Coronary Computed Tomography Angiography-Based Coronary Risk Stratification in Subjects Presenting With No or Atypical Symptoms

Shinichiro Fujimoto, MD, PhD; Takeshi Kondo, MD, PhD; Takahide Kodama, MD, PhD;
Tadaaki Orihara, MD; Junichi Sugiyama, MD; Makoto Kondo, MD; Akira Endo, MD, PhD;
Hiroshi Fukazawa, MD; Hideki Nagaoka, MD, PhD; Akitsugu Oida, MD, PhD;
Takanori Ikeda, MD, PhD; Junichi Yamazaki, MD, PhD;
Shinichi Takase, MD; Jagat Narula, MD, PhD

Background: Coronary computed tomography angiography (CTA) findings of positive vessel remodeling and low-attenuation plaque, referred to as computed tomography-verified high-risk plaque (CT-HRP), have been reported to be associated with the development of subsequent acute coronary syndromes. The aim of this study was to examine the usefulness of coronary CTA for coronary risk re-stratification of patients with asymptomatic and atypical chest symptoms.

Methods and Results: A total of 1,139 subjects (M/F 602/537; mean age, 61.5 ± 9.3 years) who were either asymptomatic or presented with atypical chest symptoms underwent coronary 64- or 320-slice multidetector computed tomography angiography and Agatston score. Age, sex, coronary risk factors, including hypertension, diabetes mellitus (DM), dyslipidemia, and smoking were investigated as predictors for CT-HRP on multivariate analysis using logistic regression analysis. CT-HRP was observed in 72 patients (6.3%). Based on Framingham risk scores (FRS), CT-HRP was observed in 0/94 subjects (0.0%) in the low-risk group, 35/806 (4.3%) in the intermediate-risk group, and 37/239 (15.5%) in the high-risk group. On logistic regression analysis significant predictors for CT-HRP in intermediate- and high-risk subjects were male sex (odds ratio [OR] 2.829; 95% confidence interval [CI] 1.460–5.479, $P=0.0021$), DM (OR 2.418; 95% CI 1.420–4.116, $P=0.0011$), and current smoking (OR 1.922; 95% CI 1.096–3.371, $P=0.0160$). CT-HRP prevalence for Agatston scores >500 and >250 was lower in the intermediate- and high-risk groups, respectively.

Conclusions: In asymptomatic subjects and those presenting with atypical chest pain who have a more than an intermediate risk, coronary CTA is contributory to FRS. Male sex, DM and smoking were independent predictors of vulnerable plaque in the more than intermediate-risk group. (*Circ J* 2012; **76**: 2419–2425)

Key Words: Coronary computed tomography angiography; Framingham risk score; Low-attenuation plaque; Positive remodeling; Vulnerable plaque

Acute coronary syndrome (ACS) may occur without precursor symptoms, and its prediction remains an important issue for cardiologists. Indeed, a meta-analysis of coronary angiography during a 5-year period before the onset of ACS reported that 68% of culprit lesions showed no significant stenosis.¹ At present, there is no established method of ACS prediction. In the risk stratification of ACS, Braunwald noted that the traditional Framingham risk score (FRS) was in-

sufficient, and expected the advent of a non-invasive diagnostic imaging tool that facilitates the detection of the higher-risk group with $>15\%$ risk of developing ACS per year.²

Naghavi et al reported various types of vulnerable plaque.³ Among them, rupture-prone, vulnerable plaque, which accounts for approximately 60% of all vulnerable plaques and causes plaque rupture, is the most commonly recognized morphology of vulnerable plaque. It has been reported that, in general, vul-

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Department of Cardiology, Takase Clinic, Takasaki (S.F., T. Kondo, T. Kodama, T.O., J.S., M.K., A.E., H.F., H.N., A.O., S.T.); Department of Cardiovascular Medicine, Toho University Omori Medical Center, Tokyo (S.F., T.I., J.Y.), Japan; and Zena and Michael A. Wiener Cardiovascular Institute and Marie-Josée and Henry R. Kravis Cardiovascular Health Center, Mount Sinai School of Medicine, New York, NY (J.N.), USA

Mailing address: Shinichiro Fujimoto, MD, PhD, Department of Cardiology, Takase Clinic, 885-2 Minami-orui, Takasaki 370-0036, Japan. E-mail: s-fujimo@tj8.so-net.ne.jp

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nerable plaque is characterized by positive vascular remodeling, plaque area >50% of the vessel's cross-sectional area, a necrotic core occupying >25% of the plaque, vasa vasorum within the plaque, a fibrous cap <65 μ m in thickness, and infiltration of the fibrous cap by macrophages expressing matrix metalloproteinases.⁴

In contrast, Motoyama et al reported that, compared with the culprit lesions of stable angina pectoris, those of ACS were significantly more frequently characterized by spotty calcification, positive remodeling, and the presence of low-attenuation plaque,⁵ and that 2-feature positive plaque (2FPP) with positive remodeling (remodeling index >1.1) and low-attenuation plaque (computed tomography [CT] number <30 Hounsfield units [HU]) resulted in ACS within 2 years with a probability of 22.2%.⁶ Thus, at present, 2FPP is most commonly recognized as rupture-prone vulnerable plaque on coronary CT angiography (CTA). Such angiographic observations, coupled with recent technological advances in CT technology to reduce the radiation exposure,^{7–11} may allow extension of the indications for coronary CTA for risk stratification of patients with asymptomatic and atypical chest symptoms, which we examined in the present study.

Methods

Subjects

Subjects were 1,139 consecutive patients with suspected obstructive coronary artery disease (M/F, 602/537; age range, 30–74 years; mean, 61.5 $\pm$ 9.3 years) who underwent coronary 64- or 320-slice coronary CTA and coronary calcium scan despite being asymptomatic or having atypical chest symptoms. The subjects consisted of patients either who were suspected angina or who had coronary CTA requested by physicians at outpatient care in the presence or absence of evidence of ischemic heart disease (eg, atypical chest symptoms, 1 or more risk factors, ECG abnormalities, preoperative evaluation or request of coronary CTA from another institution).

Patients with known coronary artery disease and those in whom the imaging was of poor quality were excluded from the study.

All subjects were classified using the FRS¹² and based on that they were categorized as low (<5%), intermediate (5–20%), or high risk (>20%). Age, sex, coronary risk factors, including hypertension (HT), diabetes mellitus (DM), dyslipidemia (DL), current smoking, body mass index (BMI) and lipid profile (total cholesterol, triglycerides [TG], low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]) were investigated as predictors for CT-verified high-risk plaque (CT-HRP) on univariate analysis using logistic regression analysis. Age, sex, and coronary risk factors including HT, DM, DL, current smoking, TG and HDL-C, were investigated as predictors for CT-HRP on multivariate analysis using logistic regression analysis.

This study was approved by the ethics committee of Takase Clinic.

Chest Symptoms

Chest symptoms were classified as typical, atypical or none. Typical symptoms were defined $\geq$ 3 of 5 characteristics based on the Duke Clinical Score.^{13,14} Atypical was defined as 1–2 of the 5 characteristics. None was defined as symptoms that did not include any of the 5 characteristics. The 5 characteristics were (1) precipitation by exercise or emotional stress; (2) brief duration (2–15 min); (3) prompt relief with rest or nitroglycerin; (4) retrosternal location; and (5) radiating to jaw, neck

or left arm.

Definition of Risk Factors

HT was defined as systemic blood pressure $\geq$ 140/90 mmHg or the use of antihypertensive treatment. DM was defined as fasting blood sugar $\geq$ 126 mg/dl, postprandial blood sugar $\geq$ 200 mg/dl, hemoglobin A_{1c} $\geq$ 6.5% or the use of treatment. DL was defined as total cholesterol $\geq$ 220 mg/dl, LDL-C $\geq$ 140 mg/dl, fasting TG $\geq$ 150 mg/dl, HDL-C <40 mg/dl or the use of lipid-lowering treatment. Current smoking was defined as smoking within 1 year of coronary CTA imaging.

64-Slice Multidetector Computed Tomography (MDCT) Protocol

Subjects with heart rate >60 beats/min and without contraindications underwent β -blockade with 25 mg atenolol by mouth the evening before the examination. Alternatively, heart rate control with a target of 60 beats/min was achieved using 2–10 mg i.v. propranolol injected before data acquisition.

The tube voltage for imaging (Aquilion 64, Toshiba Medical Systems, Tochigi, Japan) was 120 kV. The tube current range was 400–600 mA; patients with a BMI of 22 were imaged at 440 mA, and for each 2-point increase or decrease in BMI, the tube current was increased or decreased by 10 mA. For example, a patient with BMI=18 was imaged at 420 mA. The gantry rotation time (0.35–0.45 s) and beam pitch (0.125–0.26) were determined by a manufacturer-based algorithm to optimize image quality. Imaging was performed from caudal to cranial.

Between 60 and 80 ml of iodinated contrast (300–370 mg iodine/ml; Iopamiron-370, Bayer, Osaka, Japan; Omnipaque 300 and 350, Daiichi-Sankyo, Tokyo, Japan), was injected (Stellant Dual Flow, Nihon Medrad Osaka, Japan) via an antecubital vein using a 3-phase injection method: contrast alone (12 s), followed by an equal volume admixture of contrast and saline (9 s), and then saline only (2.5 s). The iodine load was weight based, and timed using manual triggering when contrast arrived in the left ventricle.

The ECG gating acquisition strategy was divided into 4 levels depending on the patient's heart rate, with the least exposure for those with the lowest heart rate (<60 beats/min), and progressively increasing for patients with faster heart rates.

320-Slice MDCT Protocol

Subjects with a heart rate >60 beats/min and without contraindications underwent β -blockade with 25 mg atenolol by mouth the evening before the examination. Alternatively, heart rate control with a target of 60 beats/min was achieved using 2–10 mg i.v. propranolol injected before data acquisition.

The imaging protocol for the second cohort paralleled that of the first, with the following differences: a 320 $\times$ 0.5 mm scanner (Aquilion ONE, Toshiba Medical Systems) operated on a v4.51 software platform; and the craniocaudal field of view was tailored to the smallest exposure (10 cm, 12 cm, 12.8 cm, or 16 cm) that encompassed the heart.

The default tube voltage was 120 kV. The tube current was modulated according to the patient's body habitus. Axial imaging had a gantry rotation time of 0.35–0.4 s per rotation.

Contrast was injected via a 2-phase protocol: contrast medium alone for 10 s, followed by saline for 8 s. The contrast and saline injection rates were calculated as the individual patient's mass in kilograms multiplied by 0.06 ml/s.

Based on prior experience with 64-detector row coronary CTA, the ECG gating acquisition strategy was divided into 5 heart rate groups.

Table 1. Baseline Clinical Characteristics of the Study Patients

Age (years)	61.5±9.3
Sex (M/F)	602/537
Hypertension (%)	60.4
Dyslipidemia (%)	78.8
Diabetes mellitus (%)	19.6
Current smoking (%)	22.6
Body mass index	24.0±3.6
Agatston score	113.1±360.0
Framingham risk score (low/intermediate/high)	94/806/239
Total cholesterol (mg/dl)	206.1±36.3
Triglycerides (mg/dl)	149.6±111.2
LDL-cholesterol (mg/dl)	126.2±33.1
HDL-cholesterol (mg/dl)	54.4±14.1
Statins (%)	47.2

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Image Reconstruction

Half-image reconstruction or segmental image reconstruction was performed in the slow filling phase and end-systolic phase using the R+absolute time method to generate images, and images with the lowest level of motion artifacts were selected on the 4-chamber cardiac cine CT.

Coronary CTA Interpretation

For plaque detection, both cross-sectional and longitudinal curved multi-planar reconstruction images were analyzed. Coronary arteries were divided into 17 segments based on the modified recommendations of the American Heart Association.¹⁵ Coronary artery segments with a diameter >2 mm were evaluated for the presence of plaque. All plaque was assessed for the presence of vessel remodeling (positive, negative, none), plaque consistency (low or intermediate attenuation) and disposition of coronary calcification (spotty, moderate, severe). Three observers were involved in the interpretation of data.

Definition of CT Plaque Characteristics

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 the cross-section and longitudinal reconstructions, was used to define 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 that of the reference segment.

Plaque Consistency If non-calcified plaque or plaque with an area of spotty calcification, either or which could be measured as the plaque's consistency on the axial image, the CT number, defined as the lowest CT number of 5 areas of minimum region of interest (0.36×0.36 mm), was measured using the axial image. Low-attenuation plaque was defined as CT <30 HU.

CT-HRP Such a plaque was defined as having positive remodeling of at least 110% and attenuation <30 HU.

Coronary Calcium Scan (Agatston Score)

All data were evaluated using workstation software (Zio M900 or ZioStation, Ziosoft). A calcified lesion was defined as ≥3

Figure 1. Relationship between Framingham risk score (FRS) and computed tomography-verified high-risk plaque (CT-HRP).

contiguous pixels with a peak attenuation ≥130 HU. The total coronary artery calcium score (Agatston score) was calculated as per the recommendations of Agatston et al.¹⁶

Patients were divided into 4 groups according to their Agatston scores (0, 1–250, 251–500, >500), based on a previous report.¹⁷

Statistical Analysis

Statistical analysis was performed using Statview J-5.0 for Windows (HULINKS, Tokyo Japan). Data are expressed as mean±SD. To determine the statistical significance of differences between groups, the chi-square test was used for comparisons between groups. Multivariate logistic regression analysis was used to determine predictors for CT-HRP. P<0.05 was considered statistically significant in all instances.

Results

Baseline clinical characteristics of all subjects are listed in Table 1.

FRS and CT-HRP

CT-HRP were observed in 72 (6.3%) of the 1,139 subjects. Based on FRS assignment, CT-HRP was observed in 0/94 subjects (0.0%) in the low-risk group (FRS <5%), 35/806 (4.3%) in the intermediate-risk group (FRS 5–20%), and 37/239 (15.5%) in the high-risk group (FRS >20%; P<0.0001; Figure 1).

FRS, Agatston Score and CT-HRP

In the intermediate- and high-risk subjects (n=1,045), CT-HRP was observed according to Agatston score categories as follows: 14/430 (3.3%), intermediate+Agatston score 0; 15/304 (4.9%), intermediate risk+Agatston score 1–250; 4/41 (9.8%), intermediate+Agatston score 251–500; 2/31 (6.5%), intermediate+Agatston score >500; 4/57 (7.0%), high+Agatston score 0; 23/115 (20.0%), high+Agatston score 1–250; 6/35 (17.1%), high+Agatston score 251–500; and 4/32 (12.5%), high+Agatston score >500 (Figure 2). The prevalence of CT-HRP in the high-risk group was significantly higher than in the inter-

Table 2. Predictors of CT-HRP for All Subjects in the More Than Intermediate-Risk Group

	OR	95% CI	P value
Univariate analysis			
Age	0.992	0.965–1.019	0.5507
Male sex	3.761	2.070–6.833	<0.0001
Hypertension	1.075	0.650–1.777	0.7774
Dyslipidemia	1.372	0.708–2.658	0.3483
Diabetes	2.887	1.761–4.733	0.0001
Current smoking	2.619	1.604–4.276	0.0001
Body mass index	1.055	0.992–1.122	0.0898
Total cholesterol	0.995	0.988–1.002	0.1604
Triglycerides	1.002	1.001–1.004	0.0026
LDL-cholesterol	0.999	0.991–1.007	0.7958
HDL-cholesterol	0.979	0.960–0.999	0.0362
Multivariate analysis			
Age	1.017	0.987–1.049	0.2719
Male sex	2.829	1.460–5.479	0.0021
Hypertension	1.011	0.587–1.739	0.9695
Dyslipidemia	1.070	0.525–2.183	0.8520
Diabetes mellitus	2.418	1.420–4.116	0.0011
Current smoking	1.922	1.096–3.371	0.0226
Triglycerides	1.002	1.000–1.003	0.0757
HDL-cholesterol	1.004	0.983–1.026	0.6978

CI, confidence interval; CT-HRP, computed tomography-verified high-risk plaque; OR, odds ratio. Other abbreviations as in Table 1.

mediate-risk group for Agatston score 1–250 only ($P<0.0001$).

Predictors of CT-HRP

In the intermediate- and high-risk subjects ($n=1,045$), univariate logistic regression analysis indicated that significant predictors for CT-HRP were male sex (odds ratio [OR] 3.761; 95% confidence interval [CI] 2.070–6.833, $P<0.0001$), DM (OR 2.887; 95% CI 1.761–4.733, $P<0.0001$), current smoking (OR 2.619; 95% CI 1.604–4.276, $P=0.0001$), TG (OR 1.002; 95% CI 1.001–1.004, $P=0.0026$), and HDL-C (OR 0.979; 95% CI 0.960–0.999, $P=0.0362$; Table 2).

On multivariate logistic regression analysis, the significant predictors for CT-HRP were male sex (OR 2.829; 95% CI 1.460–5.479, $P=0.0021$), DM (OR 2.418; 95% CI 1.420–4.116, $P=0.0011$), and current smoking (OR 1.922; 95% CI 1.096–3.371, $P=0.0226$; Table 2). When we analyzed the data according to sex, logistic regression analysis indicated significant predictors for CT-HRP to be only current smoking (OR 1.893; 95% CI 1.063–3.369, $P=0.0302$) for male subjects (Table 3) and only DM (OR 9.234; 95% CI 2.902–29.382, $P=0.0002$) for female subjects (Table 4).

Frequency of CT-HRP and Age Decades

In the intermediate- and high-risk subjects ($n=1,045$), CT-HRP was found in 1/14 (7.1%), 7/74 (9.5%), 11/134 (8.2%), 27/244 (11.1%), 12/102 (11.8%) of men in their 30s, 40s, 50s, 60s, and 70s or older, respectively, and in 0/0 (0.0%), 0/5 (0.0%), 3/93 (3.2%), 8/247 (3.2%), 3/132 (2.3%) of women in the respective decades. In men, the frequency of CT-HRP was approximately 10% in all age groups, but in the women, it was approximately 3% in those in their 50s and older. CT-HRP

Table 3. Multivariate Analysis for Predictors of CT-HRP in Male Patients in the More Than Intermediate-Risk Group

	OR	95% CI	P value
Age	1.022	0.991–1.055	0.1682
Hypertension	0.857	0.484–1.518	0.5965
Dyslipidemia	1.417	0.667–3.010	0.4481
Diabetes mellitus	1.649	0.914–2.973	0.0964
Current smoking	1.893	1.063–3.369	0.0302

Other abbreviations as in Table 2.

Table 4. Multivariate Analysis for Predictors of CT-HRP in Female Patients in the More Than Intermediate-Risk Group

	OR	95% CI	P value
Age	0.982	0.901–1.071	0.6870
Hypertension	2.201	0.451–10.731	0.3292
Dyslipidemia	0.889	0.182–4.351	0.8849
Diabetes mellitus	9.234	2.902–29.382	0.0002
Current smoking	2.383	0.566–10.023	0.2362

Other abbreviations as in Table 2.

Figure 3. Relationship between frequency of computed tomography-verified high-risk plaque (CT-HRP) and decade of age.

was more frequent in men than in women in all age groups. No CT-HRP was observed in women in their 40s or younger (Figure 3).

Discussion

It has been reported that, in general, approximately 60% of rupture-prone vulnerable plaque is not associated with significant stenotic lesions,^{1,18} which makes it difficult to predict from clinical symptoms alone. Although current guidelines do not recommend coronary CTA for screening low-risk, asymptomatic patients for coronary heart disease,¹⁹ and the clinical use of coronary CTA for the purpose of risk stratification of asymptomatic patients has not been established,²⁰ recent technological advances in coronary CTA make it possible to reduce the dose of contrast medium and radiation exposure, suggesting that the indication for coronary CTA is broader than before. The present study regarding predictors identifying CT-

HRP, which has been reported to lead to ACS within 1 year with a probability of 11%,⁶ is expected to provide useful information on higher-risk stratification, especially of intermediate- and high-risk patients presenting with no or atypical symptoms based on FRS.

The Agatston score is closely associated with the presence of coronary atherosclerosis and it is well established that the greater the Agatston score, the higher the likelihood of cardiac events.^{21,22} The present study demonstrated that the prevalence of CT-HRP with an Agatston score >500 and >250 was lower in the intermediate-risk and high-risk groups, respectively. It has been reported that culprit lesions show acute coronary thrombus in approximately 50–60% of cases of coronary sudden death, and the remainder includes severe ischemic heart disease or arrhythmia.²³ In other words, cardiac events are not necessarily caused by CT-HRP. Although it is thought that cardiac death because of severe cardiac ischemia and arrhythmia occurs if coronary atherosclerosis progresses, it is also

thought that vulnerable plaque develops if the Agatston score, which indicates the accumulation of atherosclerosis, is high, because the progression of atherosclerotic change is not homogeneous in the 3 major coronary arteries. Autopsy study has suggested large variation in the degree of calcification within coronary atherosclerotic lesions in patients with sudden coronary death.²⁴ On this point, the present results are consistent with those of previous reports with regard to Agatston scores.^{21,22} It is said that, in general, atherosclerosis develops stepwise in stages.^{3,25,26} Rupture-prone vulnerable plaque with a large necrotic core and thin fibrous cap containing many inflammatory cells such as macrophages, and characterized by positive remodeling,^{4,27} develops at a relatively early stage. In particular, positive remodeling refers to compensatory enlargement of the vessel diameter to maintain the lumen during the early stage of plaque progression.^{28,29} Because extensive calcification appears at the late stage of atherosclerotic progression, the prevalence of CT-HRP characterized by positive remodeling, low-density plaque and none or spotty calcification could decrease in extensive calcified lesions such as those with Agatston score >500. The low prevalence of CT-HRP in patients with Agatston score >500 was considered to be a reasonable result. In contrast, the prevalence of CT-HRP in Agatston=0 patients was 3.3% in the intermediate-risk group and 7.0% in the high-risk group, respectively, which implies that the presence of CT-HRP cannot be excluded in patients with Agatston score=0.

On logistic regression analysis, the significant predictors for CT-HRP were male sex, DM and current smoking in intermediate- and high-risk subjects. In particular, multivariate analysis identified male sex as the most powerful predictor. It has been reported that the age-related risk for coronary artery disease is lower in women than in men, and the risk of death from coronary artery disease in women is similar to that in men 10 years younger.³⁰ Furthermore, the younger a patient's age, the greater the ratio of postmyocardial infarction mortality in women to that in men.³¹ In the present study, the frequency of CT-HRP was higher in men than in women in each generation, but did not increase with age. This does not support the report stating that the risk of death from coronary artery disease in women is similar to that in men 10 years younger. In addition, CT-HRP was observed in approximately 10% of the male patients in all age groups, but in none of the female patients younger than 50 years old. In contrast, DL was not a significant predictor for CT-HRP. Although multivariate analysis for various lipid profiles was attempted, total cholesterol and LDL-C were not significant predictors. The development of medical therapy for plaque stability, such as statins, might be relevant to this result. In fact, 78.8% of all study subjects were defined as having DL and 60% of patients with DL were taking statins. The mean LDL-C level was 126.2 mg/dl, which is low. On the other hand, univariate analysis using logistic analysis revealed that TG and HDL-C were significant predictors for CT-HRP. Although only DL was used as a predictor in the multivariate analysis in the present study, further study of the lipid profile as a predictor for CT-HRP is needed. In analysis according to male and female sex, logistic regression analysis revealed significant predictors for CT-HRP to be only current smoking in males and DM in females. These results suggest that, when determining the need for coronary CTA for coronary risk stratification, it is necessary to consider the patient's age and sex, as well as the coronary risk factors.

We demonstrated the usefulness of coronary CTA for risk re-stratification of asymptomatic patients or those with atypical chest symptoms. CT-HRP is regarded as rupture-prone vul-

nerable plaque, and characterized by positive remodeling and low attenuation, but, to date, only Motoyama et al have reported the frequency with which CT-HRP actually result in ACS and patients with known coronary artery disease were also included in their study.⁶ In the present study, we did not observe how the frequency of CT-HRP results in ACS. Further, larger clinical trials are needed. Because CT values are influenced by factors such as the concentration of contrast medium in the coronary artery, degree of stenosis of coronary lesions, and tube voltage,³² the cut-off levels should be further evaluated.

Study Limitations

Subjects were patients who underwent coronary CTA despite being either asymptomatic or presenting with atypical chest symptoms. The subject group could be biased because the indication for coronary CTA was determined only by the outpatient physician. It is considered, however, that subjects were similar to a real-world population in clinical practice.

The FRS has been used in an American community and may not necessarily apply to Japanese populations. Additionally, the FRS is not well regarded as a predictor of coronary plaque vulnerability, but rather as a predictor of 10 year "hard" cardiovascular events. The combination of FRS and CT-HRP considered as rupture-prone vulnerable plaques, which account for approximately 60% of coronary lesion with thrombi, could be useful for cardiac event risk re-stratification, because it is considered that the vast majority of sudden coronary deaths are either the immediate result or a sequel of acute coronary arterial thrombosis.³³

Conclusions

Among asymptomatic subjects and those presenting with atypical chest pain in the more than intermediate-risk group, coronary CTA results are contributory to the FRS. Although the prevalence of CT-HRP is decreased for Agatston score >500 in intermediate-risk subjects, it decreases for Agatston score >250 in the high-risk group. Male sex, DM, and current smoking are independent predictors of vulnerable plaque in subjects with more than an intermediate risk.

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