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Association Between High-Sensitivity C-Reactive Protein and Coronary Plaque Subtypes Assessed by 64-Slice Coronary Computed Tomography Angiography in an Asymptomatic Population

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Background—Elevated levels of C-reactive protein (CRP) are associated with poor cardiovascular outcomes, even after accounting for traditional cardiovascular risk factors. We sought to analyze the relationship between levels of CRP and coronary plaque subtypes as assessed by coronary computed tomography angiography.

Methods and Results—We evaluated 1004 asymptomatic South Korean subjects (mean age, 49 ± 9.3 years) who underwent coronary computed tomography angiography as part of a health screening evaluation. We examined the association between increasing CRP levels and plaque subtypes using multivariable linear and logistic regression analysis. Coronary plaque was observed in 211 of 1004 individuals (21%). Subjects with high CRP (≥ 2 mg/L) had an increased prevalence of any plaque type (30.7% versus 16.7% $P < 0.001$) and mixed calcified arterial plaque (MCAP) (19.3% versus 6.3% $P < 0.001$) as compared with subjects with low-normal CRP. Multivariable logistic regression analysis demonstrated that elevated CRP predicted the presence of any MCAP (high versus low-normal CRP group; odds ratio, 2.81; 95% confidence interval, 1.62 to 4.89). When examining the multivariable logistic regression analysis between the presence of ≥ 2 plaques and CRP, subjects with high CRP were more likely to have MCAP than those with low-normal CRP levels (odds ratio, 3.78; 95% confidence interval, 1.49 to 9.55).

Conclusions—Elevated levels of CRP are associated with an increased prevalence of MCAP as assessed by coronary computed tomography angiography. Longitudinal studies will determine if the excess risk observed in persons with elevated CRP may be mediated, at least in part, by an increased burden of MCAP. (*Circ Cardiovasc Imaging*. 2011;4:201-209.)

Key Words: C-reactive protein ■ coronary computed tomography angiography ■ and coronary plaque subtype

Risk stratification for coronary heart disease (CHD) is used to identify individuals who probably will benefit from primary or secondary prevention therapies.¹ Despite this, the identification of subjects at increased risk of cardiovascular events by way of algorithms such as the Framingham Risk Score has been insufficient.²⁻⁵

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Imaging has been proposed as a convenient tool to assist in risk stratification. Coronary artery calcium scoring by computed tomography, mainly in intermediate-risk patients, can identify individuals at risk for coronary events and improves stratifica-

tion beyond the Framingham Risk Score⁶⁻⁹ but is limited by its inability to differentiate between coronary plaque subtypes.

Coronary computed tomography angiography (CCTA) has been shown to be a sensitive and specific tool for the detection of significant coronary stenosis and has also allowed for the visualization and characterization of plaque subtypes.¹⁰⁻¹³ Several studies have demonstrated that CCTA can provide prognostic information¹⁴⁻¹⁶ and, most importantly, incremental prognostic value over calcium scoring in patients with suspected CHD.¹⁷ Studies have also provided insight as to what specific plaque subtypes and characteristics might be associated with a worse outcome.¹⁸⁻²¹

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Concurrently, C-reactive protein (CRP) has also been proposed as a method of identifying individuals at higher cardiovascular risk. CRP is produced and secreted from the liver and smooth muscle cells surrounding atherosclerotic plaques.²² Studies have demonstrated that CRP correlates with various aspects of atherogenesis.^{23,24} Although there is ongoing debate regarding the causative role of CRP in the development of atherosclerosis, it has been demonstrated that CRP allows for independent^{25,26} and improved^{27–30} risk stratification beyond traditional risk scoring systems. A recent trial underscored the importance of CRP in risk stratification by demonstrating that treating patients considered at low risk with “near optimal lipid levels” but elevated CRP reduced cardiovascular event rates and, most importantly, reduced all-cause mortality.³¹

The role of CRP in cardiovascular risk stratification has been clearly established, and thus we sought to analyze the cross-sectional relationship between elevated levels of CRP and plaque subtypes as identified by CCTA.

Methods

Study Population

We retrospectively enrolled 1043 consecutive South Korean individuals who had undergone CCTA evaluation, using 64-slice multidetector CT as part of a general routine health evaluation in the Seoul National University Bundang Hospital (SNUBH) between December 2005 and May 2006. An initial evaluation of this subject population has been published elsewhere.³² For the present analysis, we excluded 11 individuals who had no CRP data and 28 who had missing risk factor information. As a result, a total of 1004 self-referred, middle-aged, asymptomatic subjects were finally enrolled. The institutional review board approved the study protocol, and all patients gave written informed consent.

Risk Factor Assessment and Stratification

Basic demographic data were acquired from a data base maintained by the SNUBH Health Promotion Center. All individuals were asked whether they had chest pain or equivalent symptoms according to a Rose angina questionnaire.³³ Medical history of myocardial infarction, angina, hypertension, stroke, diabetes mellitus (DM), family history of premature CHD (CHD in male first-degree relative age <55 years; CHD in female first-degree relative age <65 years), current medication profile, smoking, and social status were systematically acquired. Body weight, height, and blood pressure were also measured during their visit.

Hypertension was defined as a self-reported history of hypertension and/or use of antihypertensive medication, or a blood pressure $\geq 140/90$ mm Hg. Total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fasting blood glucose, HbA1c, blood urea nitrogen, and serum creatinine level were measured after at least a 12-hour fasting period on the same day of the study. DM was defined as a self-reported history of DM and/or use of antidiabetic medication, or a fasting glucose ≥ 126 mg/dL.

Serum CRP was measured by latex agglutination with CRP-LATEX $\times 2$ reagent (Denka Seiken Tokyo, Japan), using a chemistry autoanalyzer (Toshiba-200 FR, Tokyo, Japan) at the laboratory of SNUBH. The lower limit of detection of the assay used was 0.1 mg/L. Between days, imprecision rates were 1.94% and 2.11% for low- and high-level controls, respectively. The coefficients of variation for monthly means of controls were 4.2% and 1.1% for low- and high-level controls, respectively.

Data Acquisition

Patients with a heart rate >70 beats per minute received intravenous esmolol, 10 to 30 mg (Jeil Pharm Co, Ltd, Seocho gu, Korea), before image acquisition. CCTA was performed with the use of a 64-slice

multidetector scanner (Brilliance 64; Philips Medical Systems, Best, The Netherlands). A standard scanning protocol was applied, with 64×0.625 mm section collimation, 420-ms rotation time, 120-kV tube voltage, and 800-mA tube current. All scans were performed using ECG-gated dose modulation. A bolus of 80 mL Iomeprol (Iomeron 400; Bracco, Milan, Italy) was intravenously injected (4 mL/s) followed by a 50-mL saline chaser. The average heart rate during the scan was 58 ± 7 (40 to 81) beats per minute.

A region of interest was placed in the descending thoracic aorta, and image acquisition was automatically initiated once a selected threshold (150 Hounsfield units) had been reached using bolus tracking. The patient's ECG was simultaneously recorded to allow for retrospective segmental data reconstruction. Images were initially reconstructed at mid-diastolic phase (75% of R-R interval) of the cardiac cycle. Additional reconstructions were performed if motion artifacts were present. The mean radiation exposure of CCTA was 13.21 ± 0.82 mSv (13.2 ± 0.8 for male and 13.3 ± 0.8 for female).

Image Analysis

All scans were analyzed independently by 2 experienced radiologists who were blinded to the clinical information, using a 3D workstation (Brilliance; Philips Medical Systems, Best, The Netherlands). After making independent evaluations, a consensus interpretation was arrived at to obtain a final CCTA diagnosis. Each lesion was identified using a multiplanar reconstruction technique and maximum intensity projection of short-axis, 2-chamber, and 4-chamber views.

We analyzed plaque characteristics on a per-segment basis according to the modified American Heart Association classification.³⁴ Image quality was evaluated on a per-segment basis and classified as good (no artifact), adequate (defined as the presence of image-degrading artifacts but feasible for evaluation with a moderate confidence), or poor (the presence of image-degrading artifacts and feasible for evaluation only with a low confidence).

The contrast-enhanced portion of the coronary lumen was semi-automatically traced at the maximal stenotic site and compared with the mean value of proximal and distal nondiseased reference site. If the image was adequate or poor quality, coronary segments were visually scored for the grading of coronary artery stenosis. Each lesion identified was examined using maximum intensity projection and multiplanar reconstruction techniques on short axis and along multiple longitudinal axes. Lesions were classified by the maximal luminal diameter stenosis seen on any plane and the severity of diameter stenosis was graded as normal-appearing (0% to 24%), mild (25% to 49%), moderate (50% to 74%), and severe ($\geq 75\%$) narrowing. A stenosis of $>50\%$ and 75% was defined as significant and severe, respectively.

Coronary plaques were defined as structures >1 mm² within and/or adjacent to the vessel lumen, which could be clearly distinguished from the lumen and surrounding pericardial tissue. Plaques occupied by calcified tissue $>50\%$ of the plaque area (density >130 Hounsfield units in native scans) were classified as calcified arterial plaques (CAP), plaques with $<50\%$ calcium as mixed calcified plaques (MCAP), and plaques without any calcium were classified as noncalcified plaques (NCAP) as previously described.¹¹ This was evaluated in a visual qualitative manner. We defined coronary plaque subtype burden as the presence of 2 or more involved segments.

Coronary artery segment image quality was classified as good in 95%, adequate in 4%, and poor in 1%. Poor image quality was due to motion artifact (55%, 121 of 219 segments), blooming artifact (29%, 64 of 219 segments), or low contrast-to-noise ratio (16%, 34 of 219 segments). Interobserver and intraobserver agreement for the categorical classification of stenosis were 0.87 and 0.95, respectively (Cohen κ). For the evaluation of coronary artery stenosis, we quantitatively measured the degree of stenosis in segments with good image quality. If image quality was graded as adequate or poor, the degree of stenosis was visually scored. Thus all segments were analyzed for degree of stenosis. However, for plaque subtype analysis, we only evaluated segments with good image quality. Interobserver agreement for the detection of any plaque/subject and plaque/segment was excellent (Cohen $\kappa = 0.93$ and 0.84 , respectively).

Table 1. Baseline Characteristics of the Study Groups

Characteristic	Total (n=1004)	Low-Normal CRP (n=592)	Intermediate CRP (n=220)	High CRP (n=192)	P Value (Overall)	P Value (Intermediate Versus Normal)	P Value (High Versus Intermediate)
Age, y	48.6±9.3	49.6±10.2	49.0±10.2	50.2±9.3	0.10		
Sex, male %	64%	56%	75%	74%	<0.001	<0.001	0.90
BMI, kg/m ²	24.1±2.7	23.6±2.6	24.8±2.5	25.0±2.9	<0.001	<0.001	1.00
Smoking, %	35%	29%	43%	44%	<0.001	<0.001	0.83
Family history of premature CAD	13%	14%	12%	11%	0.68		
Hypertension, %	20%	16%	28%	24%	<0.001	<0.001	0.39
Systolic blood pressure, mm Hg	116±14	114±14	118±15	117±15	<0.001	<0.001	1.00
Diabetes, %	9%	7%	12%	14%	0.004	0.011	0.70
LDL-C, mg/dL	117±32	117±31	115±33	123±34	0.028	1.00	0.037
HDL-C, mg/dL	60±14	62±14	58±13	55±13	<0.001	<0.001	0.12
Triglycerides, mg/dL	134±90	120±77	153±104	153±100	<0.001	<0.001	1.00

BMI indicates body mass index; LDL-C, low-density lipoprotein cholesterol; and HDL-C, high-density lipoprotein cholesterol.

Data are expressed as proportions (%) or mean±SD.

Low-normal high-sensitivity (hs)CRP: ≤1.0 mg/L; intermediate hsCRP: 1.1 to 2.0 mg/L; and high hsCRP: ≥2.0 mg/L.

Statistical Analysis

Because more than half of our study population (58%) had CRP values of <1.0 mg/L, this was categorized as our reference group. Individuals with CRP >1 mg/L were further divided into 2 groups according to their median cutoff value into an intermediate CRP group (1 to 1.9 mg/L) and a high CRP group (≥2 mg/L).

Continuous variables were expressed as means and standard deviation (SD), whereas categorical variables were presented as absolute values and percentages. Differences across CRP groups were analyzed by ANOVA for continuous variables and χ^2 testing for categorical variables.

Multivariable linear and logistic models were used to examine the association between increasing categories of CRP and the presence of any plaque, ≥2 plaques, extent of plaque, and degree of stenosis. Ordinal logistic regression models were used to assess the relation between CRP categories and increasing categories of coronary artery disease (no plaque, nonobstructive, and obstructive plaque) with reference group being those with no plaque. Ordinal regression permits logistic regression allows for >2 (in this case, 3) categorical responses variables. Plaques were analyzed on a per-patient level, and initial analysis was unadjusted and progressively adjusted for age and sex (model 1) and additionally for low-density lipoprotein cholesterol, high-density

lipoprotein cholesterol, triglycerides, body mass index, smoking, DM, and family history of premature CHD (model 2). We also included a separate model (model 3) adjusting only for the Framingham Risk Score. All statistical analyses were performed using STATA version 10.0 (Austin, TX), and a probability value of <0.05 was considered statistically significant.

Results

Baseline Characteristics

We evaluated a total of 1004 individuals. Baseline characteristics according to CRP groups are listed in Table 1. Mean age was 48.6±9.3 years (64% men), and body mass index was 24.1±3 kg/m² overall and higher in the high CRP group. Compared with subjects in the low-normal CRP group, those in the high CRP category were more frequently male (74% versus 56%), smokers (44% versus 29%), hypertensive (24% versus 16%), diabetic (14% versus 7%), and had higher levels of both LDL-C (123±34 versus 117±31 mg/dL) and triglycerides (153±100 versus 120±77 mg/dL).

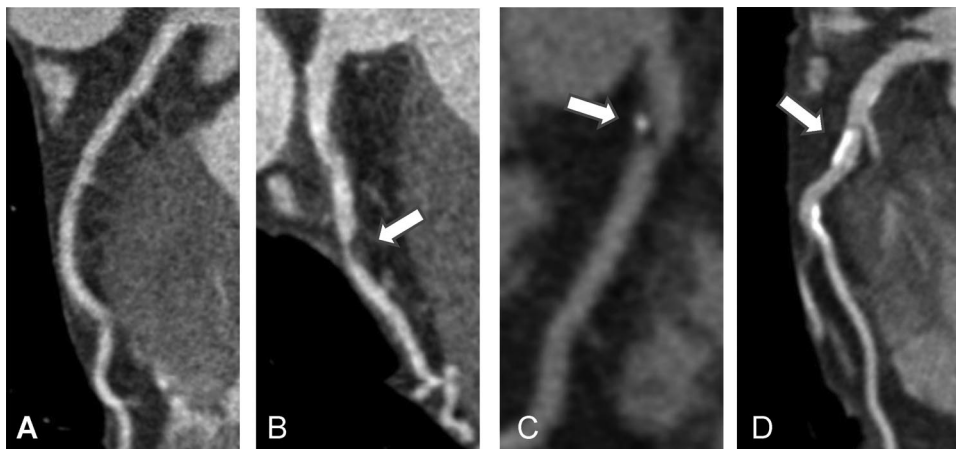


Figure 1. Examples of CCTA images demonstrating the plaque subtypes analyzed. **A**, Normal; **B**, Non-Calcified Coronary Plaque (NCAP); **C**, Mixed-calcified Plaque (MCAP); and **D**, Calcified Coronary Plaque (CAP).

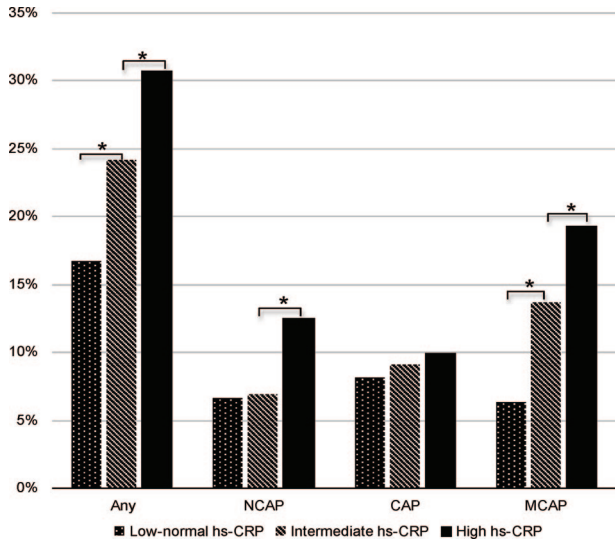


Figure 2. Percentage of individuals with any plaque subtype according to CRP category. Subjects with high levels of high-sensitivity (hs)CRP were more likely to have any plaque, NCAP, or MCAP as compared with the first and second tertiles. A statistically significant association was not found for CAP. Asterisk denotes within-group comparison probability value <0.05.

Prevalence of Coronary Plaque and Plaque Subtype

Figure 1 demonstrates the 3 coronary plaque subtypes analyzed in our study. A total of 211 patients (21%) had coronary artery disease by CCTA. The total number of subjects in our cohort with nonobstructive disease was 160 (16%), and 51 (5%) had significant stenosis. The most common plaque subtype was MCAP, followed by CAP and then NCAP (10%, 9%, and 8%, respectively). Figure 2 demonstrates the prevalence of any coronary plaque subtype according to CRP levels. Subjects with high CRP were more likely to have any plaque, MCAP ($P<0.001$), or NCAP ($P=0.024$) as compared with those with normal levels. A statistically significant association was not found for CAP.

Figure 3 demonstrates the associations between the presence of ≥ 2 coronary segments with the different plaque subtypes and CRP levels. Similar to Figure 1, a statistically significant association was found between high CRP and the presence of ≥ 2 coronary segments with any plaque, NCAP, CAP, or MCAP.

Figure 4 shows the percentage of individuals with no plaque, nonobstructive plaque, or stenosis in each CRP group. Increasing CRP was associated with greater prevalence of both nonobstructive and stenotic plaque.

Multivariable Analysis

Both the unadjusted and the multivariable logistic regression analyses for the presence of any coronary plaque and plaque subtype are listed in Table 2. Subjects were divided into groups according to CRP levels, and all analyses were performed using the low-normal CRP group as the reference category. Subjects with high CRP were observed to be at increased risk for the presence of any plaque type in the fully adjusted model (odds ratio [OR], 1.66; 95% confidence interval [CI], 1.08 to 2.56). Similar results were obtained after adjusting for the Framingham Risk Score (model 3).

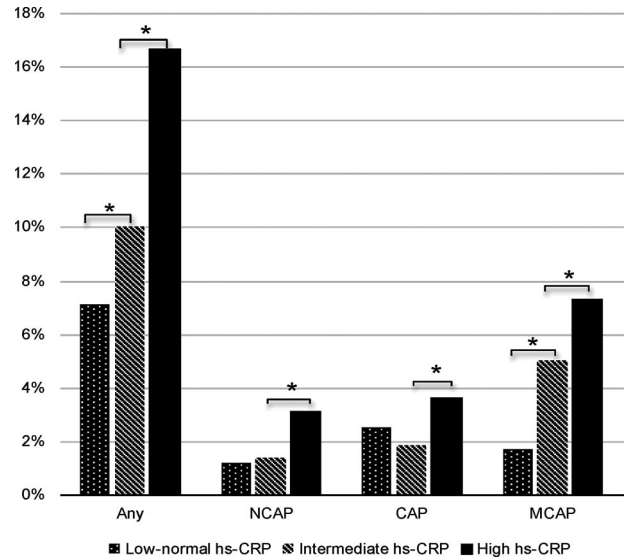


Figure 3. Percentage of individuals with ≥ 2 segments with a coronary plaque subtype according to CRP category. Subjects with high levels of high-sensitivity (hs)CRP were more likely to have ≥ 2 coronary segments with any plaque, NCAP, CAP, or MCAP. Asterisk denotes within-group comparison probability value <0.05.

When examining the presence of a specific plaque subtype, subjects with high CRP had an increased risk for the presence of MCAP for both the unadjusted and the adjusted values. (OR for the fully adjusted model, 2.81; 95% CI, 1.62 to 4.89). No difference was observed in the risk for NCAP or CAP. Similar results were obtained after adjusting for the Framingham Risk Score (model 3).

The results of the unadjusted and the multivariable logistic regression analyses for the presence of ≥ 2 segments with coronary plaque are listed in Table 3. In both the unadjusted and fully adjusted models, subjects with

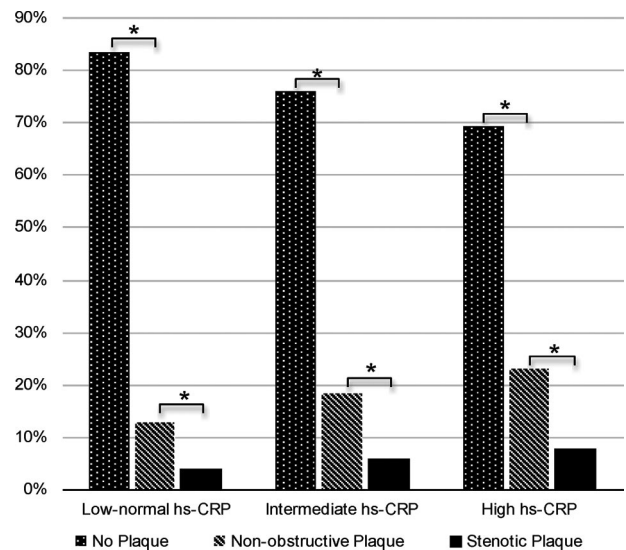


Figure 4. Percentage of individuals with no plaque, nonobstructive plaque, or stenosis, according the CRP category. Increasing levels of high-sensitivity (hs)CRP was associated with greater prevalence of both nonobstructive and stenotic plaque. Asterisk denotes within-group comparison probability value <0.05.

Table 2. Presence of Coronary Plaque and Individual Plaque Subtype

Presence of Coronary Plaque	(No. Plaques/ No. Patients)	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Any plaque type					
Low-normal CRP	99/592	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Intermediate CRP	53/220	1.58 (1.08, 2.31)	1.26 (0.83, 1.91)	1.15 (0.75, 1.77)	1.35 (0.91, 2.00)
High CRP	59/192	2.21 (1.52, 3.21)	1.81 (1.19, 2.74)	1.66 (1.08, 2.56)	1.63 (1.09, 2.44)
Noncalcified					
Low-normal CRP	39/592	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Intermediate CRP	15/220	1.04 (0.56, 1.92)	0.82 (0.44, 1.54)	0.76 (0.40, 1.44)	0.90 (0.48, 1.69)
High CRP	24/192	2.03 (1.18, 3.47)	1.60 (0.92, 2.78)	1.47 (0.83, 2.61)	1.54 (0.88, 2.70)
Mixed					
Low-normal CRP	37/592	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Intermediate CRP	30/220	2.37 (1.42, 3.94)	1.97 (1.15, 3.39)	1.72 (0.97, 3.02)	2.05 (1.21, 3.46)
High CRP	37/192	3.58 (2.20, 5.84)	3.09 (1.83, 5.22)	2.81 (1.62, 4.89)	2.61 (1.55, 4.37)
Calcified					
Low-normal CRP	48/592	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Intermediate CRP	20/220	1.13 (0.66, 1.96)	0.85 (0.48, 1.52)	0.80 (0.44, 1.45)	0.95 (0.54, 1.67)
High CRP	19/192	1.24 (0.71, 2.17)	0.92 (0.51, 1.67)	0.85 (0.46, 1.56)	0.84 (0.47, 1.53)

Model 1: Adjusted for age and sex.

Model 2: Adjusted for age, sex, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, body mass index, smoking, DM, and family history of premature CHD.

Model 3: Adjusted for the Framingham Risk Score.

high CRP were observed to be at increased risk for the presence of ≥ 2 segments of any plaque type (fully adjusted OR, 2.03; 95% CI, 1.15 to 3.57). Similar results were obtained after adjusting for the Framingham Risk Score (model 3).

When examining for the presence of ≥ 2 segments of a specific plaque subtype, subjects with high CRP had an in-

creased risk for the presence of MCAP for both the unadjusted and the fully adjusted models. (OR for the adjusted model, 3.78; 95% CI, 1.49 to 9.55). No difference was observed in the risk for NCAP or CAP. Similar results were obtained after adjusting for the Framingham Risk Score (model 3).

The results of the ordinal regression analyses for an increasing burden of obstructive disease are shown in Table 4. In both the

Table 3. Burden of Coronary Plaque and Individual Plaque Subtype

Presence of Coronary Plaque	(No. Plaque/ No. Patients)	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Any plaque type					
Low-normal CRP	42/592	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Intermediate CRP	23/220	1.46 (0.85, 2.50)	1.11 (0.62, 2.00)	1.03 (0.56, 1.89)	1.20 (0.69, 2.11)
High CRP	32/192	2.62 (1.60, 4.29)	2.18 (1.27, 3.74)	2.03 (1.15, 3.57)	1.79 (1.06, 3.04)
Noncalcified					
Low-normal CRP	7/592	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Intermediate CRP	3/220	1.16 (0.30, 4.51)	1.01 (0.26, 3.98)	0.87 (0.21, 3.56)	0.99 (0.25, 3.89)
High CRP	6/192	2.70 (0.89, 8.12)	2.33 (0.76, 7.11)	1.97 (0.61, 6.37)	1.91 (0.61, 6.04)
Mixed					
Low-normal CRP	10/592	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Intermediate CRP	11/220	3.06 (1.28, 7.32)	2.42 (0.97, 6.00)	2.53 (0.98, 6.57)	2.54 (1.04, 6.20)
High CRP	14/192	4.58 (2.00, 10.48)	3.81 (1.60, 9.10)	3.78 (1.49, 9.55)	2.85 (1.19, 6.82)
Calcified					
Low-normal CRP	15/592	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Intermediate CRP	4/220	0.71 (0.23, 2.17)	0.50 (0.16, 1.57)	0.48 (0.15, 1.55)	0.60 (0.20, 1.86)
High CRP	7/192	1.46 (0.58, 3.62)	1.06 (0.41, 2.76)	1.05 (0.40, 2.79)	1.02 (0.39, 2.64)

Model 1: Adjusted for age and sex.

Model 2: Adjusted for age, sex, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, body mass index, smoking, DM and family history of premature CHD.

Model 3: Adjusted for the Framingham Risk Score.

Table 4. Ordinal Regression Analyses for Increasing Burden of Obstructive Coronary Artery Disease by CRP Levels

CRP Categories	(No. None/No. Nonobstructive/No. Stenotic Plaque)	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Low-normal CRP	493/76/23	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Intermediate CRP	167/40/13	1.58 (1.09, 2.30)	1.28 (0.85, 1.92)	1.17 (0.77, 1.78)	1.37 (0.93, 2.02)
High CRP	133/44/15	2.20 (1.52, 3.19)	1.86 (1.24, 2.78)	1.71 (1.13, 2.58)	1.66 (1.12, 2.46)

Model 1: Adjusted for age and sex.

Model 2: Adjusted for age, sex, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, body mass index, smoking, DM, and family history of premature CHD.

Model 3: Adjusted for the Framingham Risk Score.

unadjusted and the fully adjusted models, compared with subjects with low-normal CRP, those with high CRP were at increased odds for an increasing burden of obstructive disease (OR for the adjusted model, 1.71; 95% CI, 1.13 to 2.58).

Table 5 shows the results of multivariable linear regression analyses for the association between increasing CRP and the extent of any plaque or plaque subtype. β coefficients represent the predicted increase of involved coronary segments associated with intermediate and high CRP levels, with low-normal CRP values as the reference category. In the unadjusted model, high CRP was associated with greater number of coronary segments with any plaque as well as with all the individual plaque subtypes. In the fully adjusted model, high CRP was only associated with the extent of any plaque and with MCAP.

In subgroup analysis, we explored the association between increasing CRP levels and the presence of exclusively noncalcified plaque. In both the unadjusted and the age- and sex-adjusted models, high CRP was associated with a greater odds of NCAP as compared with subjects with low-normal

CRP (OR for the age- and sex-adjusted models, 1.80; 95% CI, 1.02 to 3.19). This association was no longer statistically significant after fully adjusting for other confounders (model 2).

Discussion

To the best of our knowledge, this is the first study to systematically examine the association between CRP and coronary plaque subtypes using CCTA in a large cohort of asymptomatic individuals. We were able to demonstrate that elevated levels of CRP are associated with (1) increased risk for the presence of any plaque and MCAP but not NCAP or CAP; (2) increased risk for the presence of ≥ 2 segments of MCAP; and (3) significant coronary stenosis.

Inflammation is an important contributor to atherosclerosis. Elevated CRP, a marker of inflammation, has been clearly related to poor cardiovascular outcomes.^{25–30} One of the mechanisms by which this increased risk is thought to occur involves increased plaque vulnerability. In an effort to directly establish the relationship between in situ plaque CRP and plaque vulnerability, Ishikawa et al³⁵ demonstrated

Table 5. Univariate and Multivariable Linear Regression Demonstrating Association of CRP With Extent of Any, Noncalcified, Calcified, and Mixed Plaques

CRP Category	Plaque Extent; Mean (SD)	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Any plaque type					
Intermediate CRP	0.41 (0.89)	0.13 (−0.01, 0.27)	0.02 (−0.11, 0.15)	0.00 (−0.13, 0.13)	0.05 (−0.08, 0.18)
High CRP	0.65 (1.21)	0.36 (0.21, 0.51)*	0.23 (0.09, 0.37)*	0.21 (0.07, 0.35)*	0.21 (0.07, 0.35)*
Noncalcified					
Intermediate CRP	0.09 (0.38)	0.01 (−0.05, 0.07)	−0.01 (−0.08, 0.05)	−0.02 (−0.09, 0.04)	−0.01 (−0.07, 0.05)
High CRP	0.18 (0.57)	0.10 (0.03, 0.16)*	0.07 (0.00, 0.14)	0.06 (−0.01, 0.13)	0.06 (0.00, 0.06)
Mixed					
Intermediate CRP	0.20 (0.58)	0.12 (0.04, 0.20)*	0.08 (0.00, 0.15)	0.07 (−0.01, 0.14)	0.08 (0.01, 0.16)*
High CRP	0.30 (0.72)	0.22 (0.14, 0.30)*	0.17 (0.09, 0.24)*	0.16 (0.08, 0.24)*	0.15 (0.07, 0.23)*
Calcified					
Intermediate CRP	0.12 (0.39)	−0.01 (−0.08, 0.07)	−0.05 (−0.12, 0.02)	−0.05 (−0.12, 0.03)	−0.03 (−0.11, 0.04)
High CRP	0.17 (0.61)	0.05 (−0.03, 0.13)	0.00 (−0.08, 0.07)	0.00 (−0.08, 0.08)	0.00 (−0.08, 0.08)

β indicates beta-estimate: Predicted increase in number of segments with plaque.

*Statistically significant.

Reference group is low-normal CRP.

Model 1: Adjusted for age and sex.

Model 2: Adjusted for age, sex, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, body mass index, smoking, DM, and family history of premature CHD.

Model 3: Adjusted for the Framingham Risk Score.

greater amounts of CRP-stained cells in samples from culprit lesions of unstable angina patients as compared with lesions from patients with stable angina. They also found an increased rate of restenosis on follow-up angiography in the elevated CRP group, suggesting that CRP might be related to plaque vulnerability. Providing further support for this hypothesis, in a postmortem study, Burke et al³⁶ demonstrated that elevated serum CRP correlated with an increased number of thin-cap fibroatheromas (TCFA), a key component of vulnerable plaque.

The relationship between coronary plaque subtypes as evidenced by CCTA and cardiovascular outcomes has also been examined. In a group of 71 patients with acute coronary syndrome (ACS) or stable angina, Motoyama et al³⁷ demonstrated an association between NCAP and the occurrence of ACS. In contrast to our study, they did not have a separate MCAP group and only classified plaques as either CAP or NCAP. Mixed calcified plaque has also been associated to increased cardiovascular risk. Lin et al³⁸ showed that MCAP predicted severely abnormal perfusion abnormalities by single-photon emission CT and Pundziute et al³⁹ showed that MCAP was a significant predictor for coronary events.

Further supporting the notion that NCAP and MCAP are associated with increased cardiovascular events, Pundziute et al¹⁵ demonstrated that CAP was more prevalent in stable coronary disease, whereas NCAP and MCAP were predominantly found in patients presenting with ACS. Additionally, they found that TCFA were more prevalent in those presenting with ACS, and, most importantly, they showed that TCFA were more frequently observed in lesions classified as MCAP. These results suggest that MCAP might be associated with an increased cardiovascular risk due to the increase burden of TCFA. Finally, in a population of symptomatic subjects, Hauleiter et al⁴⁰ showed that persons with NCAP had increased levels of CRP as compared with those with CAP. Unlike their study, ours included a prespecified MCAP group, and our patient population was asymptomatic.

It has been clearly demonstrated that both elevated levels of CRP and specific plaque subtypes are associated to poor cardiovascular outcomes. Understanding how CRP and vulnerable plaques are related and using imaging techniques to assess this relationship may enable the identification of vulnerable patients.

In this regard, Avanzas et al⁴¹ found that elevated CRP levels correlated with the presence of multiple angiographically complex coronary stenosis, and Tanaka et al⁴² determined that elevated levels of CRP were associated with plaque rupture in patients presenting with ACS. Although the relationship between CRP and plaque subtypes has been studied using traditional angiography and intravascular ultrasound, our study is the first to assess this relationship by means of CCTA in a large group of asymptomatic individuals.

The potential clinical utility of identifying asymptomatic patients with high-risk coronary plaque subtypes does not necessarily justify the contrast and radiation exposure associated with CCTA. Unlike CCTA, measuring CRP is relatively safe, and, although not currently recommended for all asymptomatic subjects at low risk for cardiovascular events, we demonstrated that elevated CRP levels allowed for the

identification of high-risk coronary plaques in an asymptomatic population. Other studies are necessary to determine the efficacy and cost-effectiveness of measuring CRP in all asymptomatic subjects. Our results should be considered hypothesis-generating and should not be used to justify the use of CCTA in an asymptomatic patient population. Our findings suggest that the increased risk observed in persons with higher levels of CRP could be due, at least in part, to a greater burden of MCAP, a plaque subtype frequently associated with determinants of plaque instability.

In our study, the mean radiation exposure of CCTA was 13.2 ± 0.8 mSv. Although there is a small chance (1 in 2000) of development of a fatal cancer as the result of a 10-mSv CT study,⁴³ other studies have demonstrated that 64-slice MDCT is associated with a nonnegligible risk of cancer.⁴⁴ Additionally, with the advent of new MDCT technology, the radiation dose for CTA could be minimized to the level of background radiation (<3 mSv).⁴⁵

Our study has several limitations. This analysis is one of a cross-sectional nature, so it is not possible to make causal inferences. We studied asymptomatic subjects; therefore our results may not apply to symptomatic individuals. Because our patients were self-referred, there is a possibility of selection bias. Although the internal validity of our results should not be affected by selection bias, a population-based study design would be expected to have less selection bias and improved external validity. Additionally, our cohort is composed exclusively of Korean individuals, which affects the generalizability of our results (for example, our subjects had lower body mass index values than the general US population). Because we categorized coronary plaque subtypes into NCAP, MCAP, or CAP as opposed to quantifying in a continuous manner the burden of calcified and noncalcified plaque components, there is a chance of misclassification. Finally, because plaque was modeled in various manners and we used a 5% significance criterion, we cannot completely rule out the possibility of some false-positive results.

Despite these limitations, it is important to note that the way in which we categorized plaque subtypes has been accepted in the literature.^{38,39} We are not aware of a mechanism to directly quantify the noncalcified component of plaques. Because of the current radiation exposure associated to CCTA, the administration of a contrast agent, and the lack of imaging protocol standardization in clinical practice, there are no data justifying the use of CCTA in asymptomatic patients. We do fully support the use of CCTA as a research tool to better understand the significance of the different coronary plaque subtypes as well as other vessel changes observed with occult coronary artery disease. We believe that identifying these characteristics may help improve risk stratification efforts.

Conclusions

In an asymptomatic population, increasing levels of CRP are associated with the prevalence of any plaque and MCAP, the extent of MCAP, and the presence of significant coronary stenosis. Our study results suggest that the increased cardiovascular risk associated with increased levels of CRP could be due in part to a higher prevalence of MCAP, which has

been shown to possess some of the key elements observed in unstable plaques. The identification of MCAP using CCTA could potentially lead to better risk stratification. Future prospective studies are needed to establish a causal association between the presence of MCAP and acute coronary events.

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Disclosures

None.

References

- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. 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.
- Michos ED, Nasir K, Braunstein JB, Rumberger JA, Budoff MJ, Post WS, Blumenthal RS. Framingham risk equation underestimates subclinical atherosclerosis risk in asymptomatic women. *Atherosclerosis*. 2006;184:201–206.
- Schlendorf KH, Nasir K, Blumenthal RS. Limitations of the Framingham risk score are now much clearer. *Prev Med*. 2009;48:115–116.
- Akosah KO, Schaper A, Cogbill C, Schoenfeld P. Preventing myocardial infarction in the young adult in the first place: how do the National Cholesterol Education Panel III Guidelines Perform? *J Am Coll Cardiol*. 2003;41:1475–1479.
- Michos ED, Vasamreddy CR, Becker DM, Yanek LR, Moy TF, Fishman EK, Becker LC, Blumenthal RS. Women with a low Framingham Risk Score and a family history of premature coronary heart disease have a high prevalence of subclinical coronary atherosclerosis. *Am Heart J*. 2005;150:1276–1281.
- Budoff MJ, Achenbach S, Blumenthal RS, Carr JJ, Goldin JG, Greenland P, Guerci AD, Lima JAC, Rader DJ, Rubin GD, Shaw LJ, Wiegers SE. Intervention AHACoCIa, Intervention AHACoCRa, American Heart Association Committee on Cardiac Imaging CoCC. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and committee on Cardiac Imaging, Council on Clinical Cardiology. *Circulation*. 2006;114:1761–1791.
- Greenland P, Bonow RO, Brundage BH, Budoff MJ, Eisenberg MJ, Grundy SM, Lauer MS, Post WS, Raggi P, Redberg RF, Rodgers GP, Shaw LJ, Taylor AJ, Weintraub WS, Harrington RA, Abrams J, Anderson JL, Bates ER, Grines CL, Hlatky MA, Lichtenberg RC, Lindner JR, Pohost GM, Schofield RS, Shubrooks SJ Jr, Stein JH, Tracy CM, Vogel RA, Wesley DJ. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to update the 2000 expert consensus document on electron beam computed tomography). *Circulation*. 2007;115:402–426.
- Raggi P, Gongora MC, Gopal A, Callister TQ, Budoff M, Shaw LJ. Coronary artery calcium to predict all-cause mortality in elderly men and women. *J Am Coll Cardiol*. 2008;52:17–23.
- 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.
- Bluemke DA, Achenbach S, Budoff M, Gerber TC, Gersh B, Hillis LD, Hundley WG, Manning WJ, Printz BF, Stuber M, Woodard PK. Noninvasive coronary artery imaging: magnetic resonance angiography and multidetector computed tomography angiography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention, and the Councils on Clinical Cardiology and Cardiovascular Disease in the Young. *Circulation*. 2008;118:586–606.
- Leber AW, Becker A, Knez A, von Ziegler F, Sirol M, Nikolaou K, Ohnesorge B, Fayad ZA, Becker CR, Reiser M, Steinbeck G, Boekstegers P. Accuracy of 64-slice computed tomography to classify and quantify plaque volumes in the proximal coronary system: a comparative study using intravascular ultrasound. *J Am Coll Cardiol*. 2006;47:672–677.
- Ropers D, Rixe J, Anders K, Kuttner A, Baum U, Bautz W, Daniel WG, Achenbach S. Usefulness of multidetector row spiral computed tomography with 64- x 0.6-mm collimation and 330-ms rotation for the noninvasive detection of significant coronary artery stenoses. *Am J Cardiol*. 2006;97:343–348.
- Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, Paul N, Clouse ME, Shapiro EP, Hoe J, Lardo AC, Bush DE, de Roos A, Cox C, Brinker J, Lima JA. Diagnostic performance of coronary angiography by 64-row ct. *N Engl J Med*. 2008;359:2324–2336.
- Ostrom MP, Gopal A, Ahmadi N, Nasir K, Yang E, Kakadiaris I, Flores F, Mao SS, Budoff MJ. Mortality incidence and the severity of coronary atherosclerosis assessed by computed tomography angiography. *J Am Coll Cardiol*. 2008;52:1335–1343.
- Pundziute G, Schuijf J, Jukema J, Decramer I, Sarno G, Vanhoenacker P, Boersma E, Reiber J, Schalij M, Wijns W, Bax J. Evaluation of plaque characteristics in acute coronary syndromes: Non-invasive assessment with multi-slice computed tomography and invasive evaluation with intravascular ultrasound radiofrequency data analysis. *Eur Heart J*. 2008;29:2373.
- Kizer JR, Krauser DG, Rodeheffer RJ, Burnett JC, Okin PM, Roman MJ, Umans JG, Best LG, Lee ET, Devereux RB. Prognostic value of multiple biomarkers in American Indians free of clinically overt cardiovascular disease (from the Strong Heart Study). *Am J Cardiol*. 2009;104:247–253.
- van Werkhoven JM, Schuijf JD, Gaemperli O, Jukema JW, Kroft LJ, Boersma E, Pazhenkottil A, Valenta I, Pundziute G, de Roos A, van der Wall EE, Kaufmann PA, Bax JJ. Incremental prognostic value of multi-slice computed tomography coronary angiography over coronary artery calcium scoring in patients with suspected coronary artery disease. *Eur Heart J*. 2009;30:2622–2629.
- Leber AW, Knez A, White CW, Becker A, von Ziegler F, Muehling O, Becker C, Reiser M, Steinbeck G, Boekstegers P. Composition of coronary atherosclerotic plaques in patients with acute myocardial infarction and stable angina pectoris determined by contrast-enhanced multislice computed tomography. *Am J Cardiol*. 2003;91:714–718.
- 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.
- Braunwald E. Noninvasive detection of vulnerable coronary plaques: locking the barn door before the horse is stolen. *J Am Coll Cardiol*. 2009;54:58–59.
- Hoffmann U, Moselewski F, Nieman K, Jang I-K, Ferencik M, Rahman AM, Cury RC, Abbara S, Joneidi-Jafari H, Achenbach S, Brady TJ. Noninvasive assessment of plaque morphology and composition in culprit and stable lesions in acute coronary syndrome and stable lesions in stable angina by multidetector computed tomography. *J Am Coll Cardiol*. 2006;47:1655–1662.
- Calabro P, Willerson JT, Yeh ET. Inflammatory cytokines stimulated C-reactive protein production by human coronary artery smooth muscle cells. *Circulation*. 2003;108:1930–1932.
- Verma S, Wang CH, Li SH, Dumont AS, Fedak PJ, Badiwala MV, Dhillon B, Weisel RD, Li RK, Mickle DA, Stewart DJ. A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. *Circulation*. 2002;106:913–919.
- Danenberg HD, Szalai AJ, Swaminathan RV, Peng L, Chen Z, Seifert P, Fay WP, Simon DI, Edelman ER. Increased thrombosis after arterial injury in human c-reactive protein-transgenic mice. *Circulation*. 2003;108:512–515.
- Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of c-reactive protein, fibrinogen, homocysteine, lipoprotein (a), and standard cholesterol screening as predictors of peripheral arterial disease. *JAMA*. 2001;285:2481–2485.
- Ridker PM. Clinical application of c-reactive protein for cardiovascular disease detection and prevention. *Circulation*. 2003;107:363–369.
- Danesh J, Wheeler J, Hirschfield G, Eda S, Eiriksdottir G, Rumley A, Lowe G, Pepys M, Gudnason V. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med*. 2004;350:1387.

28. Cushman M, Arnold AM, Psaty BM, Manolio TA, Kuller LH, Burke GL, Polak JF, Tracy RP. C-reactive protein and the 10-year incidence of coronary heart disease in older men and women: the cardiovascular health study. *Circulation*. 2005;112:25–31.
29. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds risk score. *JAMA*. 2007;297:611–619.
30. Ridker PM, Paynter NP, Rifai N, Gaziano JM, Cook NR. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds risk score for men. *Circulation*. 2008;118:2243–2251.
31. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ. Group JTS. Reduction in c-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the Jupiter trial. *Lancet*. 2009;373:1175–1182.
32. Choi E-K, Choi SI, Rivera JJ, Nasir K, Chang S-A, Chun EJ, Kim H-K, Choi D-J, Blumenthal RS, Chang H-J. Coronary computed tomography angiography as a screening tool for the detection of occult coronary artery disease in asymptomatic individuals. *J Am Coll Cardiol*. 2008;52:357–365.
33. Lawlor DA, Adamson J, Ebrahim S. Performance of the who rose angina questionnaire in post-menopausal women: are all of the questions necessary? *J Epidemiol Community Health*. 2003;57:538–541.
34. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, McGoon DC, Murphy ML, Roe BB. A reporting system on patients evaluated for coronary artery disease: report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation*. 1975;51:5–40.
35. Ishikawa T, Hatakeyama K, Imamura T, Date H, Shibata Y, Hikichi Y, Asada Y, Eto T. Involvement of c-reactive protein obtained by directional coronary atherectomy in plaque instability and developing restenosis in patients with stable or unstable angina pectoris. *Am J Cardiol*. 2003;91:287–292.
36. Burke AP, Tracy RP, Kolodgie F, Malcom GT, Zieske A, Kutys R, Pestaner J, Smialek J, Virmani R. Elevated c-reactive protein values and atherosclerosis in sudden coronary death: association with different pathologies. *Circulation*. 2002;105:2019–2023.
37. 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.
38. Lin F, Shaw LJ, Berman DS, Callister TQ, Weinsaft JW, Wong FJ, Szulc M, Tandon V, Okin PM, Devereux RB, Min JK. Multidetector computed tomography coronary artery plaque predictors of stress-induced myocardial ischemia by SPECT. *Atherosclerosis*. 2008;197:700–709.
39. Pundziute G, Schuijf JD, Jukema JW, Boersma E, de Roos A, van der Wall EE, Bax JJ. Prognostic value of multislice computed tomography coronary angiography in patients with known or suspected coronary artery disease. *J Am Coll Cardiol*. 2007;49:62–70.
40. Hausleiter J, Meyer T, Hadamitzky M, Kastrati A, Martinoff S, Schomig A. Prevalence of noncalcified coronary plaques by 64-slice computed tomography in patients with an intermediate risk for significant coronary artery disease. *J Am Coll Cardiol*. 2006;48:312–318.
41. Avanzas P, Arroyo-Espiguero R, Cosin-Sales J, Aldama G, Pizzi C, Quiles J, Kaski JC. Markers of inflammation and multiple complex stenoses (pancoronary plaque vulnerability) in patients with non-ST segment elevation acute coronary syndromes. *Heart*. 2004;90:847–852.
42. Tanaka A, Shimada K, Sano T, Namba M, Sakamoto T, Nishida Y, Kawarabayashi T, Fukuda D, Yoshikawa J. Multiple plaque rupture and c-reactive protein in acute myocardial infarction. *J Am Coll Cardiol*. 2005;45:1594–1599.
43. Mieres JH, Shaw LJ, Arai A, Budoff MJ, Flamm SD, Hundley WG, Marwick TH, Mosca L, Patel AR, Quinones MA, Redberg RF, Taubert KA, Taylor AJ, Thomas GS, Wenger NK. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. *Circulation*. 2005;111:682–696.
44. Einstein AJ, Henzlova MJ, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. *JAMA*. 2007;298:317–323.
45. Abada HT, Larchez C, Daoud B, Sigal-Cinqualbre A, Paul JF. MDCT of the coronary arteries: feasibility of low-dose CT with ECG-pulsed tube current modulation to reduce radiation dose. *AJR Am J Roentgenol*. 2006;186:S387–S390.

CLINICAL PERSPECTIVE

Coronary computed tomography angiography (CCTA) has been shown to be a sensitive and specific tool for the detection of significant coronary stenosis and has also allowed for the visualization and characterization of coronary plaque subtypes. Several studies have demonstrated that CCTA can provide prognostic information in patients with suspected coronary heart disease. Studies have also provided insight as to what specific plaque subtypes and characteristics might be associated with poor outcomes. Concurrently, high-sensitivity C-reactive protein (hsCRP) has also been proposed as a method of identifying individuals at higher cardiovascular risk and has been shown to allow for the independent and improved risk stratification beyond traditional risk scoring systems. We sought to analyze the relationship between elevated levels of hsCRP and plaque subtypes as identified by CCTA. Increasing levels of hsCRP were found to be associated with the prevalence and extent of any mixed calcified plaque and the presence of significant coronary stenosis. Our results suggest that the increased cardiovascular risk associated with increased levels of hsCRP could be due, at least in part, to a higher prevalence of mixed calcified plaque, which has been shown to have some of the key elements observed in unstable coronary plaques.