



Incremental Prognostic Value of Coronary Computed Tomography Angiography: High-Risk Plaque Characteristics in Asymptomatic Patients

Kazuhisa Takamura¹, Shinichiro Fujimoto¹, Takeshi Kondo^{2,3}, Makoto Hiki¹, Yuko Kawaguchi¹, Etsuro Kato¹ and Hiroyuki Daida¹

¹Department of Cardiovascular Medicine, Juntendo University, Graduate School of Medicine, Tokyo, Japan

²Department of Cardiology, Jukokai Central Hospital, Miyoshi, Japan

³Department of Cardiology, Takase Clinic, Takasaki, Japan

Aim: Coronary computed tomography angiography (CCTA) findings of positive remodeling (index >1.1) and low-attenuation plaque (<30 Hounsfield units) are recognized as CT-verified high-risk plaque (CT-HRP). Therefore, we investigated the incremental prognostic value of evaluation of plaque characteristics using CCTA in asymptomatic patients.

Methods: Overall, 495 consecutive patients without any known coronary artery disease who underwent CCTA were included in this study. Patients who underwent revascularization within 30 days of CCTA or had scans with poor image quality were excluded. Clinical follow-up data (716.5 ± 262.6 days) were available for 339 patients, who were analyzed for the current study. Framingham risk score (FRS), coronary artery calcium score (CACS), and CT-HRP were investigated as predictors of cardiac events by multivariable analysis using Cox proportional hazard model. Improvement of predictive accuracy by including CT findings was evaluated from reclassification [net reclassification indices (NRI) and integrated discrimination improvement (IDI)] standpoints.

Results: During the follow-up period, 9 cardiac events (cardiac death: 0, nonfatal myocardial infarction: 2, hospitalization for unstable or progressive angina: 7) occurred. Multivariate Cox proportional hazard analysis demonstrated that CACS (HR, 13.23; 95% CI, 1.62–107.78, $p < 0.0164$) and CT-HRP (HR, 11.27; 95% CI, 1.24–102.12, $p < 0.0321$) were the independent predictors of cardiac events. NRI was 0.9556 ($p < 0.0007$) and IDI was 0.2582 ($p < 0.0203$), and the diagnostic performance improved by CT-HRP added to the combination of CACS and FRS.

Conclusion: Although the cardiac event rate was low, the evaluation of CCTA plaque characteristics may provide incremental prognostic value to CACS in asymptomatic patients.

Key words: Coronary computed tomography angiography, CT-verified high-risk plaque, Cardiac event, Prognostic value, Asymptomatic patient

Copyright©2017 Japan Atherosclerosis Society

This article is distributed under the terms of the latest version of CC BY-NC-SA defined by the Creative Commons Attribution License.

Introduction

Acute coronary syndrome (ACS) often develops suddenly without any precursor symptoms; therefore, it is very important to identify patients at a high risk of developing a cardiac event despite being asymptomatic¹.

atic¹.

Currently, coronary artery calcium score (CACS) is useful to predict future cardiac events and stratify risks of such events for asymptomatic patients²⁻⁴; however, the indication of coronary computed tomography angiography (CCTA) for asymptomatic patients has not been established⁵. Actually, on a sub-analysis in the CONFIRM study, a combination of CACS with CCTA did not improve the prediction of future cardiac events⁶, and screening of asymptomatic diabetic patients by CCTA did not decrease the incidence of cardiac events after 4 years in the FACTOR-64

Address for correspondence: Shinichiro Fujimoto, Department of Cardiology, Juntendo University Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan
E-mail: s-fujimo@tj8.so-net.ne.jp

Received: November 23, 2016

Accepted for publication: May 11, 2017

study⁷). On the other hand, evaluation using CCTA added an incremental prognostic value for patients with a moderately high calcium score and asymptomatic diabetic patients^{8,9}).

Motoyama *et al.* defined plaques accompanied by positive remodeling (PR: Index >1.1) and low-attenuation plaque (LAP <30 Hounsfield units) on CCTA as CT-verified high-risk plaque (CT-HRP)¹⁰, and they observed that ACS developed in patients with this type of plaque within 2 years at a 22% probability¹¹). Furthermore, the culprit lesion associated with ACS showed spotty calcification¹⁰. In addition, Otsuka *et al.* reported that plaques accompanied by a napkin-ring sign are an independent predictor of ACS¹²). We recently reported that evaluation of plaque characteristics on CCTA may increase the incremental prognostic value of the conventional predictor in symptomatic patients¹³), but no study has reported its usefulness for asymptomatic patients. Therefore, we investigated the incremental prognostic value of the evaluation of plaque characteristics using CCTA in asymptomatic patients.

Methods

1. Study Population

This is a single center retrospective study. Overall, 495 consecutive asymptomatic patients without any known coronary artery disease (CAD) underwent CCTA, and their CACS and Framingham risk score (FRS) were calculated using 64-row multiple detector CT (MDCT) or 320-row area detector CT (ADCT) at our institution between September 30, 2009, and April 30, 2012. CCTA in asymptomatic patients was indicated with high risk of having multiple coronary risk factors in 291 patients, with abnormal electrocardiograms in 101 patients, with abnormal exercise electrocardiograms in 52 patients, with abnormal echo findings in 28 patients, and with a preoperative close examination in 23 patients. Patients who underwent percutaneous coronary intervention or coronary artery bypass grafting within 30 days after CCTA ($n=56$, patients with $\geq 50\%$ diameter stenosis in left main trunk or 3-vessel disease with proximal of left anterior descending coronary artery, $\geq 90\%$ diameter stenosis in at least one branch of the coronary artery, or ischemia detected in exercise electrocardiography, stress perfusion MRI, or perfusion CT), those with a motion artifact ($n=24$), pacemaker lead ($n=12$), poor contrast enhancement ($n=3$), or missing scan data ($n=2$) were excluded. Clinical follow-up data (716.5 ± 262.6 days) were available for 339 of the remaining (85.2%) patients and were analyzed for the current study (Fig. 1).

1-1. This Study was Approved by the Ethics Committee of Our Facility.

Anonymous use of the test data for the study was orally explained to all patients, and written informed consent was obtained.

2. Definition of Risk Factor

Hypertension patients were defined as those with systemic blood pressure $\geq 140/90$ mmHg or receiving treatment with oral antihypertensive medications. Dyslipidemia patients were defined as those with total cholesterol ≥ 220 mg/dL, low-density cholesterol ≥ 140 mg/dL, fasting triglycerides ≥ 150 mg/dL, high-density cholesterol < 40 mg/dL, or receiving treatment with oral lipid-lowering medication. Diabetic patients were defined as those with a fasting blood glucose ≥ 126 mg/dL, casual blood glucose ≥ 200 mg/dL, HbA1c $\geq 6.5\%$ (NGSP), or receiving treatment for diabetes. Patients treated with dialysis and those with $30 \leq \text{eGFR} < 60$ were regarded as having chronic kidney disease (CKD). Patients with a history of cigarette smoking were defined as those who had a smoking habit within one year before CCTA.

3-1. CCTA Acquisition Method

The acquisition devices used were a 64-row MDCT, Aquilion 64 Super Hear (Toshiba, Medical System), 320-row ADCT, Aquilion ONE V4.51, and Aquilion ONE VISION Edition (Toshiba, Medical System). For the automatic contrast medium injection system, Stellant Dual Flow (Nihon Medrad K.K.) was used. For the image analysis system, Ziostation ver.1.3.1 (Ziosoft Inc.) was used. For the electrocardiography monitor, IVY3000 (Chronos Medical Device Co.) was used. For pretreatment, when the heart rate was ≥ 61 bpm, as long as there was no contraindication (past medical history of anaphylaxis to contrast medium, serious aortic valve stenosis, systolic blood pressure < 90 mmHg, severe atrioventricular block, renal dysfunction, or heart failure), 25 mg of atenolol was orally administered on the night before the test day. On the test day, 2–10 mg of propranolol or 12.5 mg of landiolol was intravenously injected immediately before acquisition to control the heart rate, as needed.

CCTA images were acquired following the protocol followed in our previous report¹⁴).

1) 64-Row MDCT Protocol

On contrast-enhanced imaging using a 64-row MDCT, the contrast medium injection time was fixed, and contrast medium was injected from the cubital vein using the 3-stage injection method: contrast medium injection for 12 s, mixed solution (con-

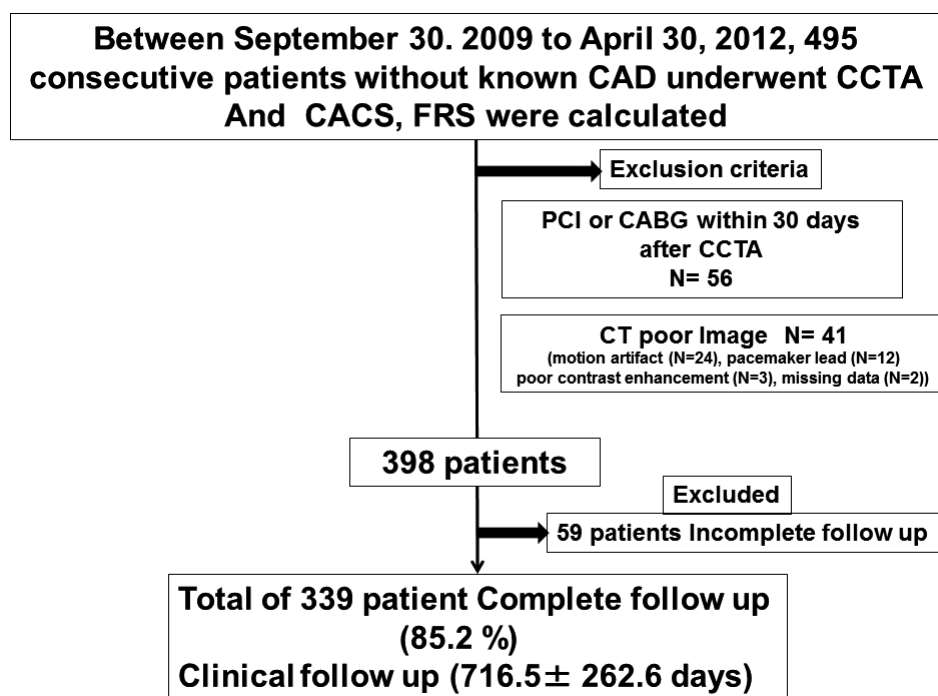


Fig. 1. Study Protocol

CAD, Coronary Artery Disease; CCTA, Coronary Computed Tomography Angiography; CACS, coronary artery calcium score; FRS, Framingham risk score; PCI, Percutaneous Coronary Intervention; CABG, Coronary Artery Bypass Grafting

trast medium: saline=50%: 50%) for 6 s, and saline for 2 s. The contrast medium injection rate (2.5–4.5 mL/s) and volume (38–62 mL) were decided based on the body weight.

The acquisition conditions were as follows: acquisition slice thickness, 0.5 mm × 64 rows; image slice thickness, 0.5 mm; reconstruction interval, 0.3 mm; acquisition tube voltage, 120 kV; and gantry rotation speed, 0.35 s/rot. The tube current was basically 440 mA for a 60 kg body weight, and it was decided in consideration of the body weight and body mass index.

2) 320-Row ADCT Protocol

The contrast medium injection time was fixed, and it was injected from the cubital vein in two stages at an injection rate of body weight × 0.06 mL/s: contrast medium injection for 10 s followed by saline injection for 8 s.

The acquisition conditions were as follows: acquisition slice thickness, 0.5 mm × 320 rows; image slice thickness, 0.5 mm; and reconstruction interval, 0.25 mm. A minimum acquisition range containing the entire coronary artery was set, referring to the plain CT image for registration. The acquisition tube voltage was 120 kV. For the tube current, the mean with a

standard deviation of 20, calculated using the automatic exposure control function, was used. The gantry rotation speed varies depending on the heart rate, but 0.35 s/rot or 0.275 s/rot was used. The prospective CTA mode was used as much as possible, and the X-ray exposure range was set at an acquisition of one heartbeat at 75% phase of RR.

3-2. Measurement of CACS

Using the registration image before CCTA, CACS was measured following the method of Agatston *et al.*^{15). On 64-row MDCT, referring to an electrocardiography-gated conventional (non-helical) plain CT image targeting mid-diastole or end-systole within an acquisition range including the aortic root over the cardiac apex at a tube voltage of 120 kV and tube current of 150 mA, half reconstruction was performed at a slice thickness of 3 mm and a slice interval of 3 mm.}

On 320-row ADCT, prospective electrocardiography-gated plain cardiac CT was performed targeting mid-diastole or end-systole using 280 rows so as to include the aortic root over the cardiac apex at a tube voltage of 120 kV and tube current of 50 mA, and the images were reconstructed at a slice thickness of 3 mm and a slice interval of 3 mm. A calcified lesion was defined as ≥3 contiguous pixel with a peak attenua-

tion ≥ 130 HU using a Ziostation ver. 1.3.1 (Ziosoft Inc.). The total CACS was calculated according to the method of Agatston *et al.*¹⁵). In addition, patients were divided into two groups according to CACS: patients with 0–99 CACS and those with ≥ 100 CACS.

3-3. Image Reconstruction

Full-image reconstruction, half-image reconstruction, or segmental-image reconstruction was performed in the slow filling phase and end-systole using the R+ absolute time method to generate images, and images with minimizing motion artifact were selected on the 4-chamber cardiac cine CT.

3-4. Definition of CT-HRP, Spotty Calcification, and Napkin-Ring Sign

CT-HRP was defined as a plaque characterized by PR and low attenuation. PR was defined as a change in the coronary diameter at the plaque site when compared to a reference segment with normal appearance (reference diameter). The remodeling index was defined as the lesion diameter divided by the reference diameter, and the measurements were made using both cross-sectional and longitudinal reconstructions. The presence of PR was defined as when the coronary diameter at the plaque site was at least 10% larger than the reference segment. Attenuation was defined as the minimum HU among five 0.36×0.36 -mm regions of interest. The lesion was defined as LAP when this minimum HU was < 30 ¹¹). Furthermore, spotty calcification was defined when < 3 mm in size on curved multiplanar reformation images and one side on cross-sectional images¹⁰). Napkin-ring sign was defined as the following criteria: 1) the presence of a ring of high attenuation around certain coronary artery plaques and 2) the CT attenuation of a ring presenting higher than those of the adjacent plaque and lower than 130 HU^{12, 16}). Each measurement was performed by two experienced cardiologists and one radiology technologist, and judgment of plaque properties was determined when two or more of them agreed.

3-5. Evaluation of Coronary Artery Stenosis on CCTA

Based on the agreement between two cardiologists and one radiological technologist, CCTA findings were evaluated in each segment of the patients following the modified AHA classification¹⁷). The percentage ratio of the stenotic lumen to the original vessel diameter of the lesion analogized to a presumed-to-be-healthy site distal and proximal to the stenosis was obtained, and the degree of stenosis was expressed by subtracting this from 100. Obstructive CAD was defined as those with $> 50\%$ diameter stenosis on

CCTA in ≥ 1 vessels (Normal: no plaque; 0 vessel: less than 50% diameter stenosis with plaque).

4. Calculation of FRS

The 10-year risk was calculated by FRS in accordance with published guidelines^{18, 19}). The study population was categorized as low- ($< 10\%$), intermediate- (10–20%), and high-risk ($< 20\%$) groups. Subjects with diabetes mellitus were automatically assigned as high risk (FRS of 20% or higher) if so calculated.

5. Study Outcome

Follow-up clinical information was obtained from the review of medical records and/or Human Research Committee-approved telephone interviews by attending physicians. The study end-point was the occurrence of cardiac events defined as cardiac death, non-fatal myocardial infarction, or hospitalization for unstable or progressive angina. All subjects without cardiac event and death were observed until April 30, 2013.

6. Statistical Analysis

Statistical analyses were performed using SPSS version 19 (IBM Corporation, Armonk, New York) and R version 3.1.0 (The R Foundation for Statistical Computing). Continuous variable was expressed as the mean \pm standard deviation, and categorical variable was presented as a percentage. Univariate analysis of FRS (low, intermediate, and high), CACS (0–99 and ≥ 100), and the presence of CT-HRP with spotty calcification, napkin-ring sign, and CT-HRP was performed using the Cox proportional hazard modeling to investigate whether or not each of these serves as a predictor of cardiac events, and significant factors in this analysis were subjected to multivariate analysis. A Kaplan–Meier curve was prepared based on the independent risk factors of cardiac events in the multivariate analysis. Regarding the power of the log-rank test, the median survival time was estimated by extrapolating changes in the 1,200-day period.

To determine the accuracy of predicting cardiac events, receiver operating characteristic (ROC) curves of FRS, CACS, and CT-HRP were individually prepared and AUCs were calculated. In addition, AUCs were calculated from the ROC curves of Model 1 (FRS), Model 2 (FRS + CACS), and Model 3 (Model 2 + CT-HRP) and compared.

Finally, net reclassification (NRI) and integrated discrimination improvement (IDI) between Models 1 and 2 and between Models 2 and 3 were calculated, and improvement of the prediction of the outcomes of cardiac events was investigated, considering $p < 0.05$ as significant.

Table 1. Patient characteristics

	All (N=339)	Cardiac events group (N=9)	Non-cardiac events group (N=330)	<i>p</i> -value
Gender (Male %)	61.4	55.6	61.5	N.S.
Age (years)	63.4 ± 10.4	65.8 ± 8.5	63.3 ± 10.4	N.S.
BMI (kg/m ²)	24.2 ± 3.51	24.2 ± 3.9	24.1 ± 12.6	N.S.
FH (%)	23.0	22.2	23.0	N.S.
HT (%)	62.2	55.6	62.4	N.S.
DL (%)	73.7	77.8	73.6	N.S.
DM (%)	24.2	33.3	23.9	N.S.
CKD (%)	3.54	11.1	3.3	N.S.
Smoking (%)	22.7	22.2	22.7	N.S.
TC (mg/dL)	199.1 ± 36.7	201.9 ± 34.7	198.8 ± 36.8	N.S.
HDL (mg/dL)	52.9 ± 13.8	50.9 ± 14.3	52.8 ± 13.8	N.S.
LDL (mg/dL)	120.8 ± 32.7	132.7 ± 31.6	120.5 ± 32.7	N.S.
TG (mg/dL)	154.7 ± 104.9	168.6 ± 72.0	154.3 ± 105.8	N.S.
CACS score	206.6 ± 770.3	593.7 ± 536.2	196.0 ± 773.6	N.S.
CACS category (0-99/100-)	239/100	1/8	238/92	0.0001
FRS	14.2 ± 7.9	16.3 ± 7.3	14.1 ± 7.9	N.S.
FRS category Low/Inter/High	110/113/116	2/4/3	108/109/113	N.S.
Obstructive CAD (%)	12.7			
Rapid progression: Obstructive CAD (%)	(N=3/5: 60.0)	55.6	11.5	0.0006
vessel disease N/0-v/1-v/2-v/3-v	94/202/27/11/5	0/4/2/1/2	94/198/25/10/3	0.0001
PR or LAP (%)	9.4	11.1	9.4	N.S.
CT-HRP with spotty calc (%)	3.5	33.3	2.7	0.0001
Napkin-ring sign (%)	1.5	11.1	1.2	N.S.
CT-HRP (%)	5.9	55.6	4.5	0.0001

BMI, Body Mass Index; FH, Family history; HT, Hypertension; DL, Dyslipidemia; DM, Diabetes mellitus; CKD, chronic kidney disease; TC, Total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; TG, Triglyceride; CACS, coronary artery calcium score; FRS, Framingham risk score; CAD, coronary artery disease; PR, positive remodeling; LAP, low attenuation plaque; CT-HRP, CT-verified high-risk plaque; calc, calcification

Results

1. Patient Characteristics

The patient background is shown in **Table 1**. The mean CACS was 206.6 ± 770.3, and CT-HRP was noted in 5.9% of all patients. Cardiac events occurred during the observation period in 9 (2.7%) patients: cardiac death (*n*=0), nonfatal myocardial infarction (*n*=2), and hospitalization for unstable or progressive angina (*n*=7). In addition, CACS category (≥100) was significantly greater in the cardiac events group.

Obstructive CAD and CT-HRP were observed in 55.6% and 55.6% patients, respectively, and these were significantly greater. Furthermore, obstructive CAD was detected in 60% of patients who developed cardiac events within a short 100–200-day period. Overall, 56 patients were excluded from the analysis because they underwent revascularization within 30 days after CCTA. Their backgrounds are presented in **Table 1-2**.

Table 1-2. Background of 56 patients excluded from analysis

PCI or CABG within 30 days after CCTA (N)	56
Gender (Male %)	83.9
Age (years)	64.3 ± 7.8
BMI (kg/m ²)	25.0 ± 2.9
FH (%)	23.2
HT (%)	73.2
DL (%)	83.9
DM (%)	46.4
CKD (%)	1.8
Smoking (%)	30.4
TC (mg/dL)	206.7 ± 47.8
HDL (mg/dL)	48.2 ± 9.9
LDL (mg/dL)	133.4 ± 43.8
TG (mg/dL)	163.2 ± 91.5
CACS	292.3 ± 371.0
CACS category (0-99/100-)	22/34
FRS	19.6 ± 5.7
FRS category Low/Inter/High	4/13/39
Obstructive CAD (%)	100
Vessel disease 1-v/2-v/3-v	34/17/5
CT-HRP with spotty calc (%) / Napkin-ring sign (%)	14.3/7.1
CT-HRP (%) / PR or LAP (%)	33.9/30.4

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; BMI, Body Mass Index; FH, Family history; HT, Hypertension; DL, Dyslipidemia; DM, Diabetes mellitus; CKD, chronic kidney disease; TC, Total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; TG, Triglyceride; CACS, coronary artery calcium score; FRS, Framingham risk score; CAD, coronary artery disease; CT-HRP, CT-verified high-risk plaque; calc, calcification; PR, positive remodeling; LAP, low attenuation plaque;

2-1. Univariate Analysis Using Cox Proportional Hazards Regression to Identify the Independent Predictors of Cardiac Events

On univariate analysis using Cox proportional hazards regression, when low risk of FRS was regarded as a reference, neither intermediate (HR: 2.02, 95% CI: 0.37–10.93, *p*=0.4176) or high (HR: 1.89, 95% CI: 0.31–11.38, *p*=0.4908) risk was a predictor of cardiac events. CACS ≥ 100 was an independent predictor of cardiac events (HR: 19.67, 95% CI: 2.49–155.59, *p*<0.0050), and CT-HRP was also an independent predictor of cardiac events (HR: 27.27, 95%

Table 2-1. Univariate analysis using Cox proportional hazards regression to identify the independent predictors of cardiac events

Variables	Univariate analysis		
	HR	95% C.I.	<i>p</i> -value
FRS category			
Low (reference)	1	1	NA
Intermediate	2.02	0.37-10.93	0.4176
High	1.89	0.31-11.38	0.4908
CACS (≥ 100)	19.67	2.49-155.59	0.0050
CT-HRP with spotty calc	17.45	4.36-69.73	0.0001
Napkin-ring sign	15.12	1.78-128.38	0.0133
CT-HRP	27.27	7.26-102.45	0.0001

HR, Hazard ratio; 95% C.I., 95% confidence interval; FRS, Framingham risk score; CACS, coronary artery calcium score; CT-HRP, CT-verified high-risk plaque; calc, calcification

Table 2-2. Multivariate analysis using Cox proportional hazards regression to identify the independent predictors of cardiac events

Variables	Multivariate analysis		
	HR	95% C.I.	<i>p</i> -value
CACS (≥ 100)	13.23	1.62-107.78	0.0164
CT-HRP with spotty calc	1.63	0.17-15.83	0.6762
Napkin-ring sign	1.51	0.09-26.03	0.7763
CT-HRP	11.27	1.24-102.12	0.0321

HR, Hazard ratio; 95% C.I., 95% confidence interval; CACS, coronary artery calcium score; CT-HRP, CT-verified high-risk plaque; calc, calcification

CI: 7.26–102.45, *p*<0.0001). Furthermore, CT-HRP with spotty calcification (HR: 17.45, 95% CI: 4.36–69.73, *p*<0.0001) and napkin-ring sign (HR: 15.12, 95% CI: 1.78–128.38, *p*<0.0133) were also independent predictors of cardiac events (**Table 2-1**).

2-2. Multivariate Analysis Using Cox Proportional Hazards Regression to Identify the Independent Predictors of Cardiac Events

CACS, CT-HRP with spotty calcification, napkin-ring sign, and CT-HRP were independent predictors of cardiac events observed on univariate analysis. When these were subjected to multivariate analysis, both CACS ≥ 100 (HR: 13.23, 95% CI: 1.62–107.78, *p*<0.0164) and CT-HRP (HR: 11.27, 95% CI: 1.24–102.12, *p*<0.0321) were independent predictors of cardiac events. However, CT-HRP with spotty calcification (HR: 1.63, 95% CI: 0.17–15.83, *p*=0.6762) and napkin-ring sign (HR: 1.51, 95% CI: 0.09–26.03,

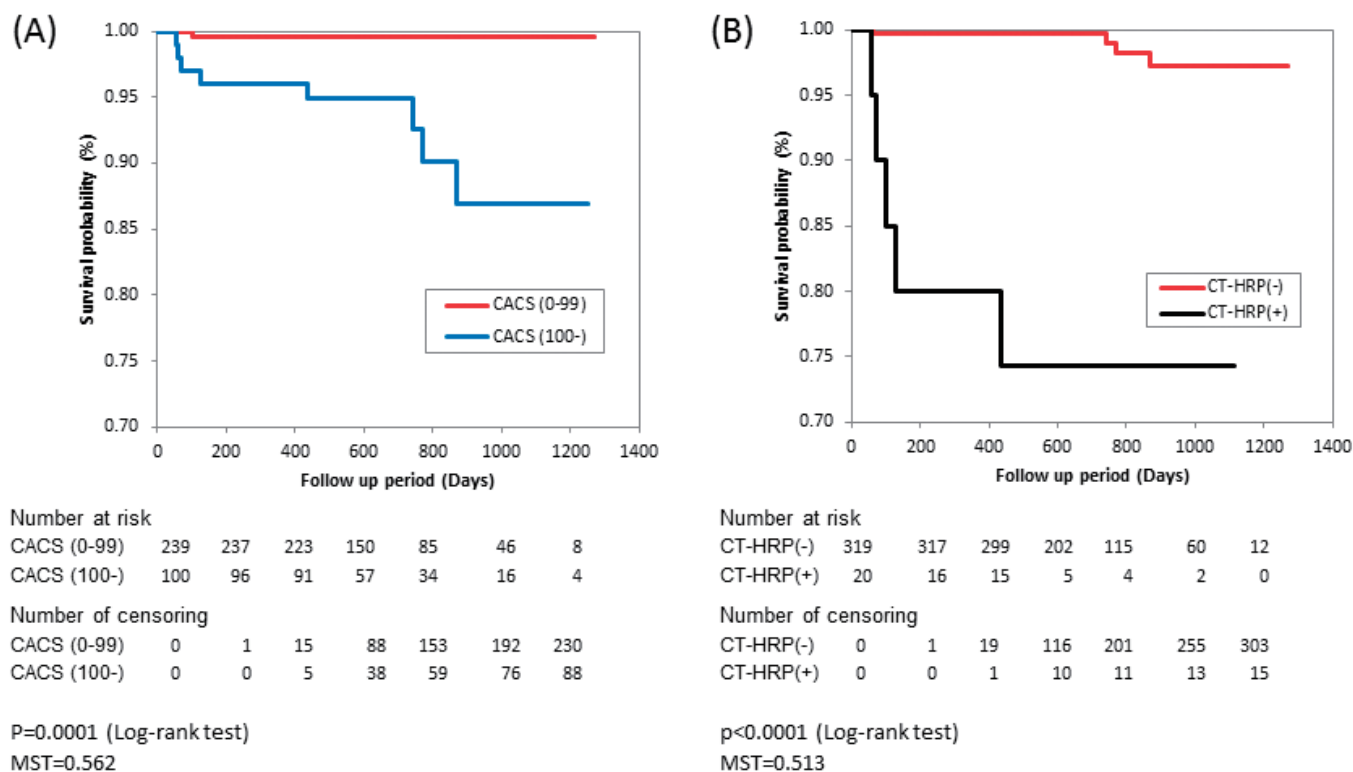


Fig. 2. Kaplan–Meier analysis for cardiac event-free survival

(A) CACS, log rank: $p=0.0001$, MST=0.562

Red line: CACS < 99, Blue line: CACS ≥ 100

(B) CT-HRP, log rank: $p<0.0001$, MST=0.513

Red line: Patients without CT-HRP, Black line: Patients with CT-HRP

MST, median survival time; CACS, coronary artery calcium score; CT-HRP, CT-verified high-risk plaque

$p=0.7763$) were not independent predictors of cardiac events (Table 2-2).

3. Kaplan–Meier Analysis for Cardiac Event-Free Survival

CACS and CT-HRP were independent predictors of multivariate analysis. Based on these, when Kaplan–Meier analysis was performed, cardiac events significantly increased when CACS ≥ 100 (log rank: $p=0.0001$) (Fig. 2-A). Cardiac events also significantly increased in patients with CT-HRP (log rank: $p<0.0001$) (Fig. 2-B).

4-1. Comparison of Diagnostic Performances for Cardiac Events between FRS and CACS and CT-HRP Alone Using ROC Curve

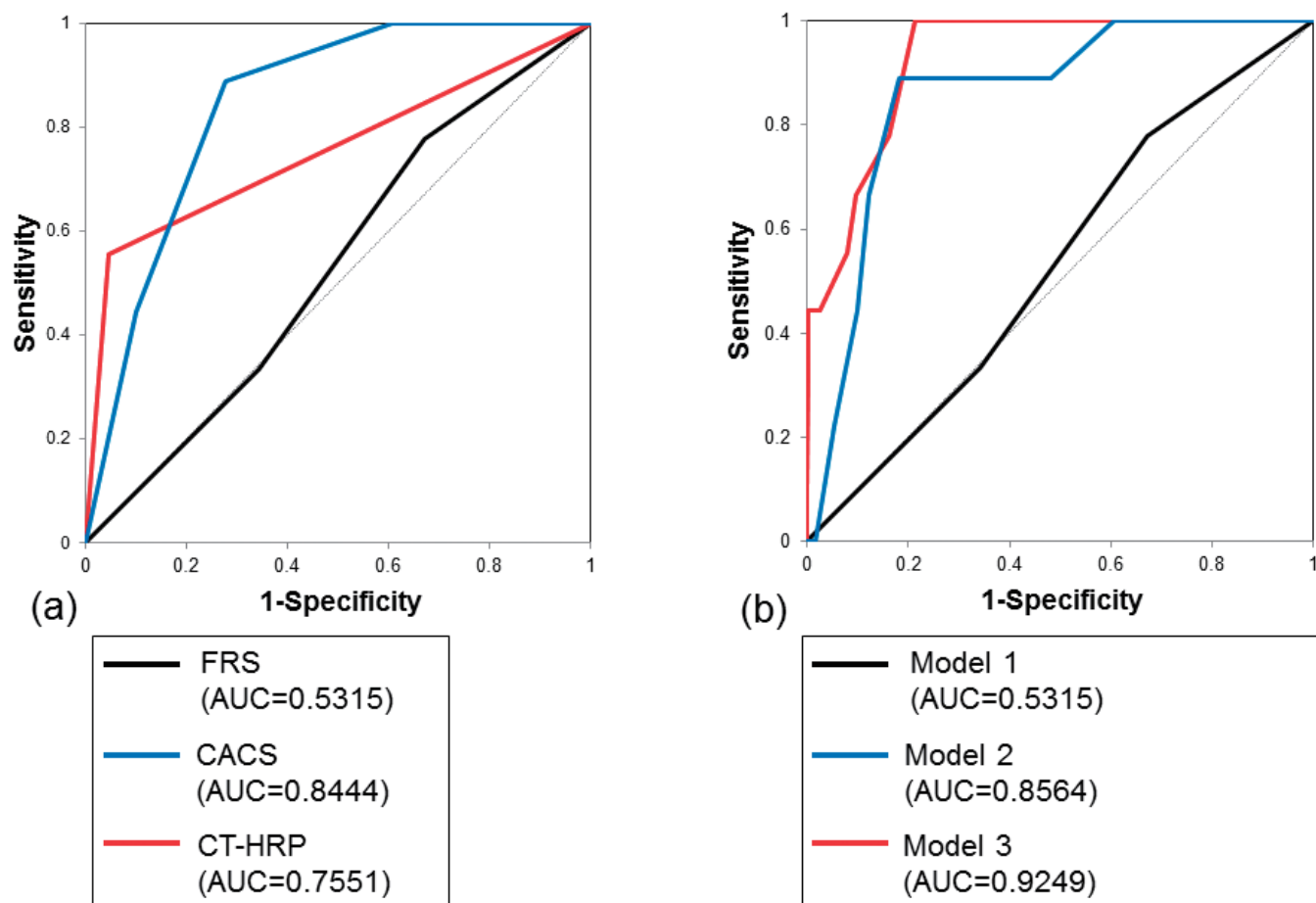
Regarding the accuracy of predicting cardiac events, AUC of FRS group was 0.5315, that of CACS ≥ 100 group was 0.8444, and that of CT-HRP group was 0.7551, all showing a superior prediction accuracy (Fig. 3-a).

4-2. Comparison of Diagnostic Performances for Cardiac Events between Models 1 and 2 and Models 2 and 3 Using ROC Curve

When the accuracy of predicting cardiac events was compared based on AUC of the ROC curve between Model 1 (FRS alone) and Model 2 (FRS plus CACS) (0.5315 vs. 0.8564), AUC was significantly higher in Model 2 ($p=0.0056$). When AUC of the ROC curve was compared between Model 2 and Model 3 (combining CT-HRP to Model 2) (0.8564 vs. 0.9249), AUC was higher in Model 3, although the difference was not significant ($p=0.1920$) (Fig. 3-b).

5. Investigate NRI and IDI

NRI in Model 2 was 0.5697 (95% CI: 0.4864–0.6530) and that in Model 3 was 0.9556 (95% CI: 0.4057–1.5054). Similarly, IDI was 0.0134 (95% CI: 0.0046–0.0222) in Model 2 and 0.2582 (95% CI: 0.0401–0.4763) in Model 3, showing that the diagnostic performance improved, adding a value to the prediction of cardiac events (Table 3).

**Fig. 3.**

(a) Comparison of diagnostic performance for cardiac events between FRS and CACS, CT-HRP alone using ROC curve

Black line: FRS, Blue line: CACS, Red line: CT-HRP

FRS, Framingham risk score; CACS, coronary artery calcium score; CT-HRP, CT-verified high-risk plaque; AUC, Area Under the Curve; ROC, Receiver Operating Characteristic Curve

(b) Comparison of diagnostic performances for cardiac events between Model 1 and Model 2, between Model 2 and Model 3 using ROC curve

Model 1: FRS

Model 2: Model 1 + CACS

Model 3: Model 2 + CT-HRP

ROC curve, Receiver Operating Characteristic Curve; FRS, Framingham risk score; CACS, coronary artery calcium score; CT-HRP, CT-verified high-risk plaque

Discussion

The usefulness of CACS for the stratification of cardiac event risks in asymptomatic patients is presented in the guidelines, but the indication of CCTA has not been established even for cases with a high risk of FRS⁵. In the PROSPECT study, in which the subjects were prospectively observed using virtual histology-intravascular ultrasound (VH-IVUS), thin-cap fibroatheroma (TCFA), a large plaque burden ($\geq 70\%$), and reduced minimal lumen area ($\leq 4.0 \text{ mm}^2$) on VH-IVUS were the cardiac event predictors, and the

importance of these for diagnosing vulnerable plaques was demonstrated in actual clinical practice. However, VH-IVUS is an invasive modality, and its use for screening many patients is difficult. In addition, the incidence of cardiac death, cardiac arrest, and acute myocardial infarction from non-culprit lesions in all patients was 1% in the 3-year period with optical medical therapy after the PROSPECT study, re-confirming the importance of early screening of patients with vulnerable plaques by less-invasive imaging to stratify risks and perform optimal medical therapy^{20, 21}. Our study initially reported that plaque evaluation

Table 3. Investigate NRI and IDI

	NRI (95% C.I.)	<i>p</i> -value
Model 2 (Model 1 + CACS)	0.5697 (0.4864-0.6530)	0.0001
Model 3 (Model 2 + CT-HRP)	0.9556 (0.4057-1.5054)	0.0007
	IDI (95% C.I.)	<i>p</i> -value
Model 2 (Model 1 + CACS)	0.0134 (0.0046-0.0222)	0.0028
Model 3 (Model 2 + CT-HRP)	0.2582 (0.0401-0.4763)	0.0203

95% C.I., 95% confidence interval; NRI, Net Reclassification Improvement; IDI: Integrated Discrimination Improvement; CACS, coronary artery calcium score; CT-HRP, CT-verified high-risk plaque
Model 1: Framingham risk score, Model 2: Framingham risk score + CACS, Model 3: Model 2 + CT-HRP

using CCTA as less-invasive modality, adding an incremental prognostic value for asymptomatic patients.

In a histopathological study on the coronary artery in patients with cardiac sudden death, ACS developed with rupture of plaques, plaque erosion, and calcified nodes in 59%–75%, 36%–44%, 2%–7% cases, respectively²². Precursor lesions of plaque rupture, which cause ACS at a high frequency, show PR with a lipid core, thin fibrous capsule covering it, and macrophage infiltration as its pathological characteristics, and it is regarded as TCFA^{23, 24}. Reportedly, plaques showing both PR and low attenuation are observed on CCTA, and plaques with a napkin-ring sign are observed on histopathology and optical coherence tomography as TCFA^{25, 26}. A high risk of developing ACS in patients with these plaques has been reported¹⁰⁻¹². Furthermore, there were many patients in whom these plaques were not calcified or only micro calcification was present^{27, 28}. Although arteriosclerosis has not extensively progressed, the presence of high-risk plaques leads to rapid plaque progression and instability, which may cause cardiac events in the near future. Moreover, asymptomatic patients examined by CCTA may have included many patients in whom arteriosclerosis has not extensively progressed. In our study, patients with 50% or greater stenosis accounted for only 12.7% (43/339 patients), and the number of vessels with obstructive CAD was not a predictor of cardiac events. Based on these findings, high-risk plaques on CCTA may be an incremental predictor independent from CACS findings.

It has been reported that a combination of FRS¹⁹, recommended in the guidelines, with CACS enables a better risk stratification of asymptomatic patients²⁹,

and a similar finding was observed in our study, but FRS alone was not extracted as an independent risk factor of cardiac events in asymptomatic patients. One reason is that FRS predicts cardiac events after 10 years, and the observation period (716.5 ± 262.6 days) may have been too short to predict the risk. In addition, therapeutic intervention was initiated early for an item of FRS, coronary arterial risk factors such as blood pressure, dyslipidemia, and cigarette smoking, and this may have influenced the reduction of events in patients diagnosed as at high risk of CAD. Therefore, imaging diagnosis capable of directly evaluating coronary arterial sclerosis may be more useful to stratify risks. Less-invasive re-stratification of risks using CCTA in asymptomatic patients may be applied for extensively effective prevention and treatment.

To establish this usefulness, verification by a large-scale prospective clinical study is necessary. However, the CT values used to evaluate the plaque characteristics are considered to be influenced by various factors such as the contrast medium level in the coronary arterial lumen, grade of coronary arterial stenosis, and tube voltage³⁰. A low CT number may be displayed due to the influence of an undershooting artifact around the calcification induced by the beam-hardening effect of calcification³¹. For such a reason, evaluation of plaque values varies among facilities^{32, 33}. Moreover, overestimation of the amount of plaque compared with that on IVUS has been reported³⁴. Therefore, establishment of an objective and quantitative evaluation method is necessary.

Limitations

There are several limitations of this study. First, this was a retrospective study performed at a single center, and patient selection was entrusted to physicians, which may have influenced the prevalence of the disease in the patients. Second, not all patients could be followed up, and this may have influenced the incidence of events. The culprit lesion was not always clarified in patients who developed an event, and whether or not CT-HRP segment directly influenced the event was not always clarified. However, it may be significant that an incremental value of CCTA was added to the analysis of plaque characteristics as a patient base. Third, oral medications could not be clarified for the whole study population. Antiplatelet agents and statin have been reported to inhibit cardiac events^{35, 36}, and statin has been reported to regress and stabilize plaques^{37, 38}. It is possible that these drugs were involved in cardiac events and changes in plaque characteristics. Fourth, since the number of cases was small and the incidence of events was low, it is neces-

sary to investigate whether the findings are worth analyzing. Since the estimated MST exceeded 0.5 in the log-rank test despite being restricted by the fact that the cardiac events were rare, the test was judged as reliable. Furthermore, although the prevalence of high-risk plaque in our previous report³⁹⁾ and the asymptomatic patients in this study were the same, the event rate was low in this study. It was considered that patients with a stabilized plaque have increased with the recent development of optical medical therapy, which subsequently decreased events, and the coronary arterial CT findings facilitated awareness of risk control on both patient and medical care-providing sides, which may have resulted in a bias.

Finally, the main objective of this study was to investigate whether CACS and CCTA findings add value to FRS, which was patient-based and not segment-based. Moreover, the number of vessels index was not investigated in this study, but this may not have influenced the investigation, because on sub-analysis in the CONFIRM study, the addition of the number of vessels with lesions to the CACS did not provide an incremental value for asymptomatic patients with regard to event development⁵⁾, and the number of vessels with lesions was not a predictor of event development in our study.

Conclusion

Although the cardiac event rate was low, evaluation of CCTA plaque characteristics may provide an incremental prognostic value to the CACS in asymptomatic patients.

Acknowledgments

We are deeply grateful to Medical English Service for assistance in translating the manuscript and Dr. Chiaki Nishimura for advice in the statistical analysis of the data.

Disclosure

Dr. Daida has received research funds from Toshiba Medical Systems Corporation that are unrelated to this project.

The other authors have declared no conflicts of interest.

References

- 1) Bax JJ, Young LH, Frye RL, Bonow RO, Steinberg HO, Barrett EJ; ADA. Screening for coronary artery disease in patients with diabetes. *Diabetes Care*. 2007; 30: 2729-2736
- 2) Budoff MJ, Shaw LJ, Liu ST, Weinstein SR, Mosler TP, Tseng PH, Flores FR, Callister TQ, Raggi P, Berman DS. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. *J Am Coll Cardiol*. 2007; 49: 1860-1870
- 3) Detrano RI, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, Liu K, Shea S, Szklo M, Bluemke DA, O'Leary DH, Tracy R, Watson K, Wong ND, Kronmal RA. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med*. 2008; 358: 1336-1345
- 4) Tota-Maharaj R, Blaha MJ, McEvoy JW, Blumenthal RS, Muse ED, Budoff MJ, Shaw LJ, Berman DS, Rana JS, Rumberger J, Callister T, Rivera J, Agatston A, Nasir K. Coronary artery calcium for the prediction of mortality in young adults <45 years old and elderly adults >75 years old. *Eur Heart J*. 2012; 33: 2955-2962
- 5) Taylor AJ, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P, Rubin GD. 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. *Circulation* 2010; 122: e525-555
- 6) Villines TC, Hulten EA, Shaw LJ, Goyal M, Dunning A, Achenbach S, Al-Mallah M, Berman DS, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Cheng VY, Chinnaiyan K, Chow BJ, Delago A, Hadamitzky M, Hausleiter J, Kaufmann P, Lin FY, Maffei E, Raff GL, Min JK; CONFIRM Registry Investigators. Prevalence and severity of coronary artery disease and adverse events among symptomatic patients with coronary artery calcification scores of zero undergoing coronary computed tomography angiography: results from the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry. *J Am Coll Cardiol*. 2011; 58: 2533-2540
- 7) Muhlestein JB, Lappé DL, Lima JA, Rosen BD, May HT, Knight S, Bluemke DA, Towner SR, Le V, Bair TL, Vavere AL, Anderson JL. Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial. *JAMA*. 2015; 312: 2234-2243
- 8) Cho I, Chang HJ, Ó Hartaigh B, Shin S, Sung JM, Lin FY, Achenbach S, Heo R, Berman DS, Budoff MJ, Callister TQ, Al-Mallah MH, Cademartiri F, Chinnaiyan K, Chow BJ, Dunning AM, DeLago A, Villines TC, Hadamitzky M, Hausleiter J, Leipsic J, Shaw LJ, Kaufmann PA, Cury RC, Feuchtner G, Kim YJ, Maffei E, Raff G, Pontone G, Andreini D, Min JK. Incremental prognostic utility of coronary CT angiography for asymptomatic patients based upon extent and severity of coronary artery calcium: results from the COronary CT Angiography

- Evaluation For Clinical Outcomes International Multi-center (CONFIRM) study. *Eur Heart J.* 2015; 36: 501-508
- 9) Min JK, Labounty TM, Gomez MJ, Achenbach S, Al-Mallah M, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Cheng V, Chinnaiyan KM, Chow B, Cury R, Delago A, Dunning A, Feuchtnr G, Hadamitzky M, Hausleiter J, Kaufmann P, Kim YJ, Leipsic J, Lin FY, Maffei E, Raff G, Shaw LJ, Villines TC, Berman DS. Incremental prognostic value of coronary computed tomographic angiography over coronary artery calcium score for risk prediction of major adverse cardiac events in asymptomatic diabetic individuals. *Atherosclerosis.* 2014; 232: 298-304
 - 10) Motoyama S, Kondo T, Sarai M, Sugiura A, Harigaya H, Sato T, Inoue K, Okumura M, Ishii J, Anno H, Virmani R, Ozaki Y, Hishida H, Narula J. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. *J Am Coll Cardiol.* 2007; 50: 319-326
 - 11) Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, Naruse H, Ishii J, Hishida H, Wong ND, Virmani R, Kondo T, Ozaki Y, Narula J. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. *J Am Coll Cardiol.* 2009; 54: 49-57
 - 12) Otsuka K, Fukuda S, Tanaka A, Nakanishi K, Taguchi H, Yoshikawa J, Shimada K, Yoshiyama M. Napkin-ring sign on coronary CT angiography for the prediction of acute coronary syndrome. *JACC Cardiovasc Imaging.* 2013; 6: 448-457
 - 13) Fujimoto S, Kondo T, Takamura K, Baber U, Shinozaki T, Nishizaki Y, Kawaguchi Y, Matsumori R, Hiki M, Miyachi K, Daida H, Hecht H, Stone GW, Narula J. Incremental prognostic value of coronary computed tomographic angiography high-risk plaque characteristics in newly symptomatic patients. *J Cardiol.* 2015. pii: S0914-5087(15)00241-5
 - 14) Fujimoto S, Matsutani H, Kondo T, Sano T, Kumamaru K, Takase S, Rybicki FJ. Image quality and radiation dose stratified by patient heart rate for coronary 64- and 320-MDCT angiography. *Am J Roentgenol* 2013; 200: 765-770
 - 15) Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990; 15: 827-832
 - 16) Kashiwagi M, Tanaka A, Kitabata H, Tsujioka H, Kataiwa H, Komukai K, Tanimoto T, Takemoto K, Takarada S, Kubo T, Hirata K, Nakamura N, Mizukoshi M, Imanishi T, Akasaka T. Feasibility of noninvasive assessment of thin-cap fibroatheroma by multidetector computed tomography. *JACC Cardiovasc Imaging.* 2009; 2: 1412-1419
 - 17) Raff GL, Abidov A, Achenbach S, Berman DS, Boxer LM, Budoff MJ, Cheng V, DeFrance T, Hellinger JC, Karlsberg RP; Society of Cardiovascular Computed Tomography. SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. *J Cardiovasc Comput Tomogr.* 2009; 3: 122-136
 - 18) Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation.* 1998; 97: 1837-1847
 - 19) Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA.* 2001; 285: 2486-2497
 - 20) Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW; PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. 2011; 364: 226-235
 - 21) Davis KL, Meyers J, Zhao Z, McCollam PL, Murakami M. High-Risk Atherosclerotic Cardiovascular Disease in a Real-World Employed Japanese Population: Prevalence, Cardiovascular Event Rates, and Costs. *J Atheroscler Thromb.* 2015; 22: 1287-1304
 - 22) Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. *J Am Coll Cardiol.* 2006; 47 (8 Suppl): C13-18
 - 23) Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol.* 2000; 20: 1262-1275
 - 24) Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. *N Engl J Med.* 1997; 336: 1276-1282
 - 25) Nakazato R, Otake H, Konishi A, Iwasaki M, Koo BK, Fukuya H, Shinke T, Hirata K, Leipsic J, Berman DS, Min JK. Atherosclerotic plaque characterization by CT angiography for identification of high-risk coronary artery lesions: a comparison to optical coherence tomography. *Eur Heart J Cardiovasc Imaging.* 2015; 16: 373-379
 - 26) Maurovich-Horvat P, Hoffmann U, Vorpahl M, Nakano M, Virmani R, Alkadhi H. The napkin-ring sign: CT signature of high-risk coronary plaques?. *JACC Cardiovasc Imaging.* 2010; 3: 440-444
 - 27) Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, Badimon JJ, Stefanadis C, Moreno P, Pasterkamp G, Fayad Z, Stone PH, Waxman S, Raggi P, Madjid M, Zarrabi A, Burke A, Yuan C, Fitzgerald PJ, Siscock DS, de Korte CL, Aikawa M, Juhani Airaksinen KE, Assmann G, Becker CR, Chesebro JH, Farb A, Galis ZS, Jackson C, Jang IK, Koenig W, Lodder RA, March K, Demirovic J, Navab M, Priori SG, Rehkter MD, Bahr R, Grundy SM, Mehran R, Colombo A, Boerwinkle E, Balantyne C, Insull W Jr, Schwartz RS, Vogel R, Serruys PW, Hansson GK, Faxon DP, Kaul S, Drexler H, Greenland P, Muller JE, Virmani R, Ridker PM, Zipes DP, Shah PK, Willerson JT. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. *Circulation.* 2003; 108: 1664-1672
 - 28) Urabe Y, Yamamoto H, Kitagawa T, Utsunomiya H, Tsumishima H, Tatsugami F, Awai K, Kihara Y. Identifying Small Coronary Calcification in Non-Contrast 0.5-mm Slice Reconstruction to Diagnose Coronary Artery Disease in Patients with a Conventional Zero Coronary Artery Calcium Score. *J Atheroscler Thromb.* 2016; 23: 1324-1333
 - 29) Greenland P, LaBree L, Azen SP, Doherty TM, Detrano

- RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA*. 2004; 291: 210-215
- 30) Cademartiri F, Mollet NR, Runza G, Bruining N, Hamers R, Somers P, Knaapen M, Verheye S, Midiri M, Krestin GP, de Feyter PJ. Influence of intracoronary attenuation on coronary plaque measurements using multislice computed tomography: observations in an ex vivo model of coronary computed tomography angiography. *Eur Radiol*. 2005; 15: 1426-1431
- 31) Zhang S, Levin DC, Halpern EJ, Fischman D, Savage M, Walinsky P. Accuracy of MDCT in assessing the degree of stenosis caused by calcified coronary artery plaques. *AJR Am J Roentgenol*. 2008; 191: 1676-1683
- 32) Kristanto W, van Ooijen PM, Jansen-van der Weide MC, Vliegenthart R, Oudkerk M. A meta analysis and hierarchical classification of HU-based atherosclerotic plaque characterization criteria. *PLoS One*. 2013; 8: e73460
- 33) Leber AW, Knez A, Becker A, Becker C, von Ziegler F, Nikolaou K, Rist C, Reiser M, White C, Steinbeck G, Boekstegers P. Accuracy of multidetector spiral computed tomography in identifying and differentiating the composition of coronary atherosclerotic plaques: a comparative study with intracoronary ultrasound. *J Am Coll Cardiol*. 2004; 43: 1241-1247
- 34) Moselewski F, Ropers D, Pohle K, Hoffmann U, Ferencik M, Chan RC, Cury RC, Abbara S, Jang IK, Brady TJ, Daniel WG, Achenbach S. Comparison of measurement of cross-sectional coronary atherosclerotic plaque and vessel areas by 16-slice multidetector computed tomography versus intravascular ultrasound. *Am J Cardiol* 2004; 94: 1294-1297
- 35) Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002; 324: 71-86
- 36) Randomised trial of cholesterol lowering in 4444 patients with coronary heartdisease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; 344: 1383-1389
- 37) Kawasaki M, Sano K, Okubo M, Yokoyama H, Ito Y, Murata I, Tsuchiya K, Minatoguchi S, Zhou X, Fujita H, Fujiwara H Volumetric quantitative analysis of tissue characteristics of coronary plaques after statin therapy using three-dimensional integrated backscatter intravascular ultrasound. *J Am Coll Cardiol* 2005; 45: 1946-1953
- 38) Takarada S, Imanishi T, Kubo T, Tanimoto T, Kitabata H, Nakamura N, Tanaka A, Mizukoshi M, Akasaka T Effect of statin therapy on coronary fibrous-cap thickness in patients with acute coronary syndrome: assessment by optical coherence tomography study. *Atherosclerosis* 2009; 202: 491-497
- 39) Fujimoto S, Kondo T, Kodama T, Orihara T, Sugiyama J, Kondo M, Endo A, Fukazawa H, Nagaoka H, Oida A, Ikeda T, Yamazaki J, Takase S, Narula J. Coronary computed tomography angiography-based coronary risk stratification in subjects presenting with no or atypical symptoms. *Circ J*. 2012; 76: 2419-2425