JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 66, NO. 4, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.05.069

ORIGINAL INVESTIGATIONS

Plaque Characterization by Coronary Computed Tomography Angiography and the Likelihood of Acute Coronary Events in Mid-Term Follow-Up

Sadako Motoyama, MD, PhD,*† Hajime Ito, MD, PhD,* Masayoshi Sarai, MD, PhD,* Takeshi Kondo, MD, PhD,* Hideki Kawai, MD, PhD,* Yasuomi Nagahara, MD,* Hiroto Harigaya, MD, PhD,*‡ Shino Kan, MD,*‡ Hirofumi Anno, MD, PhD,§ Hiroshi Takahashi, BSc,‖ Hiroyuki Naruse, MD, PhD,* Junichi Ishii, MD, PhD,* Harvey Hecht, MD,† Leslee J. Shaw, PhD,¶ Yukio Ozaki, MD, PhD,* Jagat Narula, MD, PhD†

ABSTRACT

BACKGROUND Coronary computed tomography angiography (CTA)-verified positive remodeling and low attenuation plaques are considered morphological characteristics of high-risk plaque (HRP) and predict short-term risk of acute coronary syndrome (ACS).

OBJECTIVES This study evaluated whether plaque characteristics by CTA predict mid-term likelihood of ACS.

METHODS The presence of HRP and significant stenosis (SS) of ≥70% were evaluated in 3,158 patients undergoing CTA. Serial CTA was performed in 449 patients, and plaque progression (PP) was evaluated. Outcomes (fatal and nonfatal ACS) were recorded during follow-up (mean 3.9 ± 2.4 years).

RESULTS ACS occurred in 88 (2.8%) patients: 48 (16.3%) of 294 HRP(+) and 40 (1.4%) of 2,864 HRP(−) patients. ACS was also significantly more frequent in SS(+) (36 of 659; 5.5%) than SS(−) patients (52 of 2,499; 2.1%). HRP(+)/SS(+) (19%) and HRP(+)/SS(−) (15%) had higher rates of ACS compared with no-plaque patients (0.6%). Although ACS incidence was relatively low in HRP(−) patients, the cumulative number of patients with ACS developing from HRP(−) lesions (n = 43) was similar to ACS patients with HRP(+) lesions (n = 45). In patients with serial CTA, PP also was an independent predictor of ACS, with HRP (27%; $p < 0.0001$) and without HRP (10%) compared with HRP(−)/PP(−) patients (0.3%).

CONCLUSIONS CTA-verified HRP was an independent predictor of ACS. However, the cumulative number of ACS patients with HRP(−) was similar to patients with HRP(+). Additionally, plaque progression detected by serial CTA was an independent predictor of ACS. (J Am Coll Cardiol 2015;66:337–46) © 2015 by the American College of Cardiology Foundation.

From the *Department of Cardiology, Fujita Health University, Toyoake, Japan; †Division of Cardiology, Mount Sinai Hospital and Icahn School of Medicine at Mount Sinai, New York, New York; ‡Department of Cardiology, Nagoya Memorial Hospital, Nagoya, Japan; §Department of Radiology, Fujita Health University, Toyoake, Japan; ‖Division of Medical Statistics, Fujita Health University, Toyoake, Japan; and the ¶Department of Medicine, Emory University School of Medicine, Atlanta, Georgia. Dr. Hecht is a consultant to Philips Medical Systems and HeartFlow Inc.; and has served on the Scientific Advisory Board of Arineta Ltd. Dr. Narula has received research support from Philips and GE Healthcare in the form of an equipment grant to the institution, unrelated to the current project. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Motoyama and Ito contributed equally to this work. Daniel Berman, MD, served as Guest Editor for this paper. Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

Manuscript received February 25, 2015; revised manuscript received May 5, 2015, accepted May 13, 2015.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

BMI = body mass index

CABG = coronary artery bypass graft

CAD = coronary artery disease

CI = confidence interval

CTA = computed tomography angiography

FPP = feature-positive plaque

HR = hazard ratio

HRP = high-risk plaque

IQR = interquartile range

IVUS = intravascular ultrasound

LAP = low attenuation plaque

PCI = percutaneous coronary intervention

PIT = pathological intimal thickening

PP = plaque progression

PR = positive remodeling

RI = remodeling index

SAP = stable angina pectoris

SS = significant stenosis

TCFA = thin-cap fibroatheroma

ThCFA = thick-cap fibroatheroma

Coronary computed tomography angiography (CTA) allows noninvasive assessment of luminal stenosis, as well as plaque morphology (1-4). Several reports have confirmed CTA's diagnostic accuracy for identifying significantly obstructive disease, and the severity of such stenosis was also predictive of major adverse cardiac events (5-7). Additionally, lesions predictive of major adverse cardiac events demonstrate positive remodeling (PR) and low attenuation plaque (LAP) (8,9). Noncalcified plaques with ≤30 Hounsfield unit (HU) densities identified by CTA correlate closely with intravascular ultrasound (IVUS)-verified necrotic cores in coronary atherosclerotic plaques (2). Although the presence of PR and LAP was associated with the development of acute coronary syndrome (ACS) during 2-year follow-up in our previous study (10), the mid-term prognosis on the basis of CTA findings has not been reported. In the present study, we extended the follow-up period to investigate the relationship between CTA-verified high-risk plaque (HRP) and the incidence of ACS in mid-term follow-up. In patients with serial CTA, the association between plaque progression (PP) and ACS was also evaluated.

SEE PAGE 347

METHODS

We enrolled 4,423 consecutive patients who underwent CTA for suspected or known coronary artery disease (CAD) from March 2003 to May 2011. Of these, 1,265 patients were excluded from analysis, including 604 patients who underwent coronary artery bypass graft (CABG) surgery before CTA or scheduled CABG on the basis of CTA findings, 590 patients lacking 1-year follow-up, 37 ACS patients post-CTA wherein the culprit lesions could not be identified, and 34 patients where ACS occurred at restenotic lesions. All plaques were analyzed in the remaining 3,158 patients for the study, which was performed at Fujita Health University, Nagoya Memorial Hospital, and Imai Outpatients Clinic; the study protocol was approved by the Institutional Review Board and ethics committee. Dr. Narula has been associated with this project since 2003 and has guided the proceedings of this project with Dr. Ozaki.

Of 3,158 patients, 641 had serial CTA, of whom 192 patients were excluded from analysis because of CABG history (n = 126), a short interval between first CTA (CTA-1) and second CTA (CTA-2) of <30 days (n = 8), and a short available follow-up period of <30 days since CTA-2 (n = 58). The serial analysis involved the remaining 449 patients, including 80 (17.8%) who underwent CTA-2 for occurrence/recurrence of chest pain symptoms and 122 (49.0%) for follow-up after percutaneous coronary intervention (PCI). The remaining 247 patients underwent serial CTA evaluation at the request of treating physicians for follow-up.

The study endpoint was defined as ACS occurrence on the basis of the third universal definition of myocardial infarction (11) and the Canadian Cardiovascular Society grading of angina pectoris (12). Briefly, ACS was defined as ischemic discomfort presenting with elevated troponin levels and ischemic discomfort that was Canadian Cardiovascular Society class 3 or 4 without troponin elevation. The culprit lesion was determined by a combination of electrocardiographic, echocardiographic, and invasive coronary angiographic findings. There were 187 deaths (age 70.8 ± 8.5 years; male 79%; median follow-up 1.7 years; interquartile range [IQR]: 0.6 to 4.6 years) during follow-up: 7 sudden deaths, 30 cardiac deaths, and 150 noncardiac deaths. Of 30 cardiac deaths, 12 were ACS-related and 18 died from heart failure. Because we focused on coronary artery plaque characteristics of ACS, cardiac death only as a result of ACS was included as the event in this study.

Follow-up information was obtained from hospital chart review and supplemented by information obtained via mail. However, 590 patients did not follow up with our institution or reply to the mail. Compared with patients with complete follow-up, the patients lost to follow-up were younger (61.7 ± 13.0 years vs. 65.5 ± 11.1 years), less likely to be male (60.6% vs. 69.8%), and had less HRP (5.1% vs. 9.3%). Median follow-up duration of event-free survivors was 1,143 days (IQR: 702 to 2,081 days). One of the 3 cardiologists (M.S., Y.N., S.K.) blinded to CTA findings was responsible for reviewing patient charts and clinical presentations as well as defining the ACS culprit lesion.

CTA PROTOCOL/ANALYSIS. We used 320-slice CT (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) and 64-slice CT (Aquilion 64, Toshiba Medical Systems; Brilliance CT 64-channel, Philips Healthcare, Cleveland, Ohio); older studies were performed with 16-slice CT (Aquilion 16, Toshiba Medical Systems). In patients without contraindications, oral metoprolol and/or intravenous landiolol was administered before imaging if the heart rate was >65 beats/min. Whenever possible, 0.4 mg sublingual nitroglycerin was administered 3 to 5 min before image acquisition. Tube voltage was 120 kV or 135 kV, and the maximal tube current

was 300 mA to 580 mA depending on body weight. The mean radiation dose of the 320-slice CT was 6.2 ± 3.9 mSv with 245 mg I/kg of contrast medium. For the 16- and 64-slice CT, 60 to 100 ml of contrast medium was injected. Whole-volume image acquisition was completed in a single breath-hold. The raw data were reconstructed using algorithms optimized for electrocardiographic-gated reconstruction and transferred to a computer workstation for post-processing.

CTA images were evaluated on axial, coronal, sagittal, cross-sectional, and curved multiplanar reformation images. Two cardiologists blinded to the patient's clinical information interpreted the CTA images; S.M. reviewed every study, in addition to review by 1 more cardiologist (including H.I., H. Harigaya, or H.K.). Coronary artery segments with a diameter >2 mm were evaluated for presence of plaques. Segments treated previously by PCI or by elective PCI within 3 months of the base CTA findings were excluded from assessment. Coronary atherosclerotic lesions were quantified for lumen diameter stenosis by visual estimation and graded as none (no luminal stenosis), mild (1% to 39%), moderate (40% to 69%), severe (70% to 99%) stenosis, or occluded, as per the guidelines of the Society of Cardiovascular Computed Tomography (13). Luminal stenosis ≥70% was defined as significant stenosis (SS). Manual inspection, in both cross section and longitudinal reconstruction, was used for defining the coronary artery remodeling index (RI = lesion diameter/reference diameter). HRP was defined as plaque with PR (RI ≥1.1) and/or LAP (≤30 HU), which were the high-risk characteristics resulting in ACS as previously reported (3,10,14). On the basis of the presence of the 2 high-risk features, LAP and PR, the plaques were designated as 1- or 2-feature–positive plaque (FPP) or 2-feature–negative plaques (FNP).

In addition to the presence of HRP on CTA-1 and CTA-2, PP at CTA-2 compared with CTA-1 was evaluated. PP was defined as either an increase in stenosis by at least 1 grade or an increase in the RI ratio of >1.1 between CTA-1 and CTA-2. Patients who had cardiac events before CTA-2 were excluded from serial CTA analysis.

STATISTICAL ANALYSIS. JMP software (version 10.0, SAS Institute, Cary, North Carolina) was used for all statistical analyses. Two-sided p values <0.05 were considered statistically significant. The Shapiro-Wilk test was used to assess the normality of continuous data, expressed as mean ± SD for normally distributed variables, or median and IQR for nonparametric data, and compared using the Student unpaired *t* test and Wilcoxon signed rank test, respectively. Categorical variables are presented as frequencies (percents) and compared using the chi-square test or Fisher exact test depending on the category cell size. Kaplan-Meier survival analysis was used to estimate the distribution of time to cardiac events according to the presence or absence of HRP, stenosis, or PP. Differences in time-to-event curves were compared with the log-rank statistic. The effect of the variables on cardiac events was evaluated using the univariable Cox proportional hazards models. Age and other variables with p values <0.05 in the univariable analysis were then included in multivariable Cox proportional hazard analysis. The proportional hazards assumption was assessed with log (−log [survival rate]) versus log [survival time]) plot and with models including interaction between covariates and survival time. No relevant violations were observed.

Results are reported as hazard ratios (HRs) with 95% confidence intervals (CIs). The increased discriminative value after the addition of HRP and SS to the established clinical risk factors was estimated using the C-index for the receiver-operating characteristic curve. The C-index is defined as the area under a receiver-operating characteristic curve between individual predicted probabilities and incidence of events, and is compared in a baseline model and in an enriched model with HRP, SS, and HRP + SS.

RESULTS

PATIENT-BASED ANALYSIS. In the 3,158 enrolled patients (age 66 ± 11 years, male 70%), the follow-up was a mean of 3.9 ± 2.4 years (range: 1 to 10.5 years; IQR: 1.9 to 5.7 years). HRP was detected in 294 (9.3%) patients. The HRP(+) patients differed significantly from HRP(−) patients: they were older; more likely male; more likely to have hypertension, dyslipidemia, diabetes mellitus, and a history of ACS; and more likely to be on statin therapy post-CTA (**Table 1**).

Of the 3,158 patients, significant luminal stenosis ≥70% [SS(+) group] was present in at least 1 coronary artery in 659 (21%) patients. The SS(+) group also differed significantly compared to the SS(−) patients on the basis of older age, male sex, and the presence of hypertension, dyslipidemia, diabetes mellitus, current smoking, previous ACS, and statin use after CTA (**Table 1**). Of the 3,158 patients, ACS developed in 88 (2.8%) patients during follow-up (**Figure 1**). The culprit lesion was found in the right coronary artery in 40 patients, left main trunk in 4 patients, left anterior descending coronary artery in 37, and left circumflex coronary artery in 7 patients. Two ACS events occurred in patients with apparently normal coronary arteries; IVUS at the time of the acute event demonstrated no plaque rupture, but coronary artery spasm superimposed on minimally

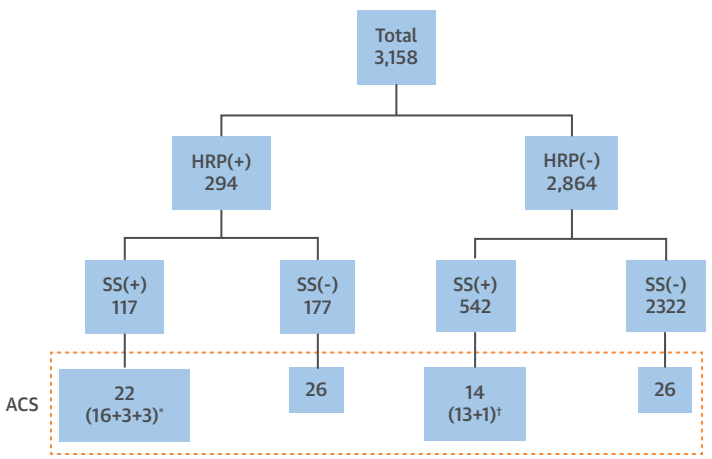
TABLE 1 Patient Characteristics

	Total (n = 3,158)	HRP(+) (n = 294, 9.3%)	HRP(−) (n = 2,864, 90.7%)	p Value	Stenosis ≥70% (n = 659, 20.9%)	Stenosis <70% (n = 2,499, 79.1%)	p Value
Age, yrs	65.5 ± 11.1	66.9 ± 9.3	65.3 ± 11.2	0.0216	68.4 ± 9.6	64.7 ± 11.4	<0.0001
Male	2,203 (69.8)	258 (87.8)	1,945 (67.9)	<0.0001	511 (77.5)	1,692 (67.7)	<0.0001
Hypertension	1,752 (55.5)	199 (67.7)	1,553 (54.2)	<0.0001	468 (71.0)	1,284 (51.4)	<0.0001
Dyslipidemia	1,518 (48.1)	171 (58.2)	1,347 (47.0)	0.0003	373 (56.6)	1,145 (45.8)	<0.0001
Diabetes	723 (22.9)	86 (29.3)	637 (22.2)	0.0064	201 (30.5)	522 (20.9)	<0.0001
Current smoking	554 (17.5)	83 (28.2)	471 (16.4)	<0.0001	128 (19.4)	426 (17.0)	0.0007
BMI >25 kg/m^2	901 (28.5)	94 (32.0)	807 (28.2)	0.1699	201 (30.5)	700 (28.0)	0.2080
Previous ACS	852 (27.0)	145 (49.3)	707 (24.7)	<0.0001	256 (38.8)	596 (23.8)	<0.0001
Statin after CTA	1,227 (38.9)	168 (57.1)	1,059 (37.0)	<0.0001	297 (45.1)	930 (37.2)	0.0002

Values are mean ± SD or n (%).
ACS = acute coronary syndrome; BMI = body mass index; CTA = computed tomography angiography; HRP = high-risk plaque.

occlusive plaques was documented during coronary angiography. Multivariable Cox hazard analysis showed that dyslipidemia, body mass index (BMI) >25 kg/m^2, previous ACS, HRP, and SS were independent predictors of developing ACS (Table 2). Patients with high-risk features on CTA developed ACS at a significantly higher rate; ACS occurred in 31 of 135 (23.0%) patients with 2-FPP, 17 of 159 (10.7%) patients with 1-FPP, 38 of 2,504 (1.6%) patients with 2-FNP, and 2 of 360 (0.6%) patients without any plaque (log-rank $p < 0.0001$) (Figure 2A). The SS group had a higher rate of developing ACS than SS(−) patients (36 of 659 [5.5%] vs. 52 of 2,499 [2.1%]; log-rank $p < 0.0001$) (Figure 2B). Patients were classified into 5 groups on the basis of HRP and SS [HRP(+)/SS(+), HRP(+)/SS(−), HRP(−)/SS(+), HRP(−)/SS(−), and no plaque], with event rates of 18.8%, 14.9%, 2.6%, 1.2%, and 0.6%, respectively. Kaplan-Meier curve analysis showed that the event rates were significantly different among these 5 groups (log-rank $p < 0.0001$) (Figure 2C). Multivariable Cox hazard analysis adjusted for age, dyslipidemia, BMI >25, and previous ACS revealed that HRP(+)/SS(+) (HR: 17.24; $p < 0.0001$) and HRP(+)/SS(−) (HR: 13.13; $p < 0.0001$) had significantly higher rates of ACS compared with no-plaque patients (Table 3). The baseline model for the C-index included age, male sex, hypertension, dyslipidemia, diabetes, BMI >25 kg/m^2, and previous ACS. As compared with the baseline model (C-index 0.805), adding HRP (0.870; $p < 0.0001$) and HRP+SS (0.874; $p < 0.0001$) to the baseline model significantly improved the C-index (Figure 3). However, the baseline model plus SS did not show improvement in C-index (0.818; $p = 0.071$).

FIGURE 1 Occurrence of ACS on the Basis of Plaque and Stenosis



Acute coronary syndrome (ACS) occurred in a number of patients shown with presence (+) or absence (−) of high-risk plaque (HRP) or significant stenosis (SS) of ≥70%. *In HRP(+)/SS(+) patients, 3 ACS occurred at the SS but accompanying non-HRP and 3 at the lesions with HRP but without SS. †In HRP(−)/SS(+) patients, 1 ACS occurred at SS(−) lesion.

LESION-BASED ANALYSIS. Of the 88 patients with events, ACS developed in 22 HRP(+)/SS(+) patients, 26 HRP(+)/SS(−) patients, 14 HRP(−)/SS(+) patients, and 26 HRP(−)/SS(−) patients (Figure 1). In HRP(+)/SS(+) patients, 3 ACS occurred at the SS but accompanying non-HRP, and 3 occurred at the lesion with HRP but without SS. In HRP(−)/SS(+), 1 ACS occurred at a SS(−) lesion. Of 88 patients with ACS, 45 (51%) patients developed ACS at HRP(+) lesions and 43 (49%) patients at HRP(−) lesions. Eighteen (40%) of 45 HRP lesions developed ACS at 1 year and 31 (69%) at 2 years. The period from CTA to ACS was significantly shorter for those developing events associated with HRP(+) lesions than for patients with ACS at HRP(−) lesions (1.7 ± 1.8 years vs. 3.4 ± 2.4 years; $p = 0.0005$) (Online Figure 1A). SS at culprit lesions on CTA was detected in 32 (36%) patients. There was no significant difference in the time interval from CTA to ACS between the patients with culprit lesions of SS(+) and SS(−) (2.5 ± 2.4 years vs. 2.6 ± 2.2 years; $p = 0.80$)

(Online Figure 1B). The numbers of patients with ACS each year on the basis of culprit lesion characteristics are shown in the **Central Illustration**. The cumulative number of patients with ACS at HRP lesions was higher in the first 5 years; however, the number of ACS at HRP(−) lesions became similar at 7 years.

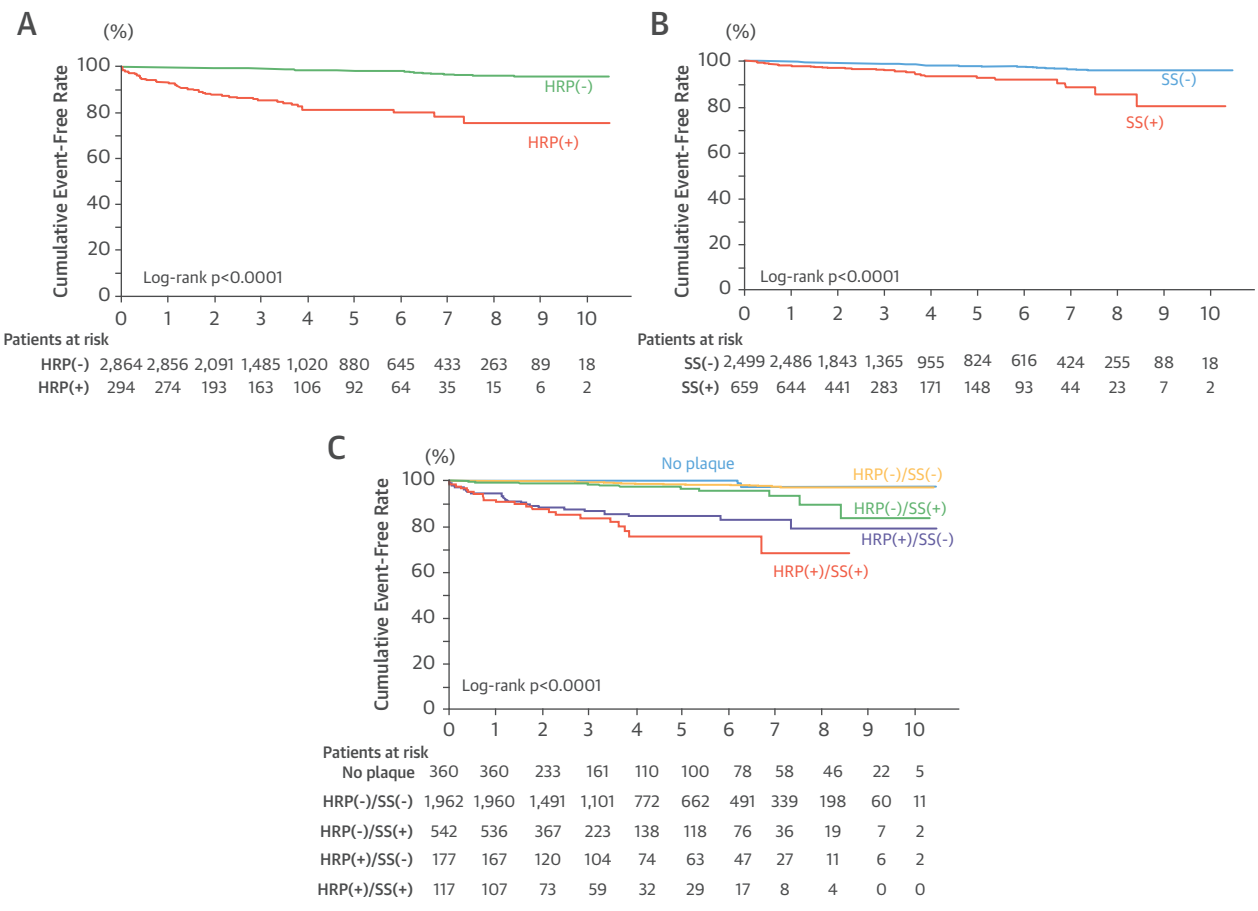
SERIAL CTA ANALYSIS. Of the 449 patients who had serial CTA available for comparative analysis, the mean age was 65 ± 11 years, and 85% were male (Online Table 1). Median follow-up was 4.1 years, and the median interval period from CTA-1 to CTA-2 was 1 year. Twenty-six patients were excluded from serial CTA analysis because of intercurrent cardiac events before CTA-2: 8 ACS and 18 elective revascularization because of stable angina pectoris (SAP) (**Figure 4A**). Of 8 ACS, 7 had HRP on CTA-1 without SS, and 1 patient

TABLE 2 Variables for ACS Development

	Univariable		Multivariable	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age	1.02 (1.00–1.04)	0.1048	1.02 (1.00–1.04)	0.0974
Male	1.83 (1.10–2.26)	0.0200	1.04 (0.60–1.93)	0.8912
Hypertension	2.96 (1.81–5.12)	<0.0001	1.12 (0.65–2.02)	0.6876
Dyslipidemia	4.63 (2.74–8.39)	<0.0001	3.34 (1.89–6.32)	<0.0001
Diabetes	1.72 (1.10–2.64)	0.0190	1.16 (0.73–1.80)	0.5246
Current smoking	1.58 (0.97–2.49)	0.0655		
BMI >25 kg/m^2	1.93 (1.26–2.94)	0.0026	1.72 (1.11–2.65)	0.0148
Previous ACS	4.10 (2.65–6.48)	<0.0001	2.11 (1.33–3.42)	0.0014
No statin after CTA	0.27 (0.16–0.43)	<0.0001		
HRP	12.33 (8.11–18.86)	<0.0001	8.24 (5.26–12.96)	<0.0001
Stenosis ≥70%	3.27 (2.11–5.00)	<.0001	1.61 (1.01–2.53)	0.0449

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

FIGURE 2 Cardiac Events on the Basis of CTA



A total of 88 (2.8%) patients developed ACS during follow-up. Patients with HRP had a higher risk of events compared with patients without HRP (16.3% vs. 1.4%) **(A)**, as did patients with SS than did those without (5.5% vs. 2.1%) **(B)**. **(C)** Patients were classified into 5 groups on the basis of plaque characteristics and luminal stenosis [HRP(+)/SS(+); HRP(+)/SS(−); HRP(−)/SS(+); HRP(−)/SS(−); and no plaque]; event rates were 18.8%, 14.9%, 2.6%, 1.2%, and 0.6%, respectively. CTA = computed tomography angiography; other abbreviations as in Figure 1.

TABLE 3 ACS Development per Plaque and Stenosis Characteristics

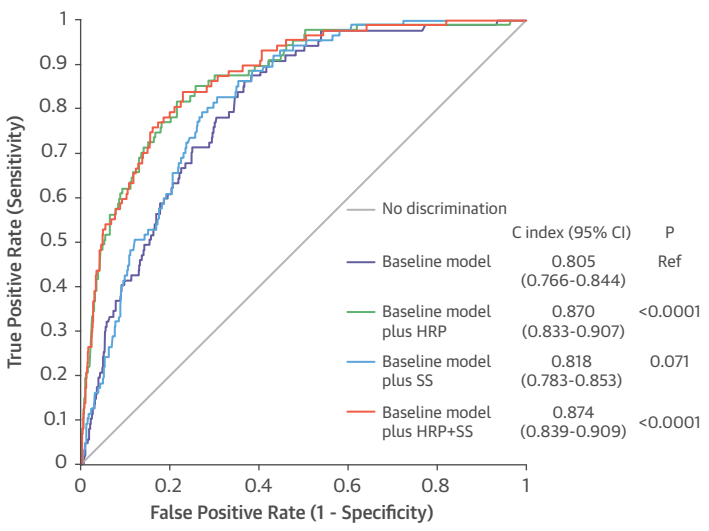
Group	ACS n (%)	Unadjusted HR (95% CI)	p Value	Adjusted HR* (95% CI)	p Value
No plaque (n = 360)	2 (0.6)	1.00	Reference	1.00	Reference
HRP(−)/SS(−) (n = 1,962)	24 (1.2)	2.01 (0.60–12.53)	0.2937	1.31 (0.38–8.19)	0.7063
HRP(−)/SS(+) (n = 542)	14 (2.6)	5.39 (1.50–34.38)	0.0071	2.89 (0.79–18.60)	0.1188
HRP(+)/SS(−) (n = 177)	26 (14.9)	25.04 (7.48–155.47)	<0.0001	13.13 (3.80–82.66)	<0.0001
HRP(+)/SS(+) (n = 117)	22 (18.8)	38.98 (11.45–243.55)	<0.0001	17.24 (4.87–109.47)	<0.0001

*Adjusted for age, dyslipidemia, BMI >25 kg/m^2, and previous ACS.
SS = significant stenosis ≥70%; other abbreviations as in Tables 1 and 2.

had neither HRP nor SS; all events occurred before CTA-2. In 18 patients with SAP before CTA-2, 2 patients were associated with HRP on CTA-1 and 16 were without HRP on CTA-1; 5 patients had cardiac events before CTA-2, and 13 patients underwent CTA-2 because of a cardiac event. Of 2 patients with HRP, 1 had SS and the other did not have SS. Of 16 patients with SAP without HRP, 1 patient had and 15 did not have SS on CTA-1. After excluding 26 patients with cardiac events before CTA-2, the remaining 423 patients were analyzed for the usefulness of serial evaluation.

On CTA-1, HRP was observed in 70 of 449 (15.6%) patients (Online Table 1). Of 423 patients who underwent CTA-2, HRP was observed in 72 (17.0%) (Figure 4A); 57 had HRP on both CTA-1 and CTA-2, and 15 patients with non-HRP on CTA-1 developed an HRP on CTA-2. Four HRPs on CTA-1 became non-HRP on CTA-2.

FIGURE 3 Incremental Value of CTA to Detect ACS



The baseline model for C-index included the following variables: age, male sex, hypertension, dyslipidemia, diabetes, BMI >25 kg/m^2, and previous ACS. Whereas adding HRP **(green)** and HRP+SS **(red)** showed significant improvement to the C-index beyond the baseline model **(purple)**, adding SS **(blue)** did not. AUC = area under the curve; BMI = body mass index; CI = confidence interval; other abbreviations as in Figures 1 and 2.

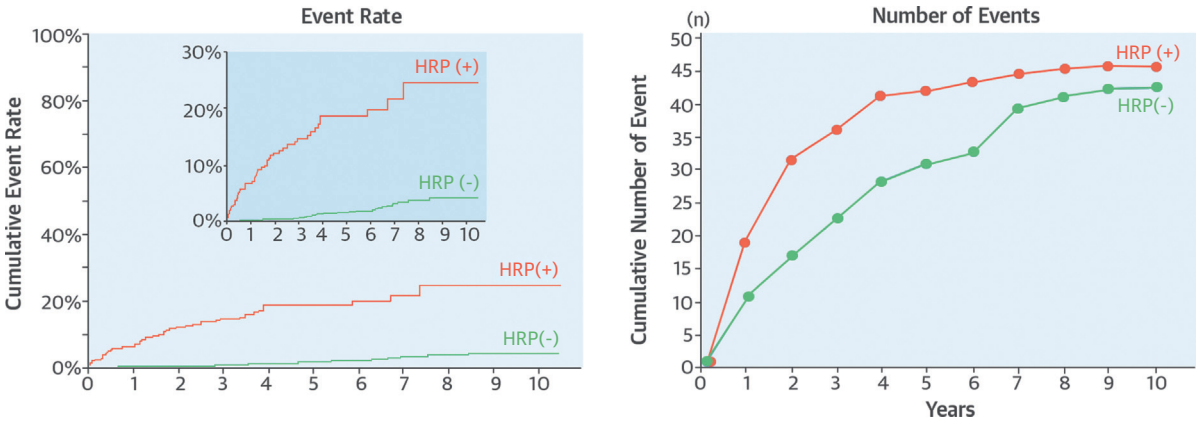
PP was observed in 56 (13.2%) patients (Figure 4A), of which 15 (26.8%) had HRP on both CTA-1 and CTA-2. Non-HRP on CTA-1 evolved to HRP on CTA-2 in 13 (23.2%) patients, and 28 (50%) non-HRP on CTA-1 remained so upon CTA-2. In the PP group, the vascular RI was significantly greater on CTA-2 than on CTA-1 (1.11 ± 0.15 vs. 1.05 ± 0.10; p < 0.0001). BMI >25 kg/m^2 (41.1 vs. 27.8%; p = 0.04), and HRP at CTA-1 (26.8 vs. 12.5 %; p = 0.0047) were significantly more frequent in the PP(+) group (Online Table 1).

ACS occurred in 8 (14.3%) of 56 patients in the PP(+) group and 1 (0.27%) of 367 in the PP(−) group (Figure 4A). Of 8 patients with ACS in the PP(+) group, 4 had HRP(+) on both CTA-1 and CTA-2, 3 had HRP(−) on CTA-1 but HRP(+) on CTA-2, and 1 had HRP(−) on both CTA-1 and CTA-2. Only 1 ACS occurred in the PP(−) group with HRP(−) on both CTA-1 and CTA-2 in the 3-year period from CTA-2 to ACS. Kaplan-Meier analysis revealed that patients with PP had a significantly higher incidence of ACS (log-rank p < 0.0001) (Figure 4B). Multivariable Cox hazard analysis (including age, BMI >25 kg/m^2, previous ACS, HRP on CTA-1, HRP on CTA-2, and PP) showed that previous ACS (HR: 8.35; 95% CI: 1.06 to 209.55; p = 0.043) and PP (HR: 33.43: 95% CI: 4.13 to 78.03; p = 0.0006) were the only independent predictors of ACS after CTA-2 (Table 4). Patients were classified into 4 groups according to the combination of HRP on CTA-1 and PP [HRP(+)/PP(+), HRP(+)/PP(−), HRP(−)/PP(+), HRP(−)/PP(−)]; the event rates were 26.7%, 0%, 9.8%, and 0.3%, respectively. In the Kaplan-Meier analysis, the HRP(+)/PP(+) group presented with ACS most frequently (n = 4 of 15; 27%; p < 0.0001); the HRP(−)/PP(+) group also had a relatively high incidence of ACS (n = 4 of 41; 10%). Conversely, the HRP(+)/PP(−) group (n = 46) had no cardiac event (Figure 4C). Multivariable Cox hazard analysis adjusted for age, current smoking, and previous ACS showed that the HRP(+)/PP(+) group (HR: 70.43; 95% CI: 8.99 to 1,500.74; p < 0.0001) and HRP(−)/PP(+) group (HR: 37.10; 95% CI: 5.41 to 730.20; p = 0.0002) had a significantly higher incidence of ACS compared to HRP(−)/PP(−) group (n = 1 of 321; 0.3%) (Online Table 2, Online Figure 2).

DISCUSSION

The presence of CTA-based HRP was an independent mid-term predictor of ACS, and all but 2 patients with

CENTRAL ILLUSTRATION **Prediction of ACS by CTA**



Motoyama, S. et al. J Am Coll Cardiol. 2015; 66(4):337–46.

Atherosclerosis is a diffuse disease, and the focus should not only be on chasing high-risk plaques (HRP), but also on prevention and treatment of atherosclerotic disease. Low attenuation (≤30 Hounsfield units) and/or positively remodeled plaques identified on computed tomography angiography (CTA) are considered HRP that are known to be associated with adverse short-term outcomes. The current study looked at the mid-term outcomes. Although the event rate **(left)** was substantially higher for HRP **(red)** as compared with non-HRP **(green)**, the total number of events arising from HRP and non-HRP at the follow-up of 3.9 ± 2.4 years (range 1 to 10.5 years) was essentially the same **(right)**. In the study of 3,158 subjects, 294 (9.3%) had HRP(+); 2,864 (90.7%) did not show HRP [HRP(−)]. On follow-up, 48 (16.3%) of the 294 HRP-carrying and 40 (1.4%) of 2,864 non-HRP-carrying subjects developed acute events. Although the outcomes were 10-fold worse in HRP(+) as compared with HRP(−), because the number of subjects with HRP(+) was 10-fold lower, equal numbers of acute events were observed in the HRP(+) and HRP(−) patients. Serial CTA examinations (**Figure 4**) revealed plaque progression and evolution from non-HRP to HRP en route acute coronary event. The focus, therefore, should be on the diffuse process of atherosclerosis. The **inset in the left panel** shows the difference between event rate from HRP and non-HRP by magnifying the y-axis scale.

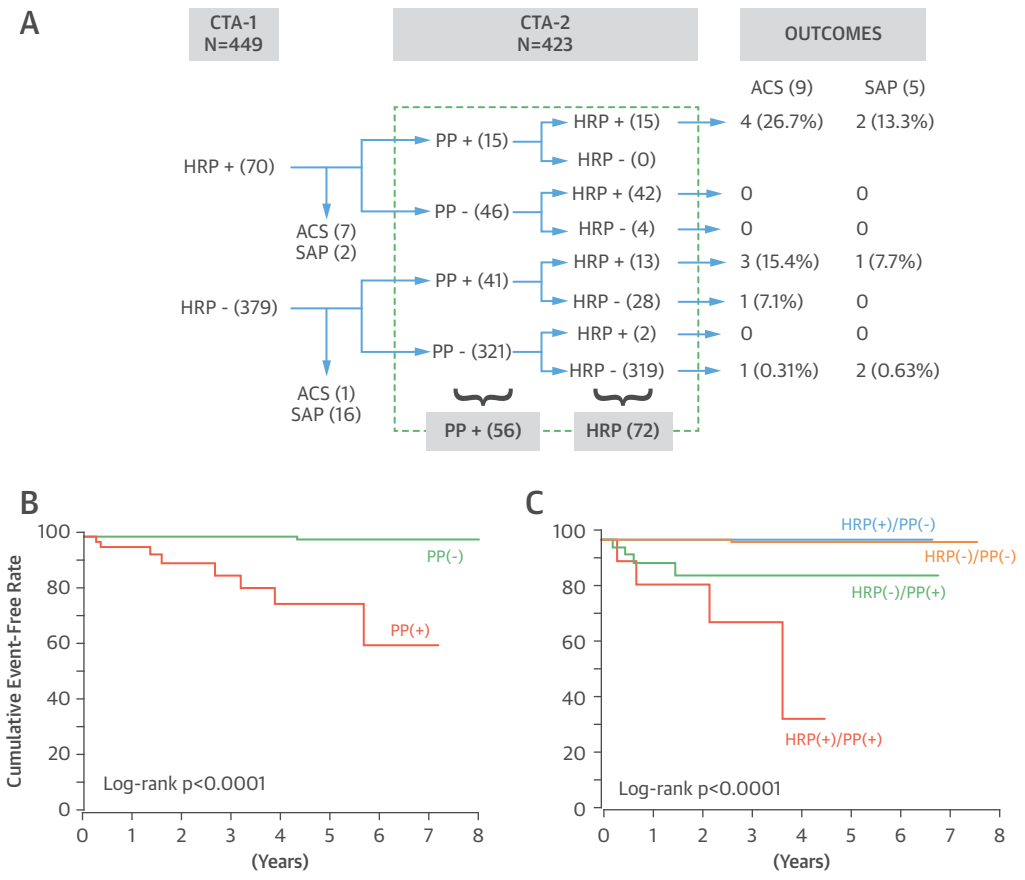
no plaques were free from ACS. However, non-HRP lesions also developed ACS, and serial CTA analysis revealed the plaques that progressed over time on a volumetric basis and evolved from non-HRP to HRP were the ones more likely to result in ACS. We had previously reported that CTA-verified HRP had a higher risk of developing ACS over a mean follow-up of 2 years in 1,059 patients; ACS developed in 15% of HRP(+) patients and in 0.5% of HRP(−) patients, but did not develop in patients without any plaques (10).

The present study demonstrated that HRP continued to be an independent predictor of ACS in mid-term follow-up in 3,158 patients (mean follow-up 3.9 ± 2.4 years; ranging from 1 to 10.5 years); ACS frequency was 16% in HRP(+) patients versus 1.6% in HRP(−) patients at baseline CTA assessment. The event rate of ACS in patients without HRP was higher in the current study compared with that reported in the previous study with a 2-year follow-up. The period from CTA to ACS was significantly shorter for those developing events associated with HRP(+) lesions than for patients with ACS at HRP(−) lesions (1.7 ± 1.8 years vs. 3.4 ± 2.4 years; $p = 0.0005$). Because fewer than 10% of patients had HRP, the cumulative number of ACS arising from HRP lesions, although larger in the first 5 years, was almost matched by the number of ACS arising from the more numerous HRP(−) lesions.

SS, in addition to HRP, was also an independent predictor of ACS. Earlier reports have discussed the prognostic value of CTA-verified stenosis for risk stratification (5–7), and a meta-analysis of 18 studies comprising 9,592 patients reported that the risk of adverse cardiac events was associated with the extent and severity of underlying CAD (6). In the present study, patients with significantly stenotic HRP had higher event rates compared with the non-stenotic HRP or stenotic non-HRP patients; very low event rates were observed in those with non-HRP, non-stenotic plaques or no plaques.

The PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) registry revealed similar data derived from IVUS, with the best predictive values attributed to larger plaque burden (>70%; HR: 5.03; 95% CI: 2.51 to 10.11), presence of thin-cap fibroatheroma (TCFA) (HR: 3.35; 95% CI: 1.77 to 6.36), and lower minimal luminal areas (<4.0 mm^2; HR: 3.21; 95% CI: 1.61 to 6.42) for the lesions likely to result in an acute event over the 3.4-year follow-up (8). A related study provided shorter serial imaging data but with results similar to those of the

FIGURE 4 Serial CTA Analysis and Cardiac Events



(A) The relationship between HRP (CTA-1 and -2), PP (CTA-2), and cardiac events is shown. On CTA-2, ACS occurred in 7 HRP(+) and 2 HRP(−) patients. Of these 9 patients, 8 patients were PP(+) and 1 PP(−). No HRP(+)/PP(−) patients on CTA-1 developed ACS. **(B)** Presence of PP produced a significantly higher incidence of ACS (14.3% vs. 0.3%). **(C)** When patients were classified according to the presence/absence of HRP on CTA-1 and PP on CTA-2, HRP(+)/PP(+) presented with the most frequent ACS (27%; log-rank $p < 0.0001$) . Conversely, the HRP(+)/PP(−) group had no cardiac events. PP = plaque progression; SAP = stable angina pectoris; other abbreviations as in **Figures 1 and 2**.

current study (15). In this IVUS study, plaques characterized as pathological intimal thickening (PIT) evolved into TCFA or thick-cap fibroatheroma (ThCFA) in 10% and 20% of patients over 12 months; 70% of PIT remained unchanged. Conversely, 75% of TCFA stabilized over the next year, and 5% of ThCFA developed high-risk features. Because fewer than 10% of initial lesions were reported as TCFA, the net number of new TCFA produced was similar to the number of TCFA that stabilized over time (16). None of the plaque characteristics, however, could predict the likelihood of developing TCFA from PIT or ThCFA, or its stabilization. This observational study suggested that atherosclerosis is a diffuse and dynamic process with plaque undergoing biological remodeling and compositional alterations. A recent optical coherence tomography study of 3-vessel imaging revealed that multiple plaques concurrently existed across the coronary tree at different stages of maturation (17).

The present exploration reveals that because of the much larger number of HRP(−) patients, the total number of ACS arising from non-HRP at the end of follow-up is similar to that of HRP(+) lesions. As detected by serial CTA, PP addresses the development of ACS from non-HRP, at least partially, and emerges as an independent predictor of cardiac events. In the patients with serial CTA, although HRP on CTA-1 was an independent predictor of subsequent cardiac events (15.7% of HRP patients resulted in ACS), 5 of 9 (56%) of ACS developed from originally HRP(−) plaque on CTA-1. Plaque progression at CTA-2 was also an independent predictor of ACS, with adverse events occurring in 8 (14.3%) of 56 patients in the PP(+) group and 1 (0.3%) of 367 in the PP(−) group. Of the 8 ACS

patients with PP at CTA-2, HRP was observed in 7 patients on CTA-2; 4 patients had HRP both on CTA-1 and CTA2, and 3 HRP(−) on CTA-1 developed HRP(+) on CTA-2. These results indicate that plaques without high-risk features may evolve to HRP, eventually leading to ACS. On the other hand, patients with HRP on CTA-1, but without PP by CTA-2, remained free of untoward events. These results suggest that serial plaque evaluation may help restratify the risk of cardiac events beyond a single evaluation.

On the basis of the 2010 Appropriateness Use Criteria for Cardiac Computed Tomography, the appropriateness of CTA for asymptomatic high-risk patients with unknown CAD is uncertain (18). Additionally, guidelines have not recommended treatment or management of HRP on the basis of CTA; the 2010 Expert Consensus Document on coronary CTA ruled that documentation of noncalcified coronary plaques, atherosclerotic burden, and vulnerable plaques provided uncertain clinical utility (19). As evidence unfolds with regard to documented HRP on CTA, expert consensus statements may require updated guidance on directed management of these patients. Moreover, clinical trial evidence would definitively inform evidentiary standards on guideline-directed care. The current study demonstrated that dyslipidemia, BMI >25 kg/m^2, previous ACS, HRP, and severe stenosis were independent predictors of ACS, and BMI >25 kg/m^2 and HRP were associated with PP. Also, patients with a history of ACS have been reported to show higher coronary event rates than those without (20–22). On the basis of these results, patients with HRP or previous ACS might be candidates for serial CTA. However, radiation dose, use of contrast media, and cost effectiveness would need to be considered. The appropriate number and frequency of serial scans remains undetermined. The current exploration combined with evidence from previous reports (16) underscores that although significant advances have been made in understanding the biology of HRP, our focus must remain on the entire atherosclerotic process and prevention of diffuse disease. Our data support the statement that seeking individual plaques may not provide the ultimate answer.

STUDY LIMITATIONS. First, this is a retrospective cohort study. Of 4,423 patients who underwent CTA, 590 (13%) were excluded because of the lack of 1-year follow-up. Second, individual physicians determined indications for repeat CTA, making selection bias a distinct possibility; thus, the data presented here should only be considered hypothesis generating. Third, in assessing serial CTA, differences in imaging platforms from 16- and 64- to 320-slice scanners could have affected image quality and comparability.

TABLE 4 Cardiac Events After CTA-2

	Univariable		Multivariable	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age	0.99 (0.94–1.06)	0.85	1.00 (0.95–1.08)	0.87
Male	1.32 (0.24–24.55)	0.78		
Hypertension	1.59 (0.39–10.70)	0.54		
Diabetes	1.13 (0.24–4.27)	0.87		
Dyslipidemia	0.86 (0.22–4.06)	0.83		
BMI >25 kg/m^2	5.58 (1.46–26.52)	0.012	3.27 (0.66–24.42)	0.15
Current smoking	2.35 (0.62–9.51)	0.20		
Previous ACS	6.26 (1.15–116.32)	0.032	8.35 (1.06–209.55)	0.043
Statin use	1.11 (0.27–7.44)	0.90		
Chest pain at CTA-2	3.09 (0.65–11.73)	0.14		
HRP at CTA-1	4.40 (1.08–16.67)	0.039	0.85 (0.07–9.01)	0.89
HRP at CTA-2	9.07 (2.38–43.11)	0.0014	2.18 (0.20–27.78)	0.51
Plaque progression	61.32 (11.24–1,137.73)	<0.0001	33.43 (4.13–78.03)	0.0006

Abbreviations as in Tables 1 and 2.

However, all CTA images were interpreted by 2 cardiologists blinded to the patient's clinical information. Fourth, it is difficult to evaluate the lumen stenosis and the presence of HRP in calcified lesions, and in such areas, luminal stenoses are likely to be overestimated and HRP underestimated. Finally, because we focused on the plaque characteristics associated with ACS, we included only those patients whose culprit plaques could be identified. However, the plaque characteristics of the patients who died without having invasive coronary angiography and of those with ACS who did not have the culprit lesion identified might have affected the considerations of the likelihood of ACS on the basis of CTA plaque characteristics. Thus, the patients without invasive coronary angiography could have added to our current understanding of HRP and incident ACS. Importantly, a prognostic analysis including these patients in a Cox model did not alter our presented findings.

CONCLUSIONS

CTA-verified HRP is an independent predictor of ACS over a mid-term follow-up of 3.9 ± 2.4 years. However, the cumulative number of ACS patients with HRP(−) is similar to patients with HRP(+). In addition to HRP, plaque progression detected by serial CTA is an independent predictor of ACS.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Sadako Motoyama, Department of Cardiology, Fujita Health University, 1-98 Dengakugakubo, Katsukake, Toyoake, Aichi 470-1192, Japan. E-mail: sadakom@fujita-hu.ac.jp OR Dr. Jagat Narula, Division of Cardiology, Mount Sinai Medical Center, One Gustave L. Levy Place, Box 1030, New York, New York 10029. E-mail: narula@mountsinai.org.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: High-risk coronary plaques, characterized by low attenuation and evidence of positive remodeling on coronary computed tomographic angiography, are associated with development of acute coronary syndromes.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Patients with high-risk plaque should receive aggressive risk factor management, regardless of the severity of arterial obstruction.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to compare the clinical outcomes associated with pharmacological and mechanical interventions in patients with nonobstructive, high-risk coronary plaque morphology.

REFERENCES

1. Hamon M, Morello R, Riddell JW, Hamon M. Coronary arteries: diagnostic performance of 16- versus 64-section spiral CT compared with invasive coronary angiography—meta-analysis. Radiology 2007;245:720–31.

2. Motoyama S, Kondo T, Anno H, et al. Atherosclerotic plaque characterization by 0.5-mm-slice multislice computed tomographic imaging. Circ J 2007;71:363–6.

3. Motoyama S, Kondo T, Sarai M, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. J Am Coll Cardiol 2007;50:319–26.

4. Kashiwagi M, Tanaka A, Kitabata H, et al. Feasibility of noninvasive assessment of thin-cap fibroatheroma by multidetector computed tomography. J Am Coll Cardiol Img 2009;2:1412–9.

5. Min JK, Dunning A, Lin FY, et al. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. J Am Coll Cardiol 2011;58:849–60.

6. Hulten EA, Carbonaro S, Petrillo SP, et al. Prognostic value of cardiac computed tomography angiography: a systematic review and meta-analysis. J Am Coll Cardiol 2011;57:1237–47.

7. Hadamitzky M, Taubert S, Deseive S, et al. Prognostic value of coronary computed tomography angiography during 5 years of follow-up in patients with suspected coronary artery disease. Eur Heart J 2013;34:3277–85.

8. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226–35.

9. Narula J, Nakano M, Virmani R, et al. Histopathologic characteristics of atherosclerotic coronary disease and implications of the findings for the invasive and noninvasive detection of vulnerable plaques. J Am Coll Cardiol 2013;61:1041–51.

10. Motoyama S, Sarai M, Harigaya H, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. J Am Coll Cardiol 2009;54:49–57.

11. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581–98.

12. Campeau L. The Canadian Cardiovascular Society grading of angina pectoris revisited 30 years later. Can J Cardiol 2002;18:371–9.

13. Raff GL, Abidov A, Achenbach S, et al. SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. J Cardiovasc Comput Tomogr 2009;3:122–36.

14. Motoyama S, Sarai M, Inoue K, et al. Morphologic and functional assessment of coronary artery disease—potential application of computed tomography angiography and myocardial perfusion imaging. Circ J 2013;77:411–7.

15. Kubo T, Maehara A, Mintz GS, et al. The dynamic nature of coronary artery lesion morphology assessed by serial virtual histology intravascular ultrasound tissue characterization. J Am Coll Cardiol 2010;55:1590–7.

16. Narula J, Kovacic JC. Putting TCFA in clinical perspective. J Am Coll Cardiol 2014;64:681–3.

17. Tian J, Dauerman H, Toma C, et al. Prevalence and characteristics of TCFA and degree of coronary artery stenosis: an OCT, IVUS, and angiographic study. J Am Coll Cardiol 2014;64:672–80.

18. Taylor AJ, Cerqueira M, Hodgson JM, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol 2010;56:1864–94.

19. Mark DB, Berman DS, Budoff MJ, et al. ACCF/ACR/AHA/NASCI/SAIP/SCAI/SCCT 2010 expert consensus document on coronary computed tomographic angiography: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. J Am Coll Cardiol 2010;55:2663–99.

20. Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neill WW. Multiple complex coronary plaques in patients with acute myocardial infarction. N Engl J Med 2000;343:915–22.

21. Milonas C, Jernberg T, Lindback J, et al. Effect of angiotensin-converting enzyme inhibition on one-year mortality and frequency of repeat acute myocardial infarction in patients with acute myocardial infarction. Am J Cardiol 2010;105:1229–34.

22. Japanese Coronary Artery Disease (JCAD) Study Investigators. Current status of the background of patients with coronary artery disease in Japan. Circ J 2006;70:1256–62.

KEY WORDS acute coronary syndrome, atherosclerosis, coronary artery disease

APPENDIX For supplemental figures and tables, please see the online version of this article.