 (16.2)	217 (49.9)	<0.001
Cardiovascular risk factors			
Hypertension	22 (59.5)	230 (52.9)	0.50
Diabetes mellitus	7 (18.9)	72 (16.6)	0.65
Dyslipidemia	25 (67.6)	191 (43.9)	0.006
Former or current smoker	25 (67.6)	211 (48.5)	0.039
Family history of premature CAD	11 (29.7)	120 (27.6)	0.85
Number of cardiovascular risk factors			0.005
0 or 1	21.6	37.5	
2 or 3	62.2	53.6	
≥4	16.2	9.0	
TIMI score			<0.001
0	35.1	63.9	
1	46.0	27.1	
2	18.9	8.1	
3	0.0	0.9	
Troponin classification			<0.001
Negative	28 (75.7)	426 (97.9)	
Borderline	6 (16.2)	8 (1.9)	
Elevated	3 (8.1)	1 (0.2)	
Invasive coronary angiography	32 (86.5)	19 (4.4)	<0.001
Significant CAD (≥50% stenosis) in angiography	31 (96.9)	5 (26.3)	<0.001
Percutaneous coronary intervention	22 (59.5)	0 (0.0)	<0.001
Coronary artery bypass graft surgery	4 (10.8)	1 (0.2)	<0.001

Values are mean ± SD, n (%), or %.

ACS = acute coronary syndromes; CAD = coronary artery disease; TIMI = Thrombolysis in Myocardial Infarction.

remodeling in 27 (12.4%), low HU plaque in 21 (9.7%), and napkin-ring sign in 10 (4.6%) patients.

A comparison of the CTA findings in patients with and without ACS is provided in Table 2. All patients with ACS had evidence of CAD (i.e., either coronary plaque with 1% to 49% stenosis or ≥50% stenosis). In the non-ACS group, almost half of the patients had no evidence of CAD ($p < 0.001$). More than 75% of patients with ACS had significant CAD with ≥50% stenosis as compared with <4% of patients without ACS ($p < 0.001$).

At least 1 high-risk plaque feature was present in 95% of patients with ACS and in 30% of patients without ACS ($p < 0.001$). All individual high-risk plaque features were more often observed in patients with ACS ($p < 0.001$). Furthermore, all patients with ACS and without ≥50% stenosis had at least 1 high-risk plaque.

The presence of ACS was strongly associated with the presence of significant CAD (≥50% stenosis) as detected by coronary CTA. In univariate analysis, patients with significant CAD (≥50% stenosis) were 34 times more likely to have ACS during the index hospitalization as compared with those without significant CAD (Fig. 2). Similar to significant CAD, the presence of any high-risk plaque was associated with ACS. Patients with at least 1 high-risk plaque feature were 32 times more likely to have ACS during the index hospitalization. All individual high-risk plaque features were associated with ACS.

In the logistic regression analysis (Table 3), the presence of high-risk plaque (odds ratio [OR]: 8.9; 95% confidence interval [CI]: 1.8 to 43.3; $p = 0.006$) remained significantly associated with ACS after adjustment for ≥50% stenosis (OR: 38.6; 95% CI: 14.2 to 104.7; $p < 0.001$) and clinical predictors (age: OR: 1.0, 95% CI: 0.9 to 1.1, $p = 0.87$; female: OR: 0.4, 95% CI: 0.1 to 1.2, $p = 0.104$; number of cardiovascular risk factors: OR: 1.3, 95% CI: 0.8 to 2.0, $p = 0.278$). Similar results were observed when significant CAD was defined as stenosis ≥70% or left main coronary stenosis ≥50%.

We demonstrated that coronary stenosis ≥50% was incremental to baseline clinical characteristics (age, sex, number of cardiovascular risk factors) in predicting ACS (model 2: AUC 0.935; 95% CI: 0.894 to 0.976 vs. model 1: AUC 0.776; 95% CI: 0.711 to 0.840; $p < 0.001$). We observed that adding the presence of high-risk plaque to the model further improved the prediction of ACS (model 3: AUC 0.959, 95% CI: 0.937 to 0.981 vs. model 1, $p < 0.001$; model 3 vs. model 2, $p = 0.03$). Similar results were observed when significant CAD was defined as stenosis ≥70% or left main coronary stenosis ≥50%.

DISCUSSION

We demonstrated that high-risk coronary plaque as detected on CTA in patients presenting to the ED with acute chest pain was associated with ACS independently and incrementally to the presence of significant CAD and clinical risk assessment. Our results suggested that CTA-based assessment of high-risk plaque improved diagnosis of ACS in patients with acute chest pain who otherwise had no ECG or enzymatic evidence of ischemia or infarction.

Our understanding of morphological features of high-risk plaque stems primarily from the histology studies of patients who died of sudden cardiac death. The histological features of the culprit plaques included large necrotic core, higher macrophage count, positive remodeling, speckled calcium,

TABLE 2 Coronary Computed Tomography Angiography Characteristics of Patients Stratified According to the Diagnosis of ACS

	ACS (n = 37)	No ACS (n = 435)	p Value
CAD category			
No CAD	0 (0.0)	210 (48.3)	<0.001
Nonobstructive CAD (1% to 49% stenosis)	8 (21.6)	209 (48.1)	0.002
Significant CAD (≥50% stenosis)	29 (78.4)	16 (3.7)	<0.001
Plaque category			
No plaque	0 (0.0)	210 (48.3)	<0.001
Calcified plaque	36 (97.3)	181 (41.6)	<0.001
Noncalcified plaque	36 (97.3)	163 (37.5)	<0.001
High-risk plaque category			
Any high-risk plaque	35 (94.6)	132 (30.3)	<0.001
Napkin-ring sign	12 (32.4)	14 (3.2)	<0.001
Positive remodeling	22 (59.5)	33 (7.6)	<0.001
Low HU plaque	16 (43.2)	24 (5.5)	<0.001
Spotty calcium	35 (94.6)	116 (26.7)	<0.001

Values are n (%).
HU = Hounsfield units; other abbreviations as in Table 1.

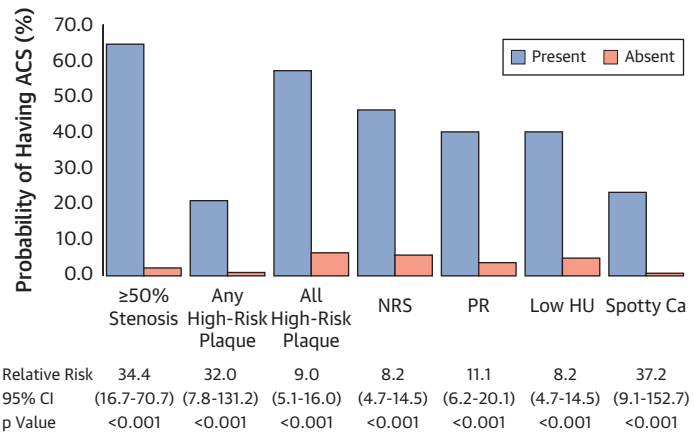


FIGURE 2 Probability of ACS During Index Hospitalization According to CTA Characteristics

The figure reports the probability of ACS during index hospitalization according to computed tomography angiography (CTA) assessment for significant coronary artery disease (≥50% stenosis) and the presence of high-risk plaque features. ACS = acute coronary syndromes; Ca = calcium; CI = confidence interval; HU = Hounsfield units; NRS = napkin-ring sign; PR = positive remodeling.

and thin fibrous cap (12,13). Similar morphological features (positive remodeling, larger plaque area, spotty calcium, and large necrotic core) were observed with intravascular imaging in culprit lesions of ACS (14,15).

The direct comparison of CTA features of high-risk plaque to virtual histology intravascular ultrasound (IVUS-VH) is challenging. In the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) trial, the researchers demonstrated that lesions associated with recurrent ACS were characterized by a plaque burden ≥70%, by a minimal luminal area ≤4.0 mm^2, or as thin-cap fibroatheroma (29). CTA characteristics of high-risk plaque in our study did not exactly correlate to IVUS-VH measurements. However, the presence of a minimal luminal area ≤4.0 mm^2 often correlates with significant stenosis, and we demonstrated that significant stenosis was an independent predictor of ACS. We did not perform quantitative analysis of plaques, which is necessary for the calculation of plaque burden. However, there is a correlation between positive remodeling and large plaque burden. Finally, the spatial resolution of CTA does not permit the detection of thin-cap fibroatheroma. However, the presence of the napkin-ring sign was very specific for the presence of advanced atheroma (23).

High-risk plaque features have been the target of noninvasive imaging with CTA. An early CTA study showed the feasibility of detecting high-risk plaque (5). The culprit plaques of ACS were often positively remodeled and had larger plaque burden compared with similarly stenotic plaques in patients with stable angina. Subsequent studies extended this observation and showed an association of plaque features such as large plaque burden, positive remodeling, spotty calcium, low HU plaque, and napkin-ring sign with ACS (7,9,19,20) and with an increased risk of future cardiovascular events (16-18). Limited data exist on the role of high-risk plaque for early diagnosis of ACS in the acute chest pain population (19,20).

We found that one-third of the patients with acute chest pain had high-risk plaque, with spotty calcium as the most frequent high-risk plaque feature (32.0%), followed by positive remodeling (11.7%), low HU plaque (8.5%), and napkin-ring sign (5.5%). The prevalence of high-risk plaque features observed in our study in the acute chest pain population is similar to that of other CTA studies (5% to 15%) performed in populations of patients undergoing invasive coronary angiography, in larger unselected patient populations, and in nonculprit vessels of patients with ACS (PROSPECT trial) (8,9,16,20,29). The reported prevalence of spotty calcium varied more dramatically in the published data (0% to 43%), most likely as a result of differences in the definition of spotty calcium

TABLE 3 Multivariable Logistic Regression Analysis for the Prediction of ACS Using Clinical Predictors and Coronary CTA Assessment

	Model 1*		Model 2†		Model 3‡	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Age	1.1 (1.0–1.1)	0.003	1.0 (1.0–1.1)	0.539	1.0 (0.9–1.1)	0.870
Female	0.2 (0.1–0.4)	<0.001	0.3 (0.1–0.8)	0.020	0.4 (0.1–1.2)	0.104
Number of risk factors§	1.4 (1.0–1.8)	0.056	1.4 (0.9–2.2)	0.124	1.3 (0.8–2.0)	0.278
Stenosis ≥50%			71.7 (27.1–189.9)	<0.001	38.6 (14.2–104.7)	<0.001
High-risk plaque					8.9 (1.8–43.3)	0.006

*Clinical predictors were age, sex, and number of cardiovascular risk factors (diabetes mellitus, hypertension, dyslipidemia, smoking status, and family history of premature CAD). †Clinical predictors were those in model 1 plus stenosis ≥50%. ‡Clinical predictors were those in model 2 plus high-risk plaque. §Number of risk factors = number of cardiovascular risk factors (diabetes mellitus, hypertension, dyslipidemia, smoking status, and family history of premature CAD).

OR = odds ratio; other abbreviations as in Table 1.

(9,20). In addition, we observed a prevalence of coronary atherosclerosis defined as any coronary plaque in 55.5% of patients, nonobstructive CAD in 46.0% of patients, and significant stenosis ≥50% in 9.5% of patients, mostly consistent with other single-center and multicenter trials in acute chest pain (1,3,30). Overall, our results demonstrated that the prevalence of high-risk plaque and its associations with CAD and ACS in the acute chest pain setting are generalizable to multiple centers and CT vendors, and they were also in accordance with observations in stable chest pain syndromes as well as in nonculprit vessels of patients with ACS undergoing percutaneous coronary interventions.

The assessment of patients presenting with acute chest pain, but without objective signs of ischemia or MI, remains a diagnostic challenge. In patients who present with acute chest pain, exclusion of a significant coronary stenosis and plaque by CTA has a high sensitivity and negative predictive value for ACS and allows early discharge (1-3). However, ACS cannot be ruled out in a significant portion of patients in whom coronary plaques are present, reducing the specificity of CTA. Significant coronary stenosis was detected in approximately 10% and 4% of patients in 2 large multicenter trials, respectively (1,3). However, ACS or major adverse cardiovascular events developed in only approximately 4% and 1% of patients. Conversely, the sensitivity of ≥50% stenosis for the detection of ACS was 77% in the ROMICAT-I trial (30). In the ROMICAT-II study, we found a very similar result, with ≥50% stenosis detected in 78% of patients with ACS. This finding concurs with those of previous invasive angiographic studies that observed an absence of significant stenosis in 12% to 14% of patients with ACS (31,32). The limited diagnostic accuracy of CTA using the traditional criterion of significant stenosis might increase frequency of downstream testing and interventions (1-3,33). A potential means to improve CTA diagnostic accuracy is by adding the assessment of high-risk plaque to stenosis, which improved the diagnostic assessment of patients with acute chest pain in the present study.

The value of high-risk plaque for the diagnosis of ACS in patients with significant stenosis was demonstrated in the ROMICAT-I trial (19). A score including positive remodeling, spotty calcium, volume of low HU plaque, and stenosis length had a good discriminatory capacity for ACS during index hospitalization but was limited to only those with significant stenosis on CTA. The addition of high-risk plaque features showed a potential to refine the diagnosis of ACS by CTA (19,20). The current study demonstrated that high-risk plaque features assessed by a qualitative read of CTA images were independent and incremental to significant stenosis and clinical risk assessment for predicting ACS during the index hospitalization. Although stenosis remained the strongest predictor of ACS, high-risk plaque was associated with a 9-fold increase in the likelihood of ACS after adjustment for the presence of stenosis ≥50% and clinical risk assessment.

The inclusion of high-risk plaque improved the detection of ACS in patients with mild stenosis (1% to 49%). All patients with mild stenosis and ACS had at least 1 high-risk plaque feature. We suggest that patients with mild stenosis and high-risk plaque cannot be safely discharged from the ED. Further evaluation with serial troponins and additional testing will be necessary. While awaiting further work-up, providers should consider aggressive medical therapy (e.g., dual antiplatelet therapy). On the other side of the spectrum, there are patients with significant stenosis. Patients with significant stenosis on CTA cannot be discharged from the ED after initial troponin and ECG (1-3). In our study, the presence of high-risk plaque was incremental to stenosis for the prediction of ACS. Therefore, providers should consider aggressive medical therapy and invasive coronary angiography in patients with significant stenosis and high-risk plaque. In patients with stenosis, but no high-risk plaque, providers should consider further work-up to confirm the

significance of the stenosis (e.g., stress test or invasive coronary angiography with fractional flow reserve). However, these strategies have not been tested in prospectively designed clinical studies, and further studies are required to include them in routine clinical practice.

STUDY LIMITATIONS. The low number of ACS outcomes (n = 37) limited our ability to perform subanalyses and include additional variables in the multivariable models. Recent studies have demonstrated the additional value of quantitative analysis of plaque by CTA (5,6,20–23); we performed qualitative assessment of stenosis and high-risk plaque. The decision to use qualitative assessment was motivated by the fact that this approach could be more feasible in routine clinical practice because it adds minimal time for the assessment and does not require specific software and hardware. We restricted our analysis to the 4 most established high-risk plaque features (positive remodeling, low HU plaque, napkin-ring sign, and spotty calcium).

CONCLUSIONS

The presence of high-risk plaque on CTA increases the likelihood of ACS independent and incremental to the presence of significant CAD and clinical risk assessment (age, sex, number of cardiovascular risk factors) in patients with acute chest pain and with no objective evidence of myocardial ischemia or MI.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among patients presenting with acute chest pain, normal initial cardiac troponin levels, and no evidence of ischemia on electrocardiogram, coronary computed tomography angiography (CTA) can identify high-risk coronary atherosclerotic lesions independently associated with acute coronary syndromes and diagnostic information incremental to the detection of ≥50% luminal stenosis.

TRANSLATIONAL OUTLOOK: Multicenter randomized trials are needed to determine whether medical therapy and/or interventions based on CTA characterization of high-risk plaque improves clinical outcomes in patients with acute chest pain.

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KEY WORDS acute chest pain, acute coronary syndrome, coronary atherosclerotic plaque, coronary computed tomography