Changes of C-reactive protein levels and coronary plaque composition after intensive statin therapy in patients with coronary artery disease

(IBIS-3 study)

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ABSTRACT

***Objective**:* To study the association between changes in serum C-reactive protein (CRP), (low density lipoprotein [LDL]) cholesterol and coronary plaque characteristics (based on invasive imaging) after 12 months of high dose rosuvastatin treatment in patients with established coronary artery disease (CAD).

***Methods**:* The IBIS-3 study is an observational study. A total of 164 patients undergoing coronary angiography (CAG) or percutaneous coronary intervention (PCI) for stable angina pectoris (SAP, N=96) or acute coronary syndrome (ACS, N=68) were treated with a high dose of rosuvastatin (40 mg daily) for 12 months. During the index procedure, intravascular ultrasound (IVUS) imaging of a non-culprit coronary segment was performed, whereas near-infrared spectroscopy (NIRS) of the same segment was performed in a subset of 118 patients. Blood samples for biomarker analyses were obtained immediately prior to the index procedure. At the end of the scheduled rosuvastatin treatment period, intracoronary imaging of the same segment and blood sampling were repeated.

***Results**:* Median (interquartile range) baseline and follow-up CRP-levels were 2.10 (0.85, 5.35) mg/L and 1.00 (0.50, 2.20) mg/L, respectively. The median change (Δ, follow-up minus baseline) in CRP was -0.45 (-2.55, 0.00) mg/L (p-value <0.001). We found no relevant differences in baseline clinical and imaging characteristics in relation to ΔCRP, except for the indication of the index procedure. Changes in CRP levels appeared considerably smaller in SAP (-0.20 [-1.10, 0.05] mg/L) than in ACS patients (-1.60 [-6.35, 0.00] mg/L). LDL-C was significantly decreased during 1-year rosuvastatin treatment, but ΔCRP was uncorrelated with ΔLCL-C (Spearman correlaton coefficient [$r_{spearman}$] -0.053 and

-0.060 in SAP and ACS, respectively). In ACS patients, but not SAP, ΔCRP was associated with IVUS-derived Δtotal plaque volume ($r_{spearman}$ 0.427), Δplaque burden ($r_{spearman}$ 0.336) and Δnecrotic core volume ($r_{spearman}$ 0.375). ΔCRP and NIRS-derived Δlipid core burden index were uncorrelated.

Conclusion: After 1 year intensive rosuvastatin therapy clinically relevant reductions in CRP levels were observed in a series of patients with established CAD. The observed CRP changes were correlated with changes in IVUS-derived plaque characteristics in ACS patients, but not in SAP. CRP changes were uncorrelated with changes in LDL-C levels. Hence, our study supports the role of in inflammation in CAD progression, but also emphasizes that the relation between blood cholesterol (LDL-C), inflammation (CRP), and extent and composition of coronary plaques is not straightforward.

INTRODUCTION

Inflammation is known to play a major role in the initiation, progression, and (in)stability of atherosclerotic plaques (1, 2). Against this background, C-reactive protein (CRP), a widely accessible, non-specific inflammatory biomarker, has been studied and proven as a risk factor for and prognostic factor in coronary artery disease (CAD) (3-7). Moreover, the recent CANTOS trial underscored the role of inflammation in the causal pathway of CAD development, as a reduction of CRP levels by canakinumab was directly accompanied by a reduction in the incidence of cardiovascular events, whereas low-density lipoprotein cholesterol (LDL-C) was not affected (4,5). The JUPITER study showed that a significant reduction of serum CRP levels can be realised by (rosuva)statin treatment in subjects with increased CAD risk (3). In JUPITER, the observed reductions in CRP (from a median of 4.2 mg/L at baseline to 1.8 mg/L at 4 year follow-up) and LDL-C levels (from 2.80 to 1.4 mmol/L), were associated with an important reduction in major adverse cardiovascular events (MACE) from 1.36 to 0.77 per 100 person-years of follow-up. On-treatment CRP levels were also associated with MACE in the SATURN study of intensive rosuvastatin or atorvastatin treatment in patients with established CAD (8). In parallel, the SATURN trialists demonstrated that the studied statin regimens resulted in a significant regression of coronary atherosclerosis, as assessed by intravascular ultrasound (IVUS) imaging at 2 year follow-up (9).

We designed the third Integrated Biomarker and Imaging Study (IBIS-3) to evaluate the effect of high-intensity (intended dose: 40 mg/day) rosuvastatin treatment for 1 year on coronary plaque characteristics in CAD patients, as assessed by multiple intravascular imaging modalities (10). Serial (radiofrequency [RF]) IVUS measurements were performed to study changes in total plaque volume and necrotic core (NC) volume, whereas near-infrared spectroscopy (NIRS) was applied to study changes in the lipid core burden index (LCBI). In IBIS-3, we observed a significant 30% reduction in LDL-C level (from a median of 2.36 mmol/L at baseline to 1.60 mmol/L at 1 year), but no reduction in NC volume (from 17.8 to 19.2 mm^3) or LCBI (from 183 to 192 in the 4 mm section with the highest values at baseline) of the study segment (11). We now studied changes in CRP levels, which we correlated with lipid levels and intracoronary imaging findings.

METHODS

Design

The IBIS-3 design details have been described elsewhere (9). Briefly, a total of 164 patients undergoing coronary angiography (CAG) or percutaneous coronary intervention (PCI) for stable angina pectoris (SAP, N=96) or acute coronary syndrome (ACS, N=68) were treated with a high dose of rosuvastatin (40 mg daily) for 12 months. During the index procedure, RF-IVUS of a non-culprit coronary segment was performed, whereas near-infrarad spectroscopy (NIRS) of the same segment was performed in a subset of 118 patients. Blood samples for biomarker analyses were obtained immediately prior to the index procedure. At the end of the scheduled rosuvastatin treatment period, intracoronary imaging of the same segment and blood sampling were repeated.

The IBIS-3 protocol was approved by the medical ethics committee of the Erasmus MC. Written informed consent was obtained from all included patients.

Intravascular imaging

Subsequent to the index procedure, invasive imaging was performed in a non-culprit coronary artery segment. This segment had to be at least 40 mm in length and without a reduction in lumen diameter >50% by online angiographic visual assessment. RF-IVUS imaging was performed with the Eagle-Eye catheter (Volcano Corporation, San Diego, CA, USA). NIRS imaging was performed with the infraredx system (InfraReDx, Burlington, Massachusetts, USA). Similar procedures were performed to

image the study segment during the follow-up visit. The RF-IVUS and NIRS images were analysed offline by an independent core research laboratory (Cardialysis BV, Rotterdam, the Netherlands) that was blinded for the timing of the measurements (baseline or follow-up), as well as for clinical and biomarker data.

Blood sampling and CRP measurements

Immediately prior to the index procedure and immediately prior to the follow-up CAG, blood samples were collected from the arterial sheath, which were transported to the clinical laboratory of the Erasmus MC within 2h for storage at -80°C. After completion of the study, high sensitivity CRP levels were batch-wise determined by using an immunoturbidimetric high sensitivity assay (Roche Diagnostics Ltd., Rotkreuz, Switzerland) on the Cobas 8000 modular analyser platform (Roche Diagnostics Ltd., Rotkreuz, Switzerland).

Study endpoints

We determined changes in CRP, cholesterol (LDL-C, HDL-C and total cholesterol [Total-C]), IVUS-derived NC volume, and NIRS-derived LCBI for the entire region of interest (ROI) ($LCBI_{ROI}$), and the 10 mm ($LCBI_{10mm}$) and 4 mm ($LCBI_{4mm}$) sections with the highest LCBI. Changes in study endpoints are reported as measurements at follow-up minus baseline values. Hence, negative values indicate a decrease over time.

Data analyses

Categorical variables are reported as numbers and percentages. Continuous variables with a normal distribution are reported as mean ± standard deviation (SD), and otherwise as median with interquartile range (IQR). Patients were stratified in tertiles according to the observed change in CRP levels. Differences in baseline clinical characteristics between these strata were evaluated by chi-square or Fisher's exact tests for categorical variables and one-way analysis of variance (ANOVA) or Kruskal-Wallis tests for continuous variables.

Correlation analyses were performed to examine the associations between changes in CRP levels and changes in cholesterol levels and intracoronary imaging characteristics. Results are presented as Spearman correlation coefficients ($r_{spearman}$). We applied (multiple) linear regression analyses to relate (changes in) CRP level with (changes in) imaging characteristics. We considered age, sex, CVD risk factors, CVD history, and the extend of CAD as potential confounders. We ran separate

analyses for SAP and ACS, since the changes in CRP levels were considerably different between these patients (see the Results section).

All statistical tests were two-tailed and p-values <0.05 were considered significant. Data were analysed with SPSS software (SPSS 23.0 IBM corp., Armonk, NY, USA).

RESULTS

Baseline and follow-up CRP levels

Median (IQR) baseline and follow-up CRP-levels were 2.10 (0.85, 5.35) mg/L and 1.00 (0.50, 2.20) mg/L, respectively. The median change in CRP was -0.45 (-2.55, 0.00) mg/L, which was statistically significant (sign test p-value <0.001). We found no relevant differences in baseline clinical (Table 1) and imaging (Table 2) characteristics in relation to CRP change, except for the indication of the index procedure. Changes in CRP levels appeared considerably smaller in SAP than in ACS patients. SAP patients had median baseline and follow-up CRP of 1.35 (0.70 to 4.25) mg/L and 0.90 (0.50, 2.55) mg/L, respectively, with a median change of -0.20 (-1.10, 0.05) mg/L (Table 3; Figure 1). ACS patients had median baseline and follow-up CRP of 2.80 (1.25 to 7.85) mg/L and 1.00 (0.40, 2.20) mg/L, respectively, with a median change of -1.60 (-6.35, 0.00) mg/L.

CRP and cholesterol

Baseline CRP and LDL-C were uncorrelated in SAP as well as ACS patients ($r_{spearman}$ -0.030 and -0.141, respectively), and so was Total-C (Figure 2). In SAP patients, high CRP levels were associated with low HDL-C ($r_{spearman}$ -0.325, p-value 0.001). Significant changes were observed during 1-year rosuvastatin treatment for LDL-C (decrease), HDL-C (increase) and Total-C values (decrease) in SAP and ACS patients, which, however, were not correlated with changes in CRP level (Figure 3).

CRP and IVUS characteristics

Baseline CRP and IVUS plaque characteristics were uncorrelated (Figure 4). No systematic changes were observed in total plaque volume and plaque burden during the 1-year treatment with rosuvastatin in SAP patients. In contrast, in ACS patients, total plaque volume (+6.8 mm^3; p-value 0.068) and plaque burden (+1.35%; p-value 0.005) tended to increase. NC volume decreased in SAP and ACS patients (-0.55 mm^3 and -0.31 mm^3, respectively). In ACS patients, not SAP, changes in CRP and changes in IVUS plaque characteristics were positively correlated (Figure 5). In

Table 1. Clinical baseline characteristics of the study patients, stratified by tertile of change in CRP level

	ΔCRP ≤ -1.6 *	-1.6 < ΔCRP < 0	ΔCRP ≥ 0	P-value †
Number of patients	54	50	60	
Age, years	57.4 (9.4)	60.4 (9.2)	61.2 (8.1)	0.108
Male	47 (87.0)	40 (80.0)	51 (85.0)	0.617
History of diabetes mellitus	12 (22.2)	12 (24.0)	11 (18.3)	0.744
History of hypertension	35 (64.8)	29 (58.0)	40 (69.0)	0.483
History of hypercholesterolemia	31 (57.4)	32 (64.0)	41 (70.7)	0.355
Baseline cholesterol measurements				
LDL-C, mmol/L	2.42 [1.82-3.02]	2.25 [1.88-2.86]	2.39 [1.93-2.87]	0.789
HDL-C, mmol/L	1.02 [0.86-1.17]	1.07 [0.89-1.28]	1.22 [0.93-1.39]	0.013
Total cholesterol, mmol/L	4.00 [3.30-5.00]	3.90 [3.20-4.60]	3.95 [3.50-4.60]	0.690
Current smoker	18 (33.3)	15 (30.0)	13 (21.7)	0.370
Positive family history of CAD	30 (56.6)	28 (56.0)	31 (51.7)	0.867
Previous MI	18 (33.3)	13 (26.0)	19 (31.7)	0.736
Previous PCI	23 (42.6)	14 (28.0)	23 (38.3)	0.291
Previous CABG	0	0	1 (1.7)	--
Previous stroke	3 (5.6)	4 (8.0)	8 (13.3)	0.386
Peripheral artery disease	1 (1.9)	4 (8.0)	2 (3.3)	0.299
History of heart failure	0	1 (2.0)	1 (1.7)	0.758
Statin use at baseline	51 (94.4)	48 (96.0)	57 (95.0)	1.000
PCI performed after index CAG	49 (90.7)	45 (90.0)	52 (86.7)	0.817
Indication for coronary angiography				<0.001
Stable angina pectoris	20 (37.0)	35 (70.0)	41 (68.3)	
ACS	34 (63.0)	15 (30.0)	19 (31.7)	

Categorical variables are presented as numbers and percentages n (%). Continuous variables are presented as mean (standard deviation) or median (interquartile range).

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CRP, c-reactive protein; HDL, high-density lipoprotein; IQR, interquartile range; LCBI, Lipid Core Burden Index; LDL, low-density lipoprotein; MI, myocardial infarction; NC, necrotic core volume; NIRS, Near-infrared spectroscopy; PCI, percutaneous coronary intervention; SAP, stable angina pectoris

* ΔCRP, follow-up minus baseline CRP level

† Based on the Fisher's exact test (categorical data) or the Kruskal-Wallis test (continuous data)

particular, 13 (68%) of the 19 ACS patients with a delta CRP ≥0 mg/L had a delta NC volume ≥0 mm^3, as compared with 20 (41%) of the 49 patients with delta CRP <0 mg/L (p-value 0.059). In a linear regression model, each 1 mg/L difference in delta CRP was associated with 0.22 mm^3 difference in delta NC volume (p-value 0.010), after adjustment for baseline NC volume, sex, previous myocardial infarction, delta LDL-C (which appeared significant predictors in multivariable analysis) and timing of the reCAG. Also, 79% of the ACS patients with delta CRP ≥0 mg/L had

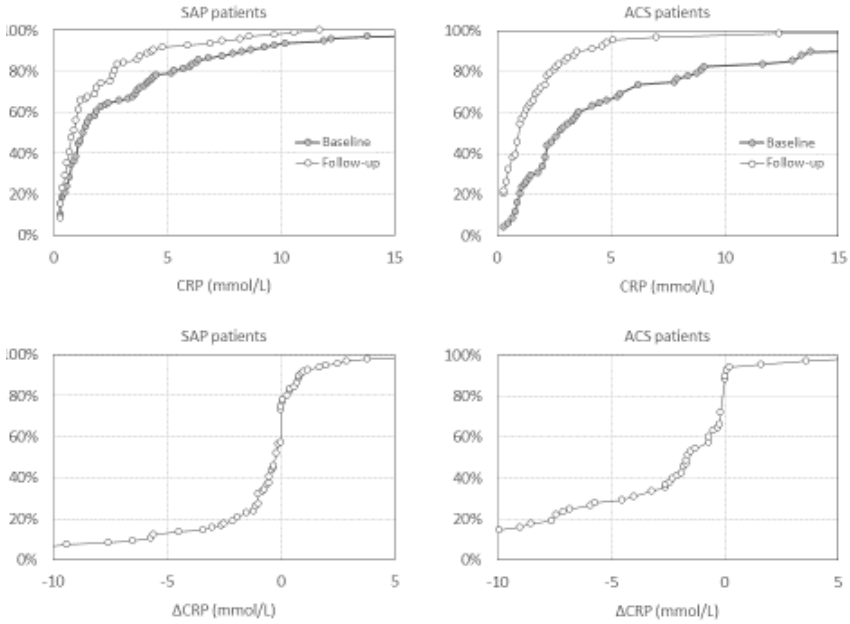
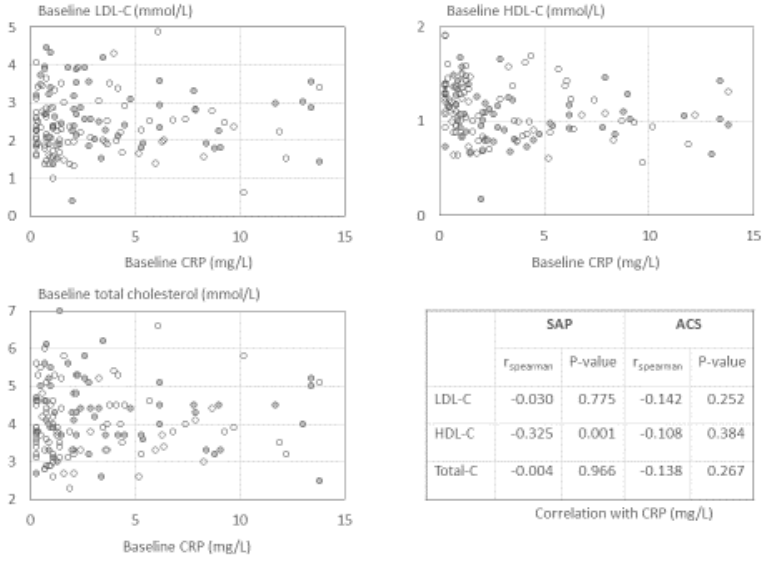


Figure 1 Cumulative distribution of baseline and follow CRP levels, as well as delta (Δ, follow-up minus baseline) CRP, in patients presenting with stable angina pectoris and acute coronary syndrome



	SAP		ACS	
	$r_{spearman}$	P-value	$r_{spearman}$	P-value
LDL-C	-0.030	0.775	-0.142	0.252
HDL-C	-0.325	0.001	-0.108	0.384
Total-C	-0.004	0.966	-0.138	0.267

Correlation with CRP (mg/L)

Figure 2 Relation between baseline CRP and baseline LDL-C, HDL-C and total cholesterol levels in patients presenting with stable angina pectoris (SAP, open bullet points) and acute coronary syndrome (ACS, closed bullet points)

Table 2. Imaging characteristics of the study patients, stratified by tertile of change in CRP level

	ΔCRP ≤ -1.6 *	-1.6 < ΔCRP < 0	ΔCRP ≥ 0	P-value †
Coronary artery disease ‡				0.645
Number of patients	54	50	60	
No significant stenosis	0	3 (6.0)	3 (5.0)	
1-vessel disease	30 (55.6)	24 (48.0)	31 (51.7)	
2-vessel disease	20 (37.0)	21 (42.0)	22 (36.7)	
3-vessel disease	4 (7.4)	2 (4.0)	4 (6.7)	
NIRS measurements				
Number of patients	35	31	37	
$LCBI_{ROI}$	29 [5-84]	36 [5-61]	40 [10-71]	0.701
$LCBI_{10mm}$	118 [9-223]	90 [10-181]	112 [28-207]	0.680
$LCBI_{4mm}$	189 [11-339]	178 [26-319]	182 [66-301]	0.921
IVUS measurements				
Number of patients	54	50	60	
Plaque volume, mm^3	201 [135-299]	190 [142-327]	217 [137-298]	0.866
Plaque burden (%)	42 [32-51]	39 [33-47]	41 [34-49]	0.779
NC volume, mm^3	17 [7-45]	13 [7-37]	20 [7-34]	0.778

Categorical variables are presented as numbers and percentages n (%). Continuous variables are presented as median (interquartile range).

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CRP, c-reactive protein; HDL, high-density lipoprotein; IQR, interquartile range; LCBI, Lipid Core Burden Index; LDL, low-density lipoprotein; MI, myocardial infarction; NC, necrotic core volume; NIRS, Near-infrared spectroscopy; PCI, percutaneous coronary intervention; SAP, stable angina pectoris

* ΔCRP, follow-up minus baseline CRP level (mmol/L)

† Based on the Fisher's exact test (categorical data) or the Kruskal-Wallis test (continuous data)

‡ A significant stenosis was defined as a stenosis ≥ 50% of the vessel diameter by visual assessment of the coronary angiogram.

a delta total plaque volume ≥0 mm^3, compared with 55% of those with delta CRP <0 mg/L (p-value 0.097). Each 1 mg/L difference in delta CRP was associated with 0.81 mm^3 difference in delta total plaque volume (p-value 0.002), after adjustment for baseline total plaque volume (significant predictor) and timing of the reCAG. Finally, a 1mg/L difference in delta CRP was related with a 0.13 percent point difference in plaque burden, after adjustment for baseline plaque burden, age, previous PCI (significant predictors), and timing of the reCAG.

CRP and NIRS characteristics

Baseline CRP and $LCBI_{ROI}$, $LCBI_{10mm}$, $LCBI_{4mm}$ were also uncorrelated (Figure 6). LCBI values did not systematically change during the 1-year treatment period. For ex-

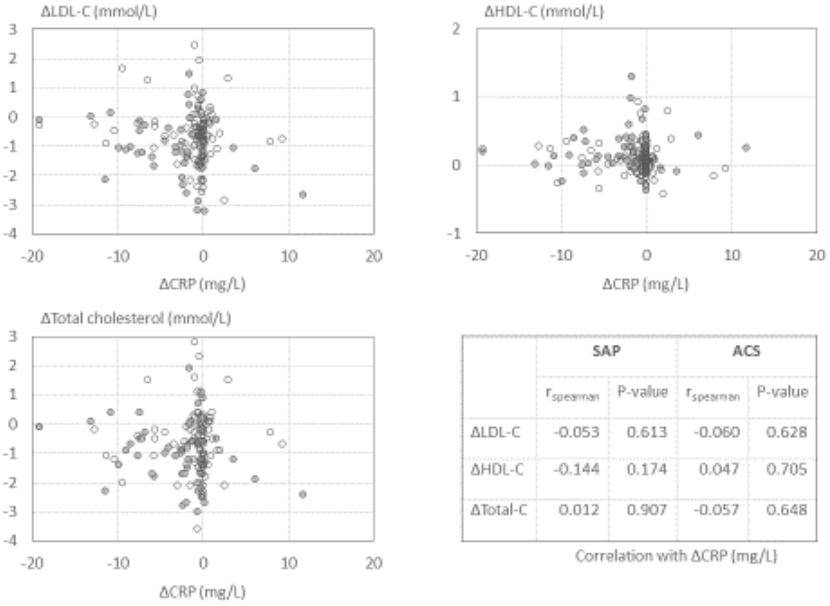
Table 3. Baseline and follow-up cholesterol and intracoronary imaging endpoints

	SAP				ACS			
	Baseline	Follow-up	Delta	P-value *	Baseline	Follow-up	Delta	P-value *
CRP, mg/L	1.35 (0.70, 4.25)	0.90 (0.50, 2.55)	-0.20 (-1.10, 0.05)	0.002	2.80 (1.25, 7.85)	1.00 (0.40, 2.20)	-1.60 (-6.35, 0.00)	<0.001
LDL-C, mmol/L	2.27 (1.88, 2.78)	1.62 (1.23, 2.11)	-0.62 (-1.08, -0.23)	<0.001	2.56 (2.03, 3.31)	1.59 (1.27, 1.92)	-1.03 (-1.67, -0.38)	<0.001
HDL-C, mmol/L	1.10 (0.91, 1.37)	1.14 (0.95, 1.44)	0.07 (-0.06, 0.20)	0.035	1.06 (0.86, 1.26)	1.21 (0.99, 1.46)	0.12 (0.02, 0.34)	<0.001
Total cholesterol, mmol/L	3.80 (3.30, 4.50)	3.30 (2.80, 3.80)	-0.60 (-1.30, -0.10)	<0.001	4.30 (3.70, 5.00)	3.20 (2.70, 3.50)	-0.95 (-1.70, -0.50)	<0.001
Plaque volume, mm^3	225 (137, 341)	231 (140, 343)	1.9 (-8.6, 16.2)	0.358	181 (144, 244)	197 (147, 252)	6.8 (-9.0, 18.2)	0.068
Plaque burden (%)	41.8 (32.8, 49.0)	41.2 (33.6, 50.3)	0.50 (-1.52, 2.80)	0.262	39 (33, 47)	41.4 (33.8, 48.0)	1.35 (-0.39, 3.40)	0.005
NC volume, mm^3	20.6 (7.4, 38.9)	19.8 (6.0, 37.4)	-0.55 (-4.27, 1.85)	0.064	16 (7, 35)	17.1 (6.0, 30.6)	-0.31 (-4.63, 1.65)	0.807
$LCBI_{ROI}$	29 (7, 64)	33 (9, 68)	0 (-16, 22)	0.798	34 (4, 73)	42 (7, 79)	5 (-22, 31)	0.133
$LCBI_{10mm}$	107 (27, 183)	106 (37, 199)	0 (-52, 69)	1.000	109 (22, 223)	119 (16, 181)	0 (-57, 50)	1.000
$LCBI_{4mm}$	183 (63, 315)	196 (89, 335)	10 (-68, 103)	0.162	184 (54, 332)	190 (39, 321)	8 (-32, 56)	0.405

Data are presented as median (interquartile range).

ACS, acute coronary syndrome; CRP, c-reactive protein; HDL, high-density lipoprotein; LCBI, Lipid Core Burden Index; LDL, low-density lipoprotein; NC, necrotic core; SAP, stable angina pectoris

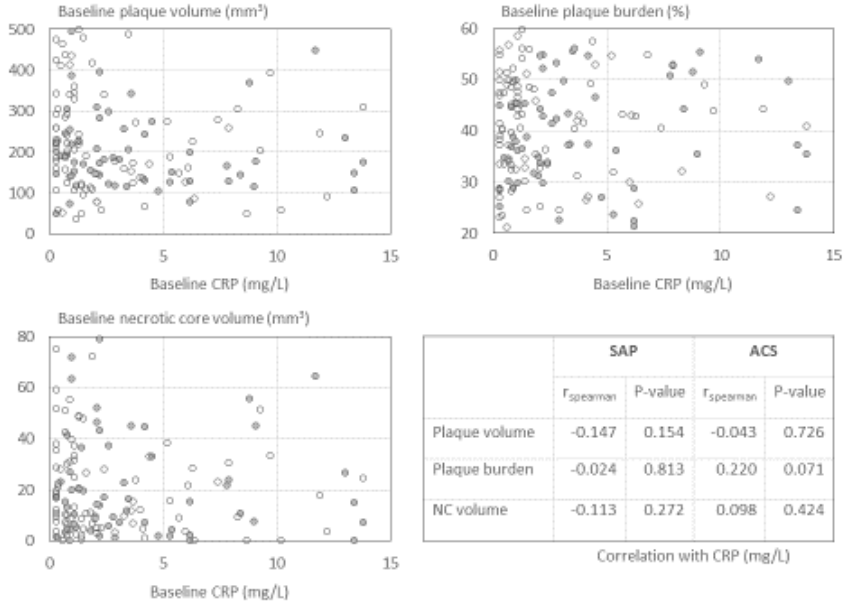
* P-value for change, based on the sign test



	SAP		ACS	
	$r_{spearman}$	P-value	$r_{spearman}$	P-value
ΔLDL-C	-0.053	0.613	-0.060	0.628
ΔHDL-C	-0.144	0.174	0.047	0.705
ΔTotal-C	0.012	0.907	-0.057	0.648

Correlation with ΔCRP (mg/L)

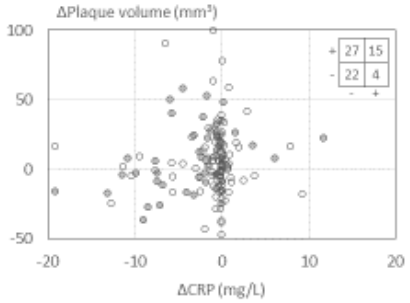
Figure 3 Relation between changes (Δ, follow-up minus baseline) in CRP and changes in LDL-C, HDL-C and total cholesterol levels in patients presenting with stable angina pectoris (SAP, open bullet points) and acute coronary syndrome (ACS, closed bullet points)

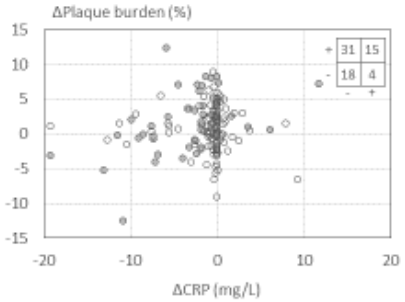


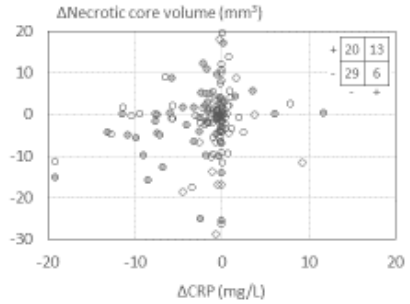
	SAP		ACS	
	$r_{spearman}$	P-value	$r_{spearman}$	P-value
Plaque volume	-0.147	0.154	-0.043	0.726
Plaque burden	-0.024	0.813	0.220	0.071
NC volume	-0.113	0.272	0.098	0.424

Correlation with CRP (mg/L)

Figure 4 Relation between baseline CRP and baseline total plaque volume, total plaque burden and necrotic core (NC) volume in patients presenting with stable angina pectoris (SAP, open bullet points) and acute coronary syndrome (ACS, closed bullet points)



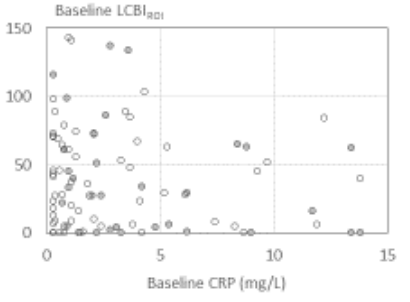


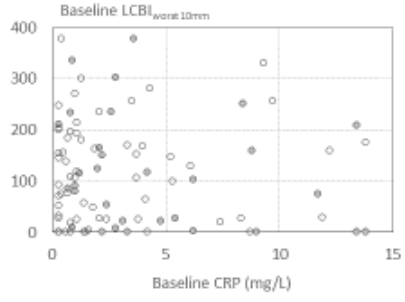


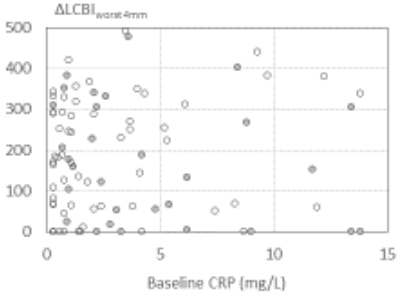
	SAP		ACS	
	$r_{spearman}$	P-value	$r_{spearman}$	P-value
ΔPlaque volume	-0.030	0.768	0.427	<0.001
ΔPlaque burden	0.156	0.129	0.336	0.005
ΔNC volume	-0.030	0.774	0.375	0.002

Correlation with ΔCRP (mg/L)

Figure 5 Relation between changes (Δ, follow-up minus baseline) in CRP and changes in total plaque volume, total plaque burden and necrotic core (NC) volume in patients presenting with stable angina pectoris (SAP, open bullet points) and acute coronary syndrome (ACS, closed bullet points)



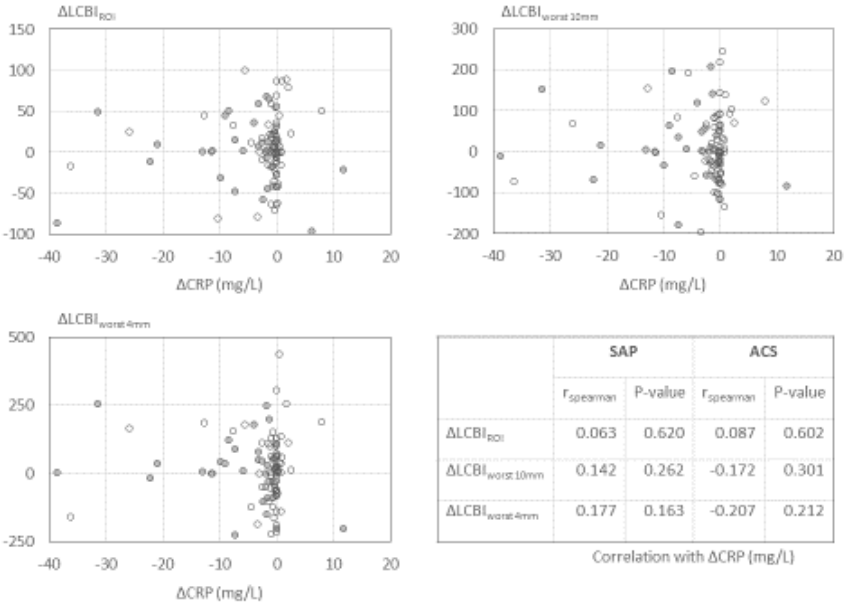




	SAP		ACS	
	$r_{spearman}$	P-value	$r_{spearman}$	P-value
$LCBI_{ROI}$	-0.057	0.653	-0.148	0.375
$LCBI_{worst\ 10mm}$	-0.024	0.849	-0.150	0.369
$LCBI_{worst\ 4mm}$	0.049	0.699	-0.190	0.253

Correlation with CRP (mg/L)

Figure 6 Relation between baseline CRP and baseline lipid core burden index (LCBI) in the total region of interest ($LCBI_{ROI}$) and the 10 mm ($LCBI_{10mm}$) and 4 mm ($LCBI_{10mm}$) sections with worst values in patients presenting with stable angina pectoris (SAP, open bullet points) and acute coronary syndrome (ACS, closed bullet points)



	SAP		ACS	
	$r_{spearman}$	P-value	$r_{spearman}$	P-value
$\Delta LCBI_{ROI}$	0.063	0.620	0.087	0.602
$\Delta LCBI_{worst\ 10mm}$	0.142	0.262	-0.172	0.301
$\Delta LCBI_{worst\ 4mm}$	0.177	0.163	-0.207	0.212

Correlation with ΔCRP (mg/L)

Figure 7 Relation between changes (Δ, follow-up minus baseline) in CRP and changes in lipid core burden index (LCBI) in the total region of interest ($LCBI_{ROI}$) and the 10 mm ($LCBI_{10mm}$) and 4 mm ($LCBI_{10mm}$) sections with worst values in patients presenting with stable angina pectoris (SAP, open bullet points) and acute coronary syndrome (ACS, closed bullet points)

ample, the median (IQR) delta $LCBI_{4mm}$ was only +10 points (IQR: -68, +103). We did not observe any association between changes in CRP levels and these key NIRS characteristics, neither in SAP, nor in ACS patients (Figure 7).

DISCUSSION

In our series of 164 patients with established CAD we found clinically relevant reductions in CRP levels after 1 year intensive (rosuva)statin therapy. These changes were observed in SAP as well as in ACS patients, but most prominent in ACS. Furthermore, in the ACS patients that we studied, CRP changes were correlated with changes in IVUS-derived plaque characteristics. We found no such correlations in SAP patients. CRP changes were uncorrelated with the also observed reductions in LDL-C.

Our findings are in agreement with previous studies that demonstrated that intensive statin treatment is capable to reduce serum cholesterol (LDL-C) as well as CRP levels (7,13,14). Our study also concurs with observations in CAD patients that (reductions in) CRP and LDL-C levels by statin therapy are largely uncorrelated. For example, in a series of 3745 ACS patients who received atorvastatin (80 mg/day) or

pravastatin (40 mg/day) for a mean of 24 months, less than 3% of the variation in achieved CRP levels was explained by the variation in achieved LDL-C (13). Furthermore, in that study, the achieved CRP and LDL-C were independently associated with the incidence of adverse coronary events. The relevance of reducing inflammation to prevent coronary events in patients with established CAD, independent of reducing LDL-C, was recently demonstrated in the CANTOS (4,5) and COLCOT trials (12).

As reported earlier, we found no relation between changes in LDL-C and changes in IVUS-derived plaque characteristics after 1 year of intensive (rosuva)statin treatment (11). In ACS patients, we now observed that changes in CRP levels were positively correlated with changes in total plaque volume, plaque burden and NC burden. These observations confirm the findings of SATURN and IBIS-4 studies in patients with ST-elevation myocardial infarction (STEMI) (15,16). In particular, in SATURN, a 'nonincreasing' CRP level was associated with a regression in plaque burden, whereas on-treatment CRP and not LDL-C was associated with adverse coronary events. We found no relation between CRP changes and changes in IVUS-derived plaque characteristics in SAP patients. In order to explain this observation, one might speculate that SAP and ACS patients have been shown to exhibit differences in pro-inflammatory and oxidative state (17). Still, it contrasts the findings by the REVERSAL investigators, who found a significant relation between CRP changes and changes in total plaque volume after 18 months of statin therapy in 502 patients with angiographically confirmed CAD (18). (Besides, interestingly, the REVERSAL investigators also reported a positive correlation between changes in LDL-C and coronary plaque characteristics.) It also contrasts, to some extent, with our findings in ATHEROREMO-IVUS, that CRP was associated with plaque volume and plaque burden in a mixed population of SAP and ACS patients, with no heterogeneity between the two phenotypes (19). Furthermore, in ATHEROREMO-IVUS, in SAP patients correlations were observed between TNF-α (positive) and IL-10 (negative) and plaque burden (20). In view of these mixed results, it appears that the relation between LDL-C reduction, inhibition of (vascular) inflammation, changes in extent and composition of coronary plaques, and coronary event reduction is not straightforward. Single study insights might easily by influenced by the clinical phenotype, intensity of the (statin) treatment, treatment duration, sample size and imaging techniques. For example, the median baseline CRP levels of the patients in the studies that we reference ranged from 1.5 (SATURN) to 4.2 (CANTOS, JUPITER) mg/L (4,7,8). Our current findings with respect to NIRS-derived LCBI should be

interpreted in this context: we found no relation between CRP (changes) and LCBI (changes), whereas we have earlier reported on a strong association between LCBI and MACE events (21,22), and others emphasized the prognostic value of serum CRP levels (4,5).

Limitations

Some limitations of this study need to be acknowledged. First, our sample size (in particular the subpopulations of SAP and ACS patients) was small, so that clinically relevant relations might have been missed. Second, intravascular imaging was performed in one pre-specified target segment of a non-culprit vessel, based on the assumption that such segment would represent the patient's atherosclerotic disease in the larger coronary tree. Although this hypothesis is supported by the fact that intravascular imaging measures on this single segment contained prognostic value (21-23), it still may be debated. Third, at study entry, most of the patients already received high-dose statin therapy. Therefore, a maximal lowering of serum CRP levels might have already occurred. Thus, the additional or incremental effect of high dose rosuvastatin might be less evident in these patients. Fourth, IBIS-3 was designed as an uncontrolled, observational study. Hence, changes in the measured serum biomarkers and intracoronary imaging characteristics during 1 year follow-up cannot be causally linked with the high-intensity statin treatment, which all patients received.

Conclusion

After 1 year intensive rosuvastatin therapy clinically relevant reductions in CRP levels were observed in a series of patients with established CAD. The observed CRP changes were correlated with changes in IVUS-derived plaque characteristics in ACS patients, but not in SAP. CRP changes were uncorrelated with changes in LDL-C levels. Hence, our study supports the role of in inflammation CAD progression, but also emphasizes that the relation between LDL-C reduction, inhibition of (vascular) inflammation, changes in extent and composition of coronary plaques, and coronary event reduction is not straightforward.

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