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Preprocedural C-Reactive Protein Levels and Cardiovascular Events After Coronary Stent Implantation

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OBJECTIVES This study assessed the predictive value of preprocedural C-reactive protein (CRP) levels on six-month clinical and angiographic outcome in patients undergoing coronary stent implantation.

BACKGROUND Recent data indicate that low-grade inflammation as detected by elevated CRP serum levels predicts the risk of recurrent coronary events.

METHODS We prospectively investigated the predictive value of preprocedural CRP-levels on restenosis and six-month clinical outcome in 276 patients after coronary stent implantation. The primary combined end point was death due to cardiac causes, myocardial infarction related to the target vessel and repeat intervention of the stented vessel.

RESULTS Grouping patients into tertiles according to preprocedural CRP-levels revealed that, despite identical angiographic and clinical characteristics at baseline and after stent implantation, a primary end point event occurred in 24 (26%) patients of the lowest tertile, in 42 (45.6%) of the middle tertile and in 38 (41.3%) of the highest CRP tertile, $p = 0.01$. On multivariate analysis, tertiles of CRP levels were independently associated with a higher risk of adverse coronary events (relative risk = 2.0 [1.1 to 3.5], tertile I vs. II and III, $p = 0.01$) in addition to the minimal lumen diameter after stent ($p = 0.04$). In addition, restenosis rates were significantly higher in the two upper tertiles compared with CRP levels in the lowest tertile (45.5% vs. 38.3% vs. 18.5%, respectively, $p = 0.002$).

CONCLUSIONS Low-grade inflammation as evidenced by elevated preprocedural serum CRP-levels is an independent predictor of adverse outcome after coronary stent implantation, suggesting that a systemically detectable inflammatory activity is associated with proliferative responses within successfully implanted stents. (J Am Coll Cardiol 2001;37:839–46) © 2001 by the American College of Cardiology

Atherosclerosis is believed to be a chronic inflammatory disease of the vessel wall (1). Recent data indicate that low-grade inflammation as detected by elevated C-reactive protein (CRP) serum levels predicts the risk of recurrent coronary events not only in patients with myocardial infarction (MI) (2,3), stable or unstable angina (4,5) but also in apparently healthy men (6). These observations suggest that an individual's reactivity to inflammatory stimuli plays an important pathophysiologic role in coronary disease progression (7,8).

Coronary angioplasty (9) or coronary stent implantation (10) has been shown to elicit an inflammatory response by itself. In addition, preprocedural CRP levels appear to be a powerful predictor of both early and late outcome in patients undergoing conventional balloon angioplasty (11), suggesting that preprocedural activation of inflammatory cells may play a role in the modulation of vessel wall response to the injury induced by balloon angioplasty.

Stent implantation provides a useful model to assess the role of inflammation for atherosclerotic disease progression that is primarily determined by neointimal hyperplasia and not affected by the chronic shrinking process after conventional balloon angioplasty (12). In addition, stent implantation may modify the biological response of a dilated lesion by providing a more homogeneous lesion geometry compared with balloon dilation.

Therefore, we prospectively investigated the predictive value of preprocedural CRP-levels on six-month angiographic and clinical outcome in 276 consecutive patients undergoing coronary stent implantation.

METHODS

Study population. The study population consisted of 276 patients undergoing coronary stent implantation for objective evidence of ischemia in patients with angina. Indications for stenting were: coronary dissection after percutaneous transluminal coronary angioplasty (PTCA), suboptimal results (≥30% residual stenosis) after PTCA, lesions in venous bypass grafts and restenotic lesions. In addition, all patients undergoing percutaneous coronary intervention for acute MI were treated by stent implantation. All patients with a stent successfully inserted in the target lesion were included in the analysis except for those undergoing stent implantation during cardiogenic shock or as a bridge to emergency aortocoronary bypass surgery. Patients with intercurrent inflammatory conditions, local hematoma or malignancies were excluded. At the time of stenting, all patients were scheduled for a six-month follow-up angio-

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Abbreviations and Acronyms

CRP = C-reactive protein
MI = myocardial infarction
MLD = minimal luminal diameter
PTCA = percutaneous transluminal coronary angioplasty
RR = relative risk
TVR = target vessel revascularization

gram, regardless of symptomatic status. All patients gave informed consent, and the study was approved by our institutional ethics committee.

Laboratory analysis. In all patients, serum was collected immediately before the initial percutaneous coronary intervention after insertion of the arterial sheath for measuring CRP levels with a commercially available kit (Turbidimetric test, Boehringer Mannheim, Germany). The measuring range is 0.3 to 24 mg/dl, with intraassay variation coefficients ranging from 0.6% to 1.3% and interassay variations from 1.3% to 6% at different levels of CRP.

Stent implantation procedure. Stent implantation was performed as previously described (13). In brief, all patients were on chronic aspirin (100 mg/day) therapy or received 500 mg of aspirin intravenously before the procedure. Fifteen thousand units of heparin was given after insertion of the arterial sheath, and if necessary, a repeat bolus of 5,000 U was administered to maintain the activated clotting time >250 s. Intracoronary glycerol trinitrate (0.2 to 0.3 mg) was given at the start of the procedure, before the final angiogram and before follow-up angiography. High-pressure balloon catheters were used for stent implantation with inflation pressures >10 atm. If necessary, multiple stents were used for complete coverage of the lesion.

Quantitative coronary angiography. Quantitative measurements were assessed by fully computerized quantitative angiography (CMS, Medis, Nuenen, Netherlands) (14). Minimal luminal diameter (MLD), reference diameter and percent diameter stenosis were measured in identical views before PTCA, immediately after stent insertion and at follow-up. Lesions were classified according to the modified American College of Cardiology/American Heart Association criteria (15). Analyses were performed per patient (only one randomly selected lesion per subject). Stent restenosis was defined as a dichotomous outcome (≥50% diameter stenosis within the stent or stents at follow-up). Acute gain was defined as the difference between MLD after stent implantation and the MLD before PTCA. Late loss was defined as the difference between the MLD after stent insertion and the MLD at follow-up, and net gain was defined as the difference between acute gain and late loss.

Postprocedure medication protocol. Ticlopidine 250 mg to 500 mg per day or Clopidogrel 75 mg/day (n = 15) was given for four weeks and aspirin 100 mg/day indefinitely. Glycoprotein IIb/IIIa inhibitors were administered in 15 patients (5.3%).

Definition of events and follow-up. The primary combined end point was death due to cardiac causes, MI related to the target vessel and repeat intervention of the stented vessel (PTCA or aortocoronary bypass surgery). The diagnosis of MI was based on typical symptoms and electrocardiographic changes plus an increase in creatine kinase ≥ twice the upper limit of normal with a concomitant rise in the MB isoenzyme or a positive troponin T test. Blood samples were routinely drawn 24 h after the procedure in all patients to detect the occurrence of myocardial necrosis regardless of symptoms.

Thirty-day clinical follow-up and six-month follow-up was available in all 276 patients on an outpatient basis. The cumulative incidence of the primary combined end point, including death due to cardiac causes, MI related to the target vessel or repeat intervention of the stented vessel were assessed by Kaplan-Meier survival curves. Follow-up coronary angiograms to evaluate angiographic stent restenosis rates were performed in 229 of 267 (85.7%) patients eligible for planned reangiography between four and six months after stent placement. Patients who had no-control angiography were contacted to obtain clinical follow-up. Target vessel revascularization (TVR) was defined as repeat intervention of restenotic lesions, which included the target site of the stent implantation or proximal and distal in the same major coronary artery. Target vessel revascularization was driven by the presence of ischemia indicated either by the recurrence of typical symptoms of angina or a positive exercise stress test.

Data and statistical analysis. Data are expressed as percentages for discrete variables and as mean ± standard deviation for continuous variables. C-reactive protein values were divided into tertiles and compared by Kruskal-Wallis test or by analysis of variance for multiple comparisons within all three groups. Categorical variables between two groups were compared by means of the chi-square test or Fisher exact test.

Continuous variables were tested for normal distribution with the Kolmogorov-Smirnov test and compared by means of Student *t* test. In case of nonnormal distribution, nonparametric methods were used (Mann-Whitney *U* test). Univariate and stepwise multivariate analysis was performed using the logistic regression model on SPSS version 8.0, SPSS Inc. All potential risk factors for stent restenosis were included. Chi-square analysis or logistic regression was used to estimate relative risk (RR) and 95% confidence intervals. Long-term clinical adverse events, death due to cardiac causes and MI of the target vessel were compared by Kaplan-Meier survival curves, and the corresponding p value was obtained from the log-rank test. Cumulative distribution curves of MLD before stenting, immediately after stenting and at follow-up were expressed as a function of CRP tertiles. For graphical reasons, the two upper tertiles were combined and compared with the lowest tertile of CRP values. Statistical significance was assumed at $p < 0.05$.

Table 1. Baseline Clinical Characteristics of the Study Population (n = 276)

	CRP < 0.5 (n = 92)	CRP 0.5–1.4 (n = 92)	CRP > 1.4 (n = 92)	p Value
Characteristics				
Age	61 ± 12	62 ± 9	62 ± 10	0.6
Women	17 (18.5%)	15 (16.3%)	24 (26.1%)	0.2
Mean LVEF (%)	53 ± 10	52 ± 12	50 ± 11	0.7
Acute coronary syndrome	39 (42.3%)	44 (47.8%)	58 (63%)	0.02
Unstable angina	22 (23.9%)	32 (35.6%)	20 (21.7%)	0.08
Acute MI	17 (18.4%)	12 (13%)	38 (41.3%)	0.001
Risk factors				
Current smoking	20 (21.7%)	22 (23.9%)	27 (29.3%)	0.7
Diabetes	12 (13%)	32 (34.8%)	18 (19.6%)	0.003
Hypertension	59 (64.1%)	45 (48.9%)	46 (50%)	0.1
Hypercholesterolemia	60 (65.2%)	60 (65.2%)	49 (53.3%)	0.2
Clinical				
Previous MI	30 (32.6%)	38 (41.3%)	31 (33.7%)	0.5
Previous CABG	17 (18.5%)	13 (14.1%)	11 (12%)	0.4
Extent of disease				
One-vessel	28 (30.4%)	29 (31.5%)	22 (24%)	0.6
Two-vessel	25 (27.2%)	26 (28.3%)	42 (45.7%)	0.01
Three-vessel	39 (42.4%)	37 (40.2%)	28 (30.4%)	0.15
CRP levels				
CRP (mg/dl)	0.17 ± 0.14	0.76 ± 0.27	2.9 ± 1.4	<0.001

CABG = coronary artery bypass grafting; CRP = C-reactive protein; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

RESULTS

Baseline characteristics. The baseline clinical and procedural characteristics of the study population are summarized in Tables 1 and 2. Patients were grouped into tertiles according to the CRP values. Elevated CRP levels were defined as those in the two upper tertiles (≥0.5 mg/dl). The range of CRP values was 0.0 to 8.0 mg/dl.

Clinical parameters did not differ between the three tertiles of CRP, with the exception that significantly more patients with elevated levels of CRP (≥0.5 mg/dl) presented

Table 2. Baseline Angiographic and Procedural Characteristics

	CRP < 0.5 (n = 92)	CRP 0.5–1.4 (n = 92)	CRP > 1.4 (n = 92)	p Value
Characteristic				
ACC/AHA lesion type				
A	0 (0%)	0 (0%)	0 (0%)	1.0
B1	7 (7.6%)	8 (8.7%)	4 (4.3%)	0.09
B2	66 (71.7%)	66 (71.7%)	66 (71.7%)	0.8
C	19 (20.6%)	18 (19.6%)	22 (23.9%)	0.8
Vessel				
LAD	48 (52.2%)	38 (41.3%)	37 (40.2%)	0.2
LCX	10 (10.9%)	16 (17.4%)	11 (12%)	0.4
RCA	28 (30.4%)	30 (32.6%)	39 (42.4%)	0.2
Vein graft	6 (6.5%)	8 (8.7%)	5 (5.4%)	0.6
Stent indication				
Dissection	27 (29.3%)	28 (30.4%)	26 (28.3%)	0.9
Restenotic lesion	16 (17.4%)	14 (15.2%)	12 (13%)	0.4
Procedural				
Lesion length (mm)	11 ± 5	13 ± 6	13 ± 6	0.3
Max inflation pressure (atm)	13.8 ± 1.7	14 ± 1.5	13.8 ± 1.7	0.5
Balloon/vessel ratio	1.05 ± 0.1	1.03 ± 0.1	1.05 ± 0.1	0.2
Stent length (mm)	22 ± 13	22 ± 12	22 ± 10	0.7
Stents/lesion	1.5 ± 0.9	1.6 ± 1	1.6 ± 1	0.6
TIMI flow grade 3	91 (98.9%)	88 (95.7%)	91 (98.9%)	0.3
Residual dissections	12 (13%)	10 (10.9%)	4 (4.3%)	0.1
Residual stenosis ≥30% (stent)	7 (7.6%)	8 (8.7%)	5 (5.4%)	0.7

ACC/AHA = American College of Cardiology-American Heart Association; CRP = C-reactive protein; LAD = left anterior descending coronary artery; LCX = left circumflex artery; RCA = right coronary artery; TIMI = Thrombolysis Myocardial Infarction.

Table 3. Baseline Quantitative Angiographic Analysis

Characteristics	CRP < 0.5 (n = 92)	CRP 0.5–1.4 (n = 92)	CRP > 1.4 (n = 92)	p Value
Quantitative analysis				
Reference diameter (mm)	2.97 ± 0.6	3.0 ± 0.5	2.97 ± 0.5	0.5
Minimal lumen diameter (mm)	0.81 ± 0.6	0.78 ± 0.5	0.7 ± 0.6	0.5
Percent stenosis	74.4 ± 17	74.8 ± 16	79.1 ± 17	0.2
Post-stent				
Reference diameter (mm)	3.0 ± 0.5	3.1 ± 0.6	3.0 ± 0.5	0.6
Minimal lumen diameter (mm)	2.66 ± 0.6	2.65 ± 0.6	2.60 ± 0.5	0.9
Percent stenosis	14.3 ± 11.6	15.4 ± 11	15.2 ± 11	0.5
Acute gain (mm)	1.9 ± 0.6	2.0 ± 0.7	1.9 ± 0.7	0.4

CRP = C-reactive protein.

with an acute coronary syndrome (defined as unstable angina Braunwald class IIIB or acute MI, p = 0.02). In addition, more patients with CRP levels in tertiles II and III were diabetic. The quantitative angiographic data at baseline and immediately after coronary stent implantation are summarized in Table 3. Angiographic parameters were identical in all three groups.

Angiographic follow-up. Table 4 summarizes the quantitative angiographic data obtained at follow-up angiography. Patients with elevated CRP levels had significantly higher restenosis rates. When the categorical criterion of ≥50% diameter stenosis at follow-up was used to assess restenosis development, the difference between the three groups was highly significant (p < 0.005), with a restenosis rate of 19% in the lowest tertile compared with 36.7% and 45.1% in the upper tertiles, respectively. Figure 1, illustrating the cumulative frequency distribution curves of the MLD, demonstrates that late lumen loss was significantly greater in the patients with elevated CRP levels (two upper tertiles ≥0.5 mg/dl) compared with patients in the lowest tertile (<0.5 mg/dl) as indicated by a leftward shift of the cumulative frequency distribution curve at follow-up angiography (Table 5).

Clinical follow-up. Table 5 shows the major adverse events during the one- and six-month follow-up period. To account for local lesion-related outcomes, only MIs in the territory of the target vessel, TVR and death due to cardiac causes were included in the end point analysis. A primary end point event occurred in 24 (26%) patients of the lowest tertile, 42 (45.6%) patients of the middle tertile and in 38 (41.3%) patients of the highest CRP-tertile, p = 0.01. Thirteen early adverse events were observed within 30 days after stent implantation. No event (MI or death) occurred in the lowest tertile of CRP (<0.5 mg/dl). Importantly, subacute stent thrombosis occurred exclusively in patients with elevated CRP levels (upper tertiles). Six-month clinical follow-up was completed in all patients. At six months, MI or cardiac death occurred only in patients with preprocedural CRP levels ≥0.5 mg/dl (p = 0.01). None of the patients died of noncardiac causes. In addition, Figure 2 illustrates that survival free of MI and TVR was significantly worse in patients with elevated preprocedural CRP levels.

Multivariate analysis. RESTENOSIS. Logistic regression analysis (Tables 6 and 7), including the classical previously described predictors of restenosis after coronary stent implantation, demonstrated that elevated preprocedural CRP levels are independently associated with increased restenosis rates (p = 0.006) in addition to MLD immediately after stent implantation (p = 0.04) and the number of stents implanted (p = 0.02), whereas reference segment diameter (p = 0.6), diabetes (p = 0.3) and total serum cholesterol levels (p = 0.3) did not independently predict subsequent restenosis development. Interestingly, the presence of an acute coronary syndrome that correlated with elevated CRP levels was not an independent predictor for subsequent recurrence rates (p = 0.9). Thus, independent of classical clinical and procedural risk factors, elevated preprocedural CRP serum levels are associated with an increased risk for in-stent restenosis, irrespective of the presence of an acute coronary syndrome before stenting (RR 3.6 [1.7 to 7.7], tertile III vs. I, p < 0.001).

CLINICAL EVENTS. Tertiles of CRP levels were also independently associated with a higher risk of adverse coronary events including MI, cardiac death and TVR (RR = 2.0

Table 4. Follow-up Quantitative Angiographic Analysis

Follow-up (n = 229)	CRP < 0.5 (n = 79)	CRP 0.5–1.4 (n = 79)	CRP > 1.4 (n = 71)	p Value
Reference diameter (mm)	3.0 ± 0.5	3.0 ± 0.5	3.0 ± 0.5	0.5
Minimal lumen diameter (mm)	1.95 ± 0.8	1.71 ± 0.8	1.67 ± 0.9	0.1*
Percent stenosis	35 ± 21	45 ± 22	45 ± 27	0.01
Late loss (mm)	0.66 ± 0.7	1.03 ± 0.8	0.97 ± 0.8	0.02
Restenosis rate	15 (19%)	29 (36.7%)	32 (45.1%)	0.002

*p = 0.05, Tertile 1 vs. Tertile 3.
CRP = C-reactive protein.

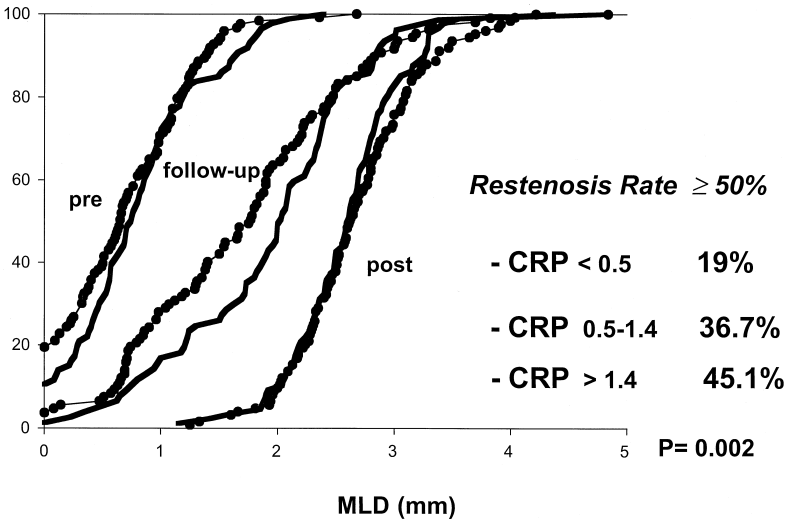

Figure 1. Cumulative frequency distribution curves of the MLD for tertiles of CRP levels pre-, post-stent implantation and at six-month follow-up angiography. For graphical reasons, the two upper tertiles (≥0.5 mg/dl) were combined **(dotted line with circles)** and compared with the lowest tertile (<0.5 mg/dl). CRP = C-reactive protein; MLD = minimal lumen diameter.

[1.1 to 3.5], tertile I vs. II and III, p = 0.01) in addition to the MLD after stent (p = 0.04). Since, in patients with acute MI, circulating CRP levels might be elevated due to myocardial necrosis, we repeated the analysis after excluding patients with acute MI. However, an almost identical RR of 2.3 ([1.2 to 4.2], tertile I vs. II and III, p = 0.006) was observed for elevated CRP levels in this subset of 208 patients, thus excluding a potential confounding effect of MI patients being more frequently distributed in the upper tertiles of CRP levels.

In contrast, stent length, reference vessel size, hypercholesterolemia, diabetes or acute coronary syndromes did not appear to be of predictive value for subsequent adverse events.

DISCUSSION

The results of this study demonstrate that elevated preprocedural CRP levels are associated with enhanced restenosis development after coronary stent implantation. Most importantly, the increased restenosis rate associated with elevated CRP levels is accompanied by a worse event-free survival.

The results of this study extend previous observations, demonstrating the predictive value of measuring CRP levels for cardiovascular events after coronary interventions. In patients undergoing conventional single-vessel balloon angioplasty, preprocedural CRP levels have been shown to be a powerful predictor of early and late clinical outcome (11).

Table 5. Major Adverse Clinical Events at One-Month and Six-Month Clinical Follow-up

One-Month Follow-up	CRP < 0.5 (n = 92)	CRP 0.5–1.4 (n = 92)	CRP > 1.4 (n = 92)	p Value
Primary combined end point (target vessel MI, death, TVR)	24 (26%)	42 (45.6%)	38 (41.3%)	0.02*
Subacute stent thrombosis	0 (0%)	3 (3.3%)	4 (4.3%)	0.1
Myocardial infarction (target vessel 30 days)	0 (0%)	2 (2.2%)	2 (2.2%)	0.3
Death (30 days)	0 (0%)	1 (1.1%)	1 (1.1%)	0.6
>1–6 Month Follow-up				
Myocardial infarction (target vessel 6 month)	0 (0%)	3 (3.3%)	5 (5.4%)	0.08
Myocardial infarction (nontarget vessel 6 month)	0 (0%)	1 (1.1%)	2 (2.2%)	0.4
Death 6 month	0 (0%)	3 (3.3%)	4 (4.3%)	0.15
Target vessel revascularization	24 (26%)	34 (36.9%)	29 (31.5%)	0.2
Cardiac events (Target vessel MI, death)	0 (0%)	8 (8.7%)	9 (9.8%)	0.01

*log-rank (Kaplan-Meier) p = 0.01.
CRP = C-reactive protein; MI = myocardial infarction; TVR = target vessel revascularization.

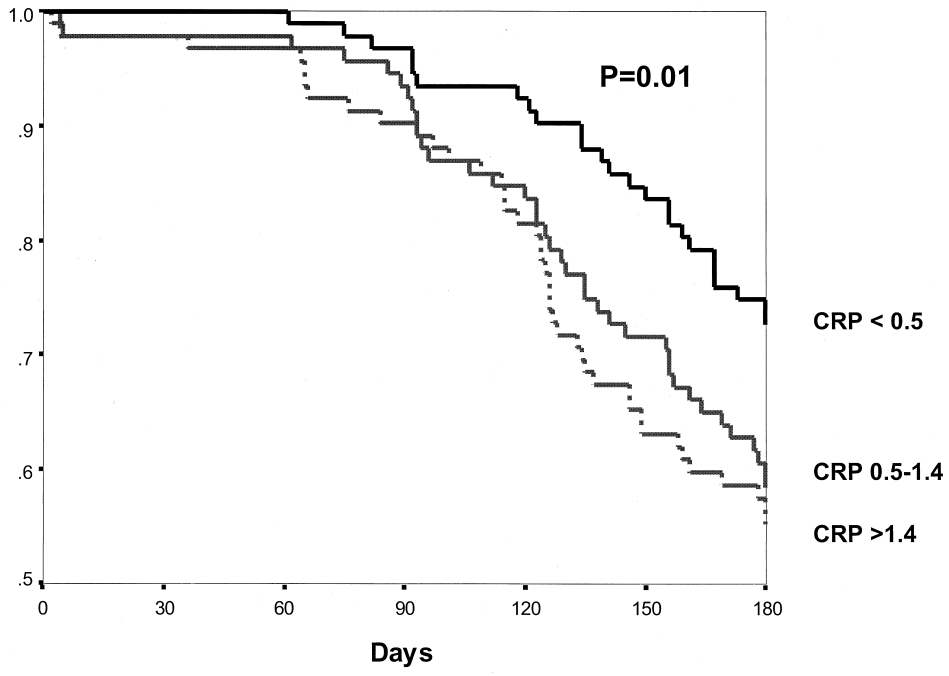

Figure 2. Long-term clinical adverse events (death due to cardiac causes, myocardial infarction of the target vessel and target vessel revascularization) within tertiles of CRP levels are compared by Kaplan-Meier survival curves, and the corresponding p value was obtained from the log-rank test. CRP = C-reactive protein.

In addition, in patients with stable angina and one-vessel disease, normalization of CRP plasma levels after coronary stenting identified patients who do not develop cardiovascular events (10). In line with a previous study in patients undergoing balloon angioplasty (11), in our population, no adverse coronary event such as MI or death within six months occurred in the subset of patients with CRP levels in the lowest tertile. Thus, preprocedural measurement of CRP levels might allow stratification of patients with respect to the individual risk for both early and late complications after coronary stent implantation.

Previous studies revealed that, in patients with unstable angina undergoing PTCA, increased baseline levels of acute-phase proteins are a marker for the hyperresponsiveness of the inflammatory system to nonspecific stimuli (9).

In-hospital complications after coronary stent implantation are mainly due to subacute stent thrombosis or occlusions caused by procedural parameters such as residual dissections (16,17). Indeed, in our study, all early complications after stent implantation within 30 days were events due to subacute thrombus formation at the stented site. Activation of inflammatory cells and cytokines can aggravate local thrombotic complications by increasing procoagulant or platelet activity or promoting thrombin generation (18–20). The finding of this study, that subacute stent thrombosis was exclusively observed in patients with elevated CRP levels, suggests an important role for low-grade systemic inflammation to amplify local thrombotic compli-

Table 6. Logistic Regression Analysis for Stent Restenosis

Variables	Multivariate Analysis Relative Risk (95% CI)	p Value
CRP (tertiles)		0.006
III vs. I	3.6 (1.7–7.7)	<0.001
II vs. I	2.7 (1.3–5.5)	0.005
II + III vs. I	3.1 (1.6–5.9)	<0.001
MLD (Stent)		0.04
Stent length (mm)		0.02
Reference diameter (mm)		0.6
Diabetes		0.3
Hypercholesterolemia		0.3
Acute coronary syndrome		0.9

CI = confidence interval; CRP = C-reactive protein; MLD = minimal lumen diameter.

Table 7. Logistic Regression Analysis for Clinical Outcome (MI, Death, TVR)

Variables	Multivariate Analysis Relative Risk (95% CI)	p Value
CRP (tertiles)		0.01
III vs. I	1.9 (1.1–3.5)	0.04
II vs. I	2.2 (1.2–4.0)	0.01
II + III vs. I	2.0 (1.1–3.5)	0.01
MLD (stent)		0.04
Stent length (mm)		0.1
Reference diameter (mm)		0.5
Diabetes		0.7
Hypercholesterolemia		0.1
Acute coronary syndrome		0.5

CI = confidence interval; CRP = C-reactive protein; MLD = minimal lumen diameter; MI = myocardial infarction; TVR = target vessel revascularization.

cations in patients undergoing coronary stent implantation (21).

Although the presence of an acute coronary syndrome correlated with elevated baseline CRP levels, by multivariate analysis it was not an independent predictor for subsequent clinical and angiographic outcome in our patient population consisting of a consecutive series of patients with various clinical conditions, including stable and unstable angina as well as MI. Likewise, diabetes did not appear to be an independent predictor, once preprocedural CRP levels were included in the analysis. Thus, since elevated CRP levels cluster in patients with diabetes (22), it is tempting to speculate that the systemic inflammatory activity as measured by CRP serum levels might be more informative than classical risk factors with respect to predicting the clinical and angiographic outcome after coronary stent implantation.

Experimental and clinical studies demonstrated that a systemic inflammatory reaction plays a pivotal role for neointima formation within stents in addition to the local vessel wall injury with the subsequent release of chemotactic and growth factors (9,23). Stent implantation has been shown to provide superior late results compared with conventional balloon angioplasty (24,25), which has been attributed to the elimination of chronic vessel wall shrinkage even at the expense of increased neointimal proliferation. Thus, coronary stent implantation provides an ideal scenario to assess the role of inflammation in atherosclerotic disease progression that is primarily determined by neointimal hyperplasia and not affected by a chronic shrinking process after conventional balloon angioplasty (12). In addition, stenting provides a more homogenous lesion geometry by covering plaque fractures and reducing exposure of atheromatous material, which might locally modify the biological response of a dilated lesion. However, the concordant finding that preprocedural CRP levels predict clinical and angiographic outcome both after balloon dilation (11) and after stent implantation suggests that—in both conditions—the preprocedural activation of inflammatory cells (26) may play a major role in the modulation of the vessel-wall response to injury.

Study limitations. In this study, CRP values were measured by a turbidimetric method and not with the recently recommended latex-enhanced high-sensitive CRP assay. However, comparison of the two assays in our institution not only revealed a very close correlation but, more importantly, demonstrated that CRP levels $\geq$0.5 mg/dl (upper limit of the lowest tertile) can be reliably detected using the turbidimetric method (data not shown). Although we achieved a high repeat angiography rate of 85.7%, we cannot fully exclude a potential bias related to incomplete angiographic follow-up. However, such bias is unlikely to be of relevance since the prospective design of the study allowed to assure that the patients without angiographic follow-up did not differ with respect to CRP distribution and clinical outcome.

Conclusions. Our study shows that low-grade inflammation measured by elevated preprocedural CRP-levels is an important and independent predictor of acute and six-month adverse outcome after coronary stent implantation, suggesting that a systemic inflammatory activity is associated with thrombotic and proliferative responses within successfully implanted stents.

Measurement of CRP levels could provide a rationale for risk stratification before coronary intervention and, thus, may offer a useful tool to target aggressive antiaggregatory or anti-inflammatory therapy to patients that are exposed to the highest risk for ischemic complications or restenosis development after coronary stent implantation.

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