Relation of C-reactive protein to coronary plaque characteristics on grayscale, radiofrequency intravascular ultrasound, and cardiovascular outcome

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ABSTRACT

The relation between C-reactive protein (CRP) and coronary atherosclerosis is not fully understood. This study aims to investigate the associations between high-sensitivity CRP, coronary plaque burden and presence of high-risk coronary lesions as measured by intravascular ultrasound (IVUS), as well as 1-year cardiovascular outcome. Between 2008 and 2011, grayscale and virtual histology IVUS imaging of a non-culprit coronary artery was performed in 581 patients who underwent coronary angiography for acute coronary syndrome (ACS) or stable angina pectoris. Primary endpoint consisted of 1-year major adverse cardiac events (MACE), defined as all-cause mortality, ACS or unplanned coronary revascularization. After adjustment for established cardiac risk factors, baseline CRP levels were independently associated with higher coronary plaque burden (p=0.002) and plaque volume (p=0.002) in the imaged coronary segment. CRP was also independently associated with presence of large lesions (plaque burden ≥70%; p=0.030), but not with presence of stenotic lesions (minimal luminal area ≤4.0mm^2; p=0.62) or IVUS virtual histology-derived thin-cap fibroatheroma (VH-TCFA) lesions (p=0.36). Cumulative incidence of 1-year MACE was 9.7%. CRP levels >3mg/L were independently associated with a higher incidence of MACE (HR2.17, 95%CI 1.01-4.67, p=0.046) and of all-cause mortality and ACS only (HR3.58, 95%CI 1.04-13.0, p=0.043), when compared to CRP levels <1mg/L. In conclusion, in patients undergoing coronary angiography, high-sensitivity CRP is a marker of coronary plaque burden, but is not related to the presence of VH-TCFA lesions and stenotic lesions. CRP levels of >3 mg/L are predictive for adverse cardiovascular outcome at 1 year.

INTRODUCTION

C-reactive protein (CRP) is a prognostic marker of cardiovascular outcome in patients with stable coronary artery disease and patients with acute coronary syndrome (ACS).[1-3] Although CRP has also been postulated to reflect the extent of coronary atherosclerosis as well as plaque vulnerability, these relations are not yet fully understood.[4] Previous studies have only shown weak associations between CRP and the extent of coronary artery disease on angiography and the degree of coronary calcification on computed tomography.[3,5,6] Furthermore, the associations between CRP and the presence of high-risk vulnerable plaque morphology has not been investigated yet.[7] Grayscale intravascular ultrasound (IVUS) imaging of the coronary arteries allows for accurate measurement of coronary plaque burden and plaque volume, as well as identification of large or stenotic lesions.[8-10] Additionally, IVUS virtual histology (IVUS-VH) (i.e. analysis of IVUS radiofrequency backscatter), allows tissue characterization and for identification of virtual histology-derived thin-cap fibroatheroma (VH-TCFA) lesions.[8-13] This study aims to investigate the associations between high sensitivity CRP, coronary plaque burden and presence of high-risk coronary lesions (i.e. VH-TCFA lesions, lesions with large plaque burden, and stenotic lesions) as measured by grayscale and radiofrequency IVUS, as well as 1-year cardiovascular outcome.

METHODS

The design of The European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis – Intravascular Ultrasound (ATHEROREMO-IVUS) study has been described in detail elsewhere.[9,14] In brief, 581 patients who underwent diagnostic coronary angiography or percutaneous coronary intervention (PCI) for ACS or stable angina pectoris have been included between 2008 and 2011 in the Erasmus MC, Rotterdam, the Netherlands. The ATHEROREMO-IVUS study was approved by the medical ethics committee of the Erasmus MC. The study was performed in accordance with the criteria described in the declaration of Helsinki. Written informed consent was obtained from all included patients. This study is registered in ClinicalTrials.gov, number NCT01789411.

Blood samples were drawn from the arterial sheath prior to the coronary angiography procedure. The blood samples stored at temperature of –80°C within 2 hours after blood collection. CRP was measured in the stored serum samples (n=576) using a immunoturbidimetric high sensitivity assay (Roche Diagnostics Ltd., Rotkreuz, Switzerland) on the Cobas 8000 modular analyzer platform (Roche Diagnostics Ltd., Rotkreuz, Switzerland). The diagnostic range of this assay is 0.3-350 mg/L with a coefficient of variation of 1.3%

at a mean value of 2.63 mg/L. In 5 patients, serum samples were not available for CRP measurement.

Following the standard coronary angiography procedure, IVUS imaging of the most proximal part of a non-culprit coronary artery was performed. Selection of the non-culprit vessel was predefined in the study protocol. The order of preference for selection of the non-culprit vessel was: 1. left anterior descending (LAD) artery; 2. right coronary artery (RCA); 3. left circumflex (LCX) artery. All IVUS data were acquired with the Volcano s5/s5i Imaging System (Volcano Corp., San Diego, CA, USA) using a Volcano Eagle Eye Gold IVUS catheter (20 MHz). An automatic pullback system was used with a standard pull back speed of 0.5 mm per second. The baseline IVUS images were sent to an independent core laboratory (Cardialysis BV, Rotterdam, the Netherlands) for offline analysis. The core laboratory personnel were blinded for baseline patient characteristics and clinical outcomes data. The IVUS grayscale and virtual histology analyses were performed using pcVH 2.1 and qVH (Volcano Corp., San Diego, CA, USA) software.

The external elastic membrane and luminal borders were contoured for each frame (median interslice distance, 0.40 mm). Extent and phenotype of the atherosclerotic plaque were assessed. Plaque burden was defined as plaque and media cross-sectional area divided by external elastic membrane cross-sectional area (Figure 1). A coronary lesion was defined as a segment with a plaque burden of more than 40% in at least 3 consecutive frames. Using IVUS-VH, the composition of the atherosclerotic lesions was characterized into 4 different tissue types: fibrous, fibro-fatty, dense calcium and necrotic core.[12] Three types of high-risk lesions were identified: 1. VH-TCFA lesion, defined as a lesion with presence of >10% confluent necrotic core in direct contact with the lumen in at least 3 consecutive frames; 2. lesion with large plaque burden, defined as a lesion with a plaque burden of ≥70% in at least 3 consecutive frames; 3. stenotic lesion, defined as a lesion with a minimal luminal area of ≤4.0 mm^2 in at least 3 consecutive frames (Figure 1).[8-11,13]

Clinical follow-up started at inclusion and lasted 1 year. Post-discharge survival status was obtained from municipal civil registries. Post-discharge rehospitalizations were prospectively assessed during follow-up. Questionnaires focusing on the occurrence of major adverse cardiac events (MACE) were sent to all living patients. Subsequently, hospital discharge letters were obtained and treating physicians and institutions were contacted for additional information (i.e. discharge letters and coronary angiogram) whenever necessary. All events were adjudicated as related to a coronary site that was treated during the index procedure (culprit lesion related event) or as related to a coronary site that was not treated during the index procedure (non-culprit lesion related event). Events that were related to both the culprit lesion and a non-culprit site (e.g. revascularization of multiple vessels) were classified into both categories. When information was not sufficient to classify an event as either culprit lesion related or non-culprit lesion related,

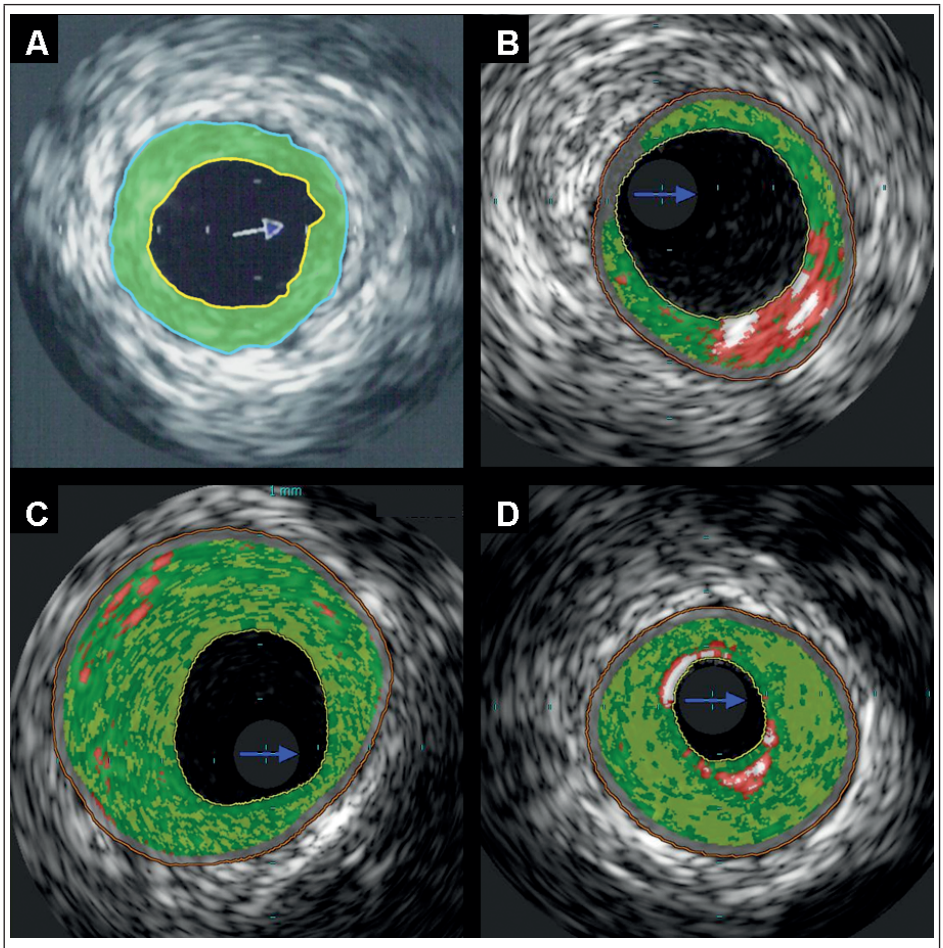

Figure 1. Measurement of plaque burden and identification of high risk lesions with intravascular ultrasound
A: Plaque burden is defined as plaque and media cross-sectional area (green) divided by external elastic membrane cross-sectional area (contoured in blue). B: Thin-cap fibroatheroma lesion, defined as a lesion with presence of >10% confluent necrotic core (red) in direct contact with the lumen. C: Lesion with plaque burden of ≥70%. D: Lesion with a minimal luminal area of ≤4.0 mm^2.

the event was classified as indeterminate. The endpoints were adjudicated by a clinical event committee that had no knowledge of the CRP and IVUS data.

The primary clinical endpoint was MACE, defined as all-cause mortality, ACS or unplanned coronary revascularization. ACS was defined as the clinical diagnosis of ST segment elevation myocardial infarction (STEMI), non-STEMI or unstable angina pectoris in accordance with the guidelines of the European Society of Cardiology.[15] Unplanned coronary revascularization was defined as unplanned repeat PCI (either culprit or non-culprit coronary artery) or coronary artery bypass grafting (CABG). The secondary end-

point was defined as the composite of all-cause mortality or ACS. Additional analyses were performed on non-culprit lesion-related and indeterminate events only (definite culprit lesion-related events were excluded in these analyses).

The distributions of the continuous variables, including CRP levels and the IVUS parameters, were tested for normality by visual examination of the histogram. CRP was not normally distributed and was therefore ln-transformed when analyzed as continuous variable. CRP levels were also categorized as low (<1 mg/L), average (1-3 mg/L) or high (>3 mg/L) according to the recommendations from the Centers for Disease Control and Prevention and the American Heart Association.[16] Categorical variables are presented as numbers and percentages. We examined associations of CRP concentration with plaque burden, plaque volume and presence of high-risk coronary lesions. Plaque volume was normalized for the imaged segment length (normalized plaque volume = plaque volume / imaged segment length * median segment length of study population). To test for trends, we used linear regression and logistic regression analyses with continuous ln-transformed CRP concentration as independent variable. Z-test for heterogeneity was performed to test for differences in effect estimates between patients admitted with and without ACS. In multivariable analyses, the variables age, gender, diabetes mellitus, hypertension, hypercholesterolemia, smoking, peripheral artery disease, history of PCI, statin use at time of hospital admission and indication for coronary angiography were considered as potential confounders (specifically: the variables age, gender, diabetes mellitus, hypertension, hypercholesterolemia and smoking represent the traditional cardiac risk factors; the variables peripheral artery disease and history of PCI represent the presence of clinically manifest atherosclerosis; statin use may modulate baseline CRP levels; and the different indications for coronary angiography represent different patient risk classes) and were therefore entered into the each multivariate model.

Patients lost to follow-up were considered at risk until the date of last contact, at which time-point they were censored. Cumulative event rates were estimated according to the Kaplan-Meier method. Cox proportional hazards regression analyses were performed to evaluate the associations between CRP and study endpoints. The final results are presented as crude and adjusted hazard ratios (HR) with 95% confidence interval (95% CI). All data were analyzed with SPSS software (SPSS 20.0, IBM corp.,Armonk,NY,USA). All statistical tests were two-tailed and p-values <0.05 were considered statistically significant.

RESULTS

Mean age of the patients was 61.5 ± 11.3 years, 76% were men, and 55% had ACS (Table 1). Mean plaque burden in the imaged coronary segment was 38.2% ± 11.5% and mean

Table 1. Baseline characteristics

Variable	Total (n=576)	C-reactive protein (mg/L) <1 (n=172)	1-3 (n=185)	>3 (n=219)	P
Age (years)	61.5 ± 11.3	61.0 ± 10.2	61.3 ± 12.0	62.1 ± 11.6	0.59
Men	435 (75.5%)	140 (81.4%)	143 (77.3%)	152 (69.4%)	0.019
Diabetes mellitus	99 (17.2%)	28 (16.3%)	30 (16.2%)	41 (18.7%)	0.75
Hypertension[a]	300 (52.1%)	93 (54.1%)	95 (51.4%)	112 (51.1%)	0.84
Hypercholesterolemia[a]	320 (55.6%)	107 (62.2%)	102 (55.1%)	111 (50.7%)	0.082
Smoker	167 (29.0%)	34 (19.8%)	56 (30.3%)	77 (35.2%)	0.003
Positive family history[b]	300 (52.1%)	99 (57.6%)	91 (49.2%)	110 (50.2%)	0.20
Previous MI	183 (31.8%)	52 (30.2%)	61 (33.0%)	70 (32.0%)	0.85
Previous coronary intervention	186 (32.3%)	62 (36.0%)	66 (35.7%)	58 (26.5%)	0.065
Previous coronary bypass	18 (3.1%)	5 (2.9%)	8 (4.3%)	5 (2.3%)	0.49
Previous stroke	26 (4.5%)	8 (4.7%)	8 (4.3%)	10 (4.6%)	0.99
Peripheral artery disease	36 (6.2%)	5 (2.9%)	15 (8.1%)	16 (7.3%)	0.091
History of renal insufficiency	32 (5.6%)	12 (7.0%)	9 (4.9%)	11 (5.0%)	0.62
History of heart failure	19 (3.3%)	6 (3.5%)	7 (3.8%)	6 (2.7%)	0.83
High sensitivity CRP (mg/L)	2.1 [0.9-5.4]				
Indication for coronary angiography					<0.001
ACS	314 (54.5%)	71 (41.3%)	90 (48.6%)	153 (69.9%)	
ST-elevation MI	164 (28.5%)	45 (26.2%)	54 (29.2%)	65 (29.7%)	
Non-ST-elevation ACS	150 (26.0%)	26 (15.1%)	36 (19.5%)	88 (40.2%)	
Stable angina pectoris	262 (45.5%)	101 (58.7%)	95 (51.4%)	66 (30.1%)	
Number of narrowed coronary arteries					0.71
None	42 (7.3%)	14 (8.1%)	10 (5.4%)	18 (8.2%)	
1	306 (53.1%)	96 (55.8%)	93 (50.3%)	117 (53.4%)	
2	167 (29.0%)	46 (26.7%)	61 (33.0%)	60 (27.4%)	
3	61 (10.6%)	16 (9.3%)	21 (11.4%)	24 (11.0%)	
PCI performed	507 (88.0%)	153 (89.0%)	163 (88.1%)	191 (87.2%)	
Imaged coronary artery					0.14
Left anterior descending	207 (35.9%)	49 (28.5%)	74 (40.0%)	84 (38.4%)	
Left circumflex	193 (33.5%)	63 (36.6%)	55 (29.7%)	75 (34.2%)	
Right coronary artery	176 (30.6%)	60 (34.9%)	56 (30.3%)	60 (27.4%)	
Segment length (mm)	44.3 [33.8-55.4]	44.6 [36.4-54.3]	42.9 [32.5-54.6]	44.4 [32.0-56.3]	0.67

Data are presented as mean ± standard deviation or as median [interquartile range].

[a] Presence of hypertension and hypercholesterolemia were defined as a clinical diagnosis of these conditions as reported by the treating physician in the medical chart.

[b] Patient-reported positive family history of ischemic heart disease.

ACS, acute coronary syndrome; CRP, C-reactive protein; MI, myocardial infarction; PCI, percutaneous coronary intervention.

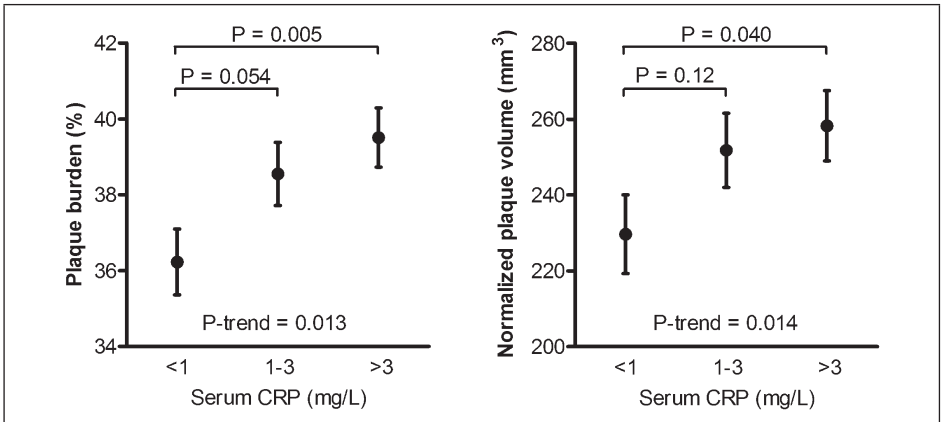

Figure 2. Association of CRP with coronary plaque burden and plaque volume of imaged coronary segment
CRP, C-reactive protein.

normalized plaque volume was 248 ± 136 mm^3. A total of 241 (42%) patients had ≥1 VH-TCFA lesion, 124 (22%) patients had ≥1 lesion with large plaque burden (plaque burden ≥70%) and 181 (31%) patients had ≥1 stenotic lesion (minimal luminal area ≤4.0 mm^2).

Higher CRP levels were associated with higher mean coronary plaque burden (p for trend = 0.013) and higher mean normalized plaque volume (p for trend = 0.015) in the imaged coronary segment (Figure 2). Higher CRP levels showed a tendency towards an association with the presence of lesions with large plaque burden (plaque burden ≥70%; p for trend = 0.093), while CRP was not associated with the presence of VH-TCFA lesions (p for trend = 0.36) or stenotic lesions (minimal luminal area ≤4.0 mm^2; p for trend = 0.62) on IVUS (Figure 3). There was no heterogeneity between ACS patients and patients with stable angina (heterogeneity on association with plaque burden p=0.45; plaque volume

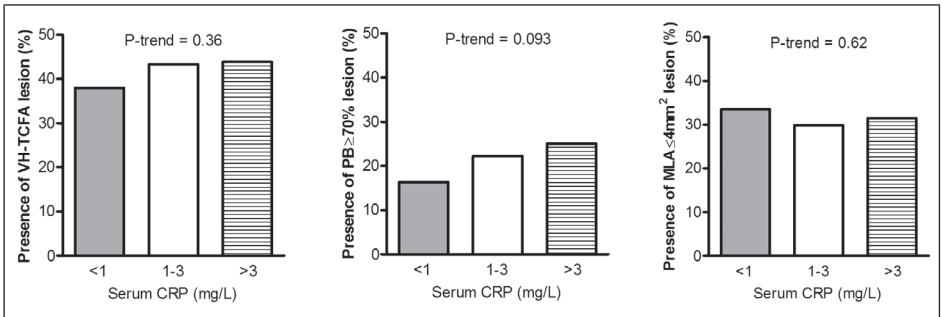

Figure 3. Association with presence of high risk coronary lesions
CRP, C-reactive protein; MLA, minimal luminal area; PB, plaque burden; VH-TCFA, virtual histology-derived thin-cap fibroatheroma.

p=0.71; lesions with large plaque burden p=0.21; VH-TCFA lesions p=0.70; stenotic lesions p=0.99) (Supplemental table 1). After adjustment for established cardiovascular risk factors, statin use, and the indication for coronary angiography, higher CRP levels remained significantly associated with higher plaque burden (per SD increase in ln-transformed CRP: β 1.49, 95% CI 0.55-2.43, p for trend = 0.002), plaque volume (per SD increase in ln-transformed CRP: β 0.080, 95% CI 0.030-0.131, p for trend = 0.002) and presence of lesions with large plaque burden (plaque burden ≥70%; OR per SD increase in CRP 1.27, 95% CI 1.02-1.58, p for trend = 0.030).

Vital status at 1-year follow-up could be acquired for 574 (99.7%) patients. Response rate of the questionnaires that were sent to all living patients was 92.4%. After 1 year of follow-up, 56 patients had experienced a MACE (Table 2). The cumulative Kaplan-Meier incidences of the 30-day, 6-month and 1-year MACE (primary endpoint) were 0.9%, 5.6%, and 9.7%, respectively. The cumulative Kaplan-Meier incidences of the 30-day, 6-month and 1-year composite of death or ACS were 0.9%, 3.8%, and 5.6%, respectively.

In univariable analysis, higher CRP levels were associated with a higher incidence of MACE during follow-up (>3 vs. <1 mg/L: 11.9% vs. 5.8%, HR 2.11, 95%CI 1.02-4.38, p=0.044; 1-3 vs <1 mg/L: 10.8% vs. 5.8, HR 1.92, 95%CI 0.90-4.10, p=0.092) (Table 3, Figure 4). There was no heterogeneity in the hazard ratio estimate between ACS patients and patients with stable angina (Supplemental table 2). Higher CRP levels were also associated with the composite of death or ACS only (>3 vs <1 mg/L: 8.7% vs. 1.7%, HR 5.13, 95%CI 1.52-17.3, p=0.009; 1-3 vs <1 mg/L: 5.4% vs. 1.7%, HR 3.14, 95%CI 0.86-11.4, p=0.082). After adjustment for established cardiovascular risk factors, statin use and the indication for coronary angiography, CRP levels of >3 mg/L remained independently

Table 2. Incidence of major adverse cardiac events (n=56)

Variable	Definite culprit lesion related events	Definite non-culprit lesion related events	Indeterminate events	Non-culprit lesion related and indeterminate events combined	All events
Composite of major adverse cardiac events	11	27	18	45[b]	56[a]
Death from any cause	1	1	16	17	18
Definite cardiac or unexplained death	1	1	6	7	8
Acute coronary syndrome	3	9	2	11	14
Myocardial infarction	2	3	2	5	7
Unplanned coronary revascularization	7	17	0	17	24
Composite of death or acute coronary syndrome	4	10	18	28[b]	32[b]

[a] Primary endpoint
[b] Secondary endpoint

Table 3. Prediction of cardiovascular outcome

Variable	Unadjusted HR (95%CI)	P	Adjusted[a] HR (95%CI)	P
MACE				
CRP 1-3 vs <1 mg/L	1.92 (0.90-4.10)	0.092	1.75 (0.80-3.81)	0.16
CRP >3 vs <1 mg/L	2.11 (1.02-4.38)	0.044	2.17 (1.01-4.67)	0.046
Composite of death or ACS				
CRP 1-3 vs <1 mg/L	3.14 (0.86-11.4)	0.082	2.23 (0.59-8.37)	0.24
CRP >3 vs <1 mg/L	5.13 (1.52-17.3)	0.009	3.68 (1.04-13.0)	0.043

[a] Adjusted for age, gender, diabetes mellitus, hypertension, hypercholesterolemia, smoking, peripheral artery disease, history of percutaneous coronary intervention, statin use and indication for coronary angiography.
ACS, acute coronary syndrome; CRP, C-reactive protein; MACE, major adverse cardiac event.

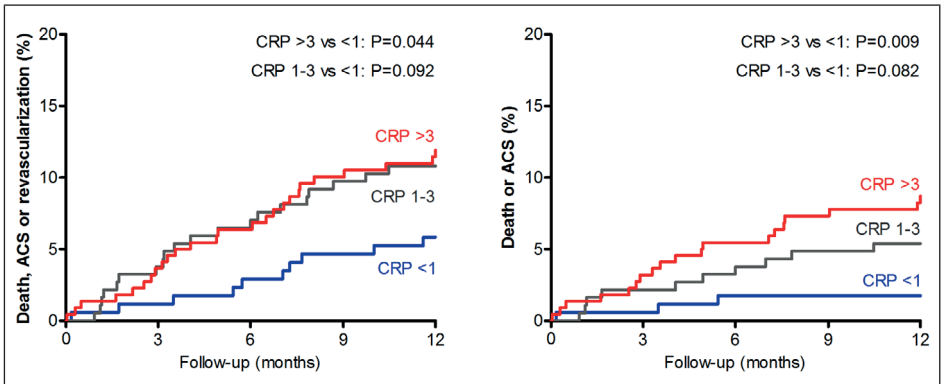

Figure 4. Prediction of cardiovascular outcome
ACS, acute coronary syndrome; CRP, C-reactive protein.

predictive for higher MACE rate (HR 2.17, 95%CI 1.01-4.67, p=0.046) and for the composite of death or ACS only (HR 3.58, 95%CI 1.04-13.0, p=0.043).

Additional analyses were performed on non-culprit lesion-related and indeterminate events only (definite culprit lesion-related events were excluded in these analyses). Although statistical significance disappeared for some associations because of the lower statistical power (less events), the estimates of the associations with non-culprit lesion-related and indeterminate events only were materially the same (Supplemental table 3).

DISCUSSION

This study investigated the associations of circulating CRP concentration with extent of coronary atherosclerosis, the presence of high-risk lesions, and the risk of adverse

cardiovascular outcome in patients who underwent coronary angiography for ACS or stable angina pectoris. The present study is the first large study that investigated the relation between high sensitivity CRP and coronary plaque characteristics using IVUS-VH. The main findings are that high CRP concentrations were associated with a higher coronary plaque burden and the presence of large lesions, but not with presence of VH-TCFA and stenotic lesions on grayscale IVUS and IVUS-VH.

Many epidemiologic studies have shown associations between elevated serum CRP concentrations and the risk of recurrent cardiovascular events among patients with established coronary artery disease, and the incidence of first cardiovascular events among individuals with cardiovascular risk factors.[16,17] In line with these findings, this study demonstrates that baseline CRP levels were predictive of a higher rate of cardiovascular events during the first year after coronary angiography in patients with known coronary artery disease.

CRP is hypothesized to reflect the extent of underlying atherosclerosis.[16,17] However, previous studies only found a weak (or even no) association with the extent of coronary artery disease on angiography and the degree of coronary artery calcification on computed tomography.[3,5,18] IVUS imaging may provide more accurate measures of the extent of coronary atherosclerosis. Our results support the hypothesis that serum CRP levels reflect the presence and extent of underlying atherosclerosis.

Other studies have suggested that CRP is a marker of plaque instability and plaque rupture.[19] This hypothesis was primarily based on the fact that CRP was found to be elevated in patients with ACS and that it displayed prognostic value for cardiovascular outcome. A population-based study also showed that high serum CRP levels were associated with the presence of mixed calcified arterial plaques on coronary computed tomography angiography, suggesting an association with plaque vulnerability.[20] In contrast, previous large studies showed conflicting results regarding to a direct pathogenic role of CRP in development of plaque vulnerability.[7,21] In the present study, we did not find an association between serum CRP and the presence of VH-TCFA lesions. A plausible explanation for our finding that CRP is still predictive for coronary events may be that CRP has a role in the evolution of stable coronary plaque to unstable plaque.[22] Furthermore, a substantial part of ACS cases are not attributable to plaque rupture, but to plaque erosion due to endothelial inflammation.[23] CRP may have a role in such endothelial inflammation as well.[24]

Patients with ACS had higher CRP levels than those with stable angina pectoris. Nevertheless, the distribution of CRP of both groups largely overlapped, so that the same standard cut-off values for CRP (<1, 1-3 and >3 mg/L) could be used for both groups. Although there was no heterogeneity on the associations with plaque characteristics and cardiovascular outcome between ACS patients and patients with stable angina pectoris, it should be acknowledged that heterogeneity is difficult to detect with the relatively small number endpoints in this study.

Some limitations of this study need to be acknowledged. Firstly, a single non-culprit coronary vessel was imaged in this study. High risk lesions (e.g. VH-TCFA lesions and stenotic lesions) elsewhere in the coronary tree could not be detected in our study. This may have lead to an underestimation of the association between CRP and the presence of high risk lesions in the coronary tree. Secondly, the spatial resolution of IVUS-VH (150µm) is insufficient to exactly replicate histopathologic definitions of a thin fibrous cap (<65µm).[25] Therefore, IVUS-VH tends to over-estimate the number of thin-cap fibroatheroma lesions. Nevertheless, the presence of VH-TCFA lesions has been shown to have prognostic information.[8-10] Thirdly, repeat intracoronary imaging with IVUS was not performed. Therefore, the dynamic nature of coronary artery lesion morphology could not be investigated. Finally, the number of endpoints was relatively small. Consequently, we may have lacked statistical power to detect small effect sizes (e.g. in presence of VH-TCFA lesions). Furthermore, we were not able to evaluate whether adding CRP to a prognostic model with conventional risk factors would result in improved risk prediction and discrimination.

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SUPPLEMENTAL TABLES

Supplemental table 1. Associations between C-reactive protein and coronary plaque characteristics stratified by patients with acute coronary syndrome and patients with stable coronary artery disease

	Total study population	ACS patients	Stable CAD patients	P for heterogeneity
Plaque burden	β 0.80 (0.17 ; 1.44) p=0.013	β 1.31 (0.42 ; 2.20) p=0.004	β 0.81 (–0.13 ; 1.76) p=0.094	0.45
Normalized plaque volume (ln-transformed)	β 0.042 (0.008 ; 0.075) p=0.014	β 0.047 (0.001 ; 0.094) p=0.046	β 0.060 (0.009 ; 0.111) p=0.022	0.71
≥1 VH-TCFA lesion	OR 1.05 (0.94-1.18) p=0.36	OR 1.01 (0.87-1.18) p=0.91	OR 1.06 (0.88-1.26) p=0.55	0.70
≥1 lesion with plaque burden ≥70%	OR 1.12 (0.98-1.29) p=0.093	OR 1.28 (1.05-1.56) p=0.016	OR 1.07 (0.87-1.30) p=0.54	0.21
≥1 lesion with minimal luminal area ≤4.0 mm^2	OR 0.97 (0.86-1.09) p=0.62	OR 0.99 (0.83-1.17) p=0.89	OR 0.99 (0.83-1.19) p=0.92	0.99

Presented results are unadjusted β per standard deviation increase in ln-transformed C-reactive protein or unadjusted odds ratio per standard deviation increase in ln-transformed C-reactive protein with 95% confidence interval.

ACS, acute coronary syndrome; CAD, coronary artery disease; CRP, C-reactive protein; VH-TCFA, virtual histology-derived thin-cap fibroatheroma.

Supplemental table 2. Associations between C-reactive protein and cardiovascular outcome stratified by patients with acute coronary syndrome and patients with stable coronary artery disease

	Total study population	ACS patients	Stable CAD patients	P for heterogeneity
MACE				
CRP 1-3 vs <1 mg/L	HR 1.92 (0.90-4.10) p=0.092	HR 9.10 (1.17-70.5) p=0.035	HR 1.07 (0.42-2.69) p=0.89	0.061
CRP >3 vs <1 mg/L	HR 2.11 (1.02-4.38) p=0.044	HR 6.71 (0.88-51.0) p=0.066	HR 2.15 (0.91-5.10) p=0.083	0.31
Composite of death or ACS				
CRP 1-3 vs <1 mg/L	HR 3.14 (0.86-11.4) p=0.082	HR 5.63 (0.69-45.8) p=0.11	HR 1.60 (0.27-9.59) p=0.61	0.37
CRP >3 vs <1 mg/L	HR 5.13 (1.52-17.3) p=0.009	HR 5.73 (0.74-44.0) p=0.094	HR 5.54 (1.15-26.7) p=0.033	0.98

Presented results are unadjusted hazard ratios with 95% confidence intervals.

ACS, acute coronary syndrome; CAD, coronary artery disease; CRP, C-reactive protein; MACE, major adverse cardiac events.

Supplemental table 3. **Association with non-culprit lesion related and indeterminate events only**				
	Unadjusted HR (95%CI)	**P**	**Adjusted* HR (95%CI)**	**P**
MACE				
CRP 1-3 vs <1 mg/L	1.91 (0.82-4.46)	0.14	1.60 (0.67-3.83)	0.29
CRP >3 vs <1 mg/L	2.12 (0.94-4.78)	0.071	1.91 (0.81-4.49)	0.14
Composite of death or ACS				
CRP 1-3 vs <1 mg/L	2.50 (0.66-9.43)	0.18	1.74 (0.44-6.85)	0.43
CRP >3 vs <1 mg/L	4.58 (1.34-15.6)	0.015	3.40 (0.94-12.3)	0.061

Definite culprit lesion-related events were excluded in the current analyses.

* Adjusted for age, gender, diabetes mellitus, hypertension, hypercholesterolemia, smoking, peripheral artery disease, history of percutaneous coronary intervention, statin use at time of hospital admission and indication for coronary angiography.

ACS, acute coronary syndrome; CRP, C-reactive protein; MACE, major adverse cardiac event.