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Statin Therapy, Inflammation and Recurrent Coronary Events in Patients Following Coronary Stent Implantation

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OBJECTIVES We sought to investigate whether statin therapy affects the association between preprocedural C-reactive protein (CRP) levels and the risk for recurrent coronary events in patients undergoing coronary stent implantation.

BACKGROUND Low-grade inflammation as detected by elevated CRP levels predicts the risk of recurrent coronary events. The effect of inflammation on coronary risk may be attenuated by statin therapy.

METHODS We investigated a potential interrelation among statin therapy, serum evidence of inflammation, and the risk for recurrent coronary events in 388 consecutive patients undergoing coronary stent implantation. Patients were grouped according to the median CRP level (0.6 mg/dl) and to the presence of statin therapy.

RESULTS A primary combined end point event occurred significantly more frequently in patients with elevated CRP levels without statin therapy (RR [relative risk] 2.37, 95% CI [confidence interval] [1.3 to 4.2]). Importantly, in the presence of statin therapy, the RR for recurrent events was significantly reduced in the patients with elevated CRP levels (RR 1.27 [0.7 to 2.1]) to about the same degree as in patients with CRP levels below 0.6 mg/dl and who did not receive statin therapy (RR 1.1 [0.8 to 1.3]).

CONCLUSIONS Statin therapy significantly attenuates the increased risk for major adverse cardiac events in patients with elevated CRP levels undergoing coronary stent implantation, suggesting that statin therapy interferes with the detrimental effects of inflammation on accelerated atherosclerotic disease progression following coronary stenting. (J Am Coll Cardiol 2001;38: 2006–12) © 2001 by the American College of Cardiology

Recent data indicate that low-grade inflammation as measured by elevated C-reactive protein (CRP) serum levels predicts the risk of recurrent coronary events not only in patients with myocardial infarction (MI) (1), stable or unstable angina (2–4), but also in apparently healthy men (5). Preprocedural CRP levels also appear to be a powerful predictor of both early and late outcome in patients undergoing conventional balloon angioplasty (6) and stent implantation (7,8), suggesting that preprocedural activation of inflammatory cells may play a role in the modulation of vessel wall responses to the injury induced by balloon angioplasty. Recent data from the Cholesterol And Recurrent Events (CARE) trial demonstrated that in patients with stable coronary artery disease, the effect of inflammation as measured by CRP levels on coronary risk may be attenuated by pravastatin therapy (9), suggesting an anti-inflammatory effect of statins in addition to the well-established lipid-lowering properties (10–12).

Stent implantation provides a useful model to assess a potential interrelation among serum evidence of inflammation, statin therapy and atherosclerotic disease progression, which is primarily determined by neointimal hyperplasia. Therefore, we investigated whether statin therapy affects the association between preprocedural CRP levels and the risk for recurrent coronary events in patients undergoing implantation of coronary stent.

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METHODS

Study population. The study population consisted of 388 consecutive patients undergoing coronary stent implantation. Indications for stenting were coronary dissection after percutaneous transluminal coronary angioplasty (PTCA), suboptimal results (≥30% residual stenosis) after PTCA, lesions in venous bypass grafts, restenotic lesions, and revascularization during acute MI. 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 bridge to emergency aorto-coronary 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 angiogram, regardless of symptomatic status. All patients gave informed consent, and the study was approved by our institutional ethics committee. In the present study, only 118 of 388 patients (30.6%) were overlapping with our previous study investigating the effect of statin therapy on stent restenosis (13).

Laboratory analysis. In all patients, serum was collected immediately before the stent implantation for measuring

Abbreviations and Acronyms

CI	=	confidence interval
CARE	=	Cholesterol And Recurrent Events trial
CRP	=	C-reactive protein
MI	=	myocardial infarction
MIRACL	=	Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering trial
MLD	=	minimal lumen diameter
PTCA	=	percutaneous transluminal coronary angioplasty
RR	=	relative risk
TVR	=	target vessel revascularization

CRP levels using a commercially available kit (Turbidimetric test, Boehringer Mannheim, Germany). The measuring range is 0.3 to 24 mg/dl, with intra-assay variation coefficients ranging from 0.6% to 1.3% and interassay variation from 1.3% to 6% at different levels of CRP. In a subset of 60 patients, the accuracy of the turbidimetric CRP measurement was validated against the latex-enhanced high-sensitivity CRP assay (Dade Behring, Germany). Comparison of the two assays not only revealed a close correlation ($r = 0.82$, $p < 0.001$), but, more importantly, demonstrated that CRP levels ≥0.5 mg/dl can be reliably detected using the turbidimetric test. Serum cholesterol levels were measured before the initial angioplasty as well as at follow-up.

Stent implantation procedure. Stent implantation of four different types of slotted-tube stents (Palmaz-Schatz, Jomed, Inflow, and Multilink stents) using high-pressure balloons was performed as previously described (8,13). All patients were on chronic aspirin (100 mg/day) therapy or received 500 mg of aspirin intravenously before the procedure. Patients received 10,000 to 15,000 U heparin 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. Glycoprotein IIb/IIIa inhibitors were administered in 34 patients (8.7%).

Quantitative coronary angiography. Quantitative measurements were performed by fully computerized quantitative angiography (CMS, Medis, Nuenen, Netherlands) to obtain minimal luminal diameter (MLD), reference diameter and percent diameter stenosis. Lesions were classified according to the modified American College of Cardiology/American Heart Association criteria (14). 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. Either ticlopidine 250 to 500 mg/day ($n = 343$) or clopidogrel 75 mg/day ($n = 45$) was given for four weeks and aspirin 100 mg/day indefinitely.

Most patients (176; 70.7%) received simvastatin; 16 (6.4%) received lovastatin, 42 (16.9%) received atorvastatin, 6 (2.4%) received fluvastatin, 6 (2.4%) received pravastatin and 3 (1.2%) received cerivastatin, respectively. Forty-five of 388 (11.6%) patients were on statin therapy prior to the stent implantation procedure and were continued on statin therapy. In 204 patients, statin therapy was initiated the day after stent insertion and continued throughout the study period.

Definition of events and follow-up. The primary combined end point was death due to cardiac causes, MI related to the target vessel or repeat intervention of the stented vessel (PTCA or aortocoronary bypass surgery). The diagnosis of MI was based on anginal symptoms and typical 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. Clinical six-month follow-up was available in all 388 patients. Follow-up coronary angiograms to evaluate angiographic stent restenosis rates were performed in 337 of 378 (89.1%) patients eligible for planned reangiography between four to six months after stent placement. 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. The TVR 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 ± SD for continuous variables. Continuous variables were compared by means of the Student *t* test or the Mann-Whitney *U* test. Multiple comparisons were performed by either the Kruskal-Wallis test or analysis of variance with the Bonferroni correction. A multivariate logistic regression analysis was performed to examine independent predictors of restenosis using SPSS version 9.0, by entering the following variables: CRP levels ≥0.6 mg/dl, statin therapy and the previously described classical risk factors for restenosis such as MLD, number of stents implanted, reference vessel size, diabetes mellitus and cholesterol levels. A forward entry stepping algorithm was used with the entry criteria probability of F (0.05). An additional logistic regression analysis and also a multivariate Cox regression analysis were performed, analyzing the predictability of the same variables on clinical events. Chi-square analysis or logistic regression was used to estimate relative risk (RR) and 95% confidence intervals (CIs). Long-term clinical adverse events were compared by the Kruskal-Wallis test for multiple comparisons or Kaplan-Meier survival curves, and the corresponding p value was obtained from the log-rank test. Statistical significance was assumed at $p < 0.05$.

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Table 1. Baseline Clinical and Procedural Characteristics of the Study Population

Characteristic	No Statin (n = 139 [35.8%])	Statin (n = 249 [64.2%])	p Value
Age (median, yrs)	64	61	
Women	27 (19.4%)	55 (22.1%)	0.5
Ejection fraction (%)	50 ± 11	51 ± 11	0.3
Acute coronary syndromes	72 (51.7%)	133 (53.4%)	0.2
Current cigarette smoking	36 (26.1%)	70 (28.1%)	0.2
Insulin-dependent diabetes	19 (13.6%)	25 (10%)	0.2
Systemic hypertension	84 (60.4%)	151 (60.1%)	0.9
Previous myocardial infarction	55 (39.6%)	92 (37%)	0.3
History of CABG	19 (13.6%)	35 (14%)	0.5
Baseline cholesterol	204 ± 36	233 ± 42	0.001
Baseline low-density lipoprotein	123 ± 33	146 ± 36	0.001
Baseline high-density lipoprotein	48 ± 15	49 ± 12	0.6
Triglycerides	161 ± 92	178 ± 83	0.09
CRP level (mg/dl)	1.3 ± 1.6	1.2 ± 1.5	0.4
No. of diseased vessels			
1	40 (28.7%)	76 (30.5%)	
2	41 (29.5%)	75 (30.1%)	0.8
3	58 (41.8%)	98 (39.4%)	
Lesion type (ACC-AHA)			
A	0 (0%)	2 (0.8%)	
B	108 (77.7%)	191 (76.8%)	0.3
C	31 (22.3%)	56 (22.4%)	
Treated vessel			
LAD	57 (41%)	124 (49.8%)	
LCX	26 (18.7%)	31 (12.5%)	0.2
RCA	50 (36%)	77 (30.9%)	
SVG	6 (4.3%)	17 (6.8%)	
Maximum inflation pressure (atm)	14 ± 2	14 ± 2	0.3
Ballon/vessel ratio	1.06 ± 0.1	1.05 ± 0.1	0.3
Cumulative stent length (mm)	21 ± 12	22 ± 13	0.6

ACC-AHA = American College of Cardiology–American Heart Association lesion classification; CABG = coronary artery bypass graft; CRP = C-reactive protein; LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery; SVG = saphenous vein graft.

RESULTS

Baseline characteristics. The baseline clinical, angiographic, and procedural characteristics of the study population are summarized in Table 1. Except for cholesterol levels, patients with or without statin therapy did not differ in any clinical or procedural variable. The CRP levels ranged from 0.0 to 8.0 mg/dl, with a median value of 0.6 mg/dl.

Effects of statin therapy. To investigate for evidence of an interrelation between inflammation and statin therapy, the patients were divided into four groups on the basis of the presence or absence of elevated CRP levels (above median value) and on the presence or absence of statin therapy. As shown in Figure 1, a significantly increased risk for recurrent adverse coronary events existed across the four groups of patients ($p = 0.003$). Compared with the lowest-risk group (patients with CRP levels below the median level receiving statin therapy), patients with elevated CRP levels without statin therapy experienced the highest risk of recurrent coronary events (RR 2.37, 95% CI [1.3 to 4.2]). Importantly, in the presence of statin therapy, the RR for recurrent events was significantly reduced in patients with elevated CRP levels (RR 1.27 [0.7 to 2.1]) to about the same degree as in patients with CRP levels below 0.6 mg/dl and who did not receive statin therapy (RR 1.1 [0.8 to 1.3]).

Table 2 summarizes the individual clinical end points combined for the primary end point analysis as illustrated by Kaplan-Meier survival curves (Fig. 2). Myocardial infarctions that were not related to the target vessel occurred in three patients with elevated CRP levels receiving statin therapy. The effect of lipid lowering was essentially identical in the two groups of patients receiving statin treatment (30.8 ± 32 mg/dl vs. 34.3 ± 40 mg/dl, $p = 0.6$), whereas lipid levels remained unchanged in the no-statin groups.

Angiographic follow-up. Table 3 summarizes the quantitative angiographic data obtained at baseline and at follow-up angiography. Patients with elevated CRP levels had significantly higher restenosis rates. However, statin therapy reduced the excess risk for restenosis development especially in patients with elevated CRP levels (34.9% vs. 50%, $p = 0.04$, respectively). When the categorical criterion of ≥50% diameter stenosis at follow-up was used to assess restenosis development, the difference among the four groups (treated or nontreated) was highly significant ($p < 0.005$).

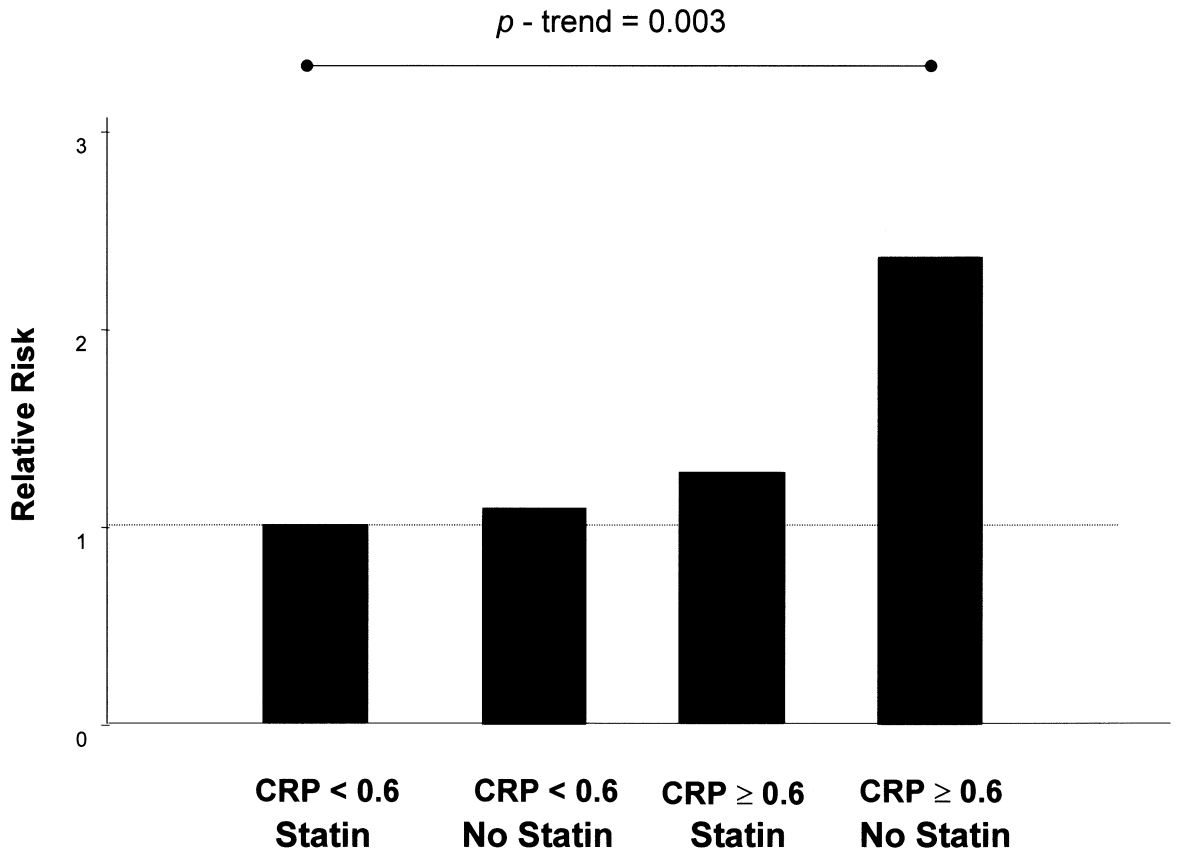

Figure 1. Relative risks for primary combined end point events (death, myocardial infarction, target vessel revascularization) within six-month follow-up according to the presence or absence of elevated C-reactive protein (CRP) levels (above median value 0.6 mg/dl) or presence or absence of statin treatment in patients following coronary stent implantation.

Multivariate analysis. RESTENOSIS. Logistic regression analysis revealed that statin therapy ($p = 0.04$), elevated CRP levels ($p = 0.02$), MLD post-stent implantation ($p = 0.02$) and the number of stents implanted ($p = 0.03$), but not reference segment diameter ($p = 0.6$), diabetes ($p = 0.15$) or total serum cholesterol levels ($p = 0.15$), were independent predictors of stent restenosis.

CLINICAL EVENTS. On logistic regression analysis, statin therapy ($p = 0.03$), MLD post-stent ($p = 0.04$), and stent length ($p = 0.01$), but not reference vessel size ($p = 0.5$), cholesterol levels ($p = 0.1$), and diabetes ($p = 0.2$) were independently associated with the occurrence of a primary clinical end point. Furthermore, when a multivariate Cox regression analysis was performed, only statin therapy ($p = 0.04$), MLD post-stent ($p = 0.04$) and stent length ($p = 0.02$) remained independent predictors of an adverse clinical outcome. Importantly, in the presence of statin therapy, an elevated CRP level was no longer an independent predictor for subsequent adverse coronary events.

DISCUSSION

Major findings. The results of the present study demonstrate that statin therapy abrogates the increased risk for adverse cardiac events associated with elevated CRP serum

Table 2. Clinical Events at Six-Month Clinical Follow-Up

	CRP < 0.6 mg/dl (n = 181)			CRP ≥ 0.6 mg/dl (n = 207)		
Six-months (n = 388)	No Statin (n = 56)	Statin (n = 125)	p Value	No Statin (n = 83)	Statin (n = 124)	p Value
Subacute stent thrombosis	0 (0%)	0 (0%)	0.9	4 (4.8%)	4 (3.2%)	0.5 (0.056)*
MI (target vessel)	0 (0%)	2 (1.6%)	0.4	6 (7.2%)	6 (4.8%)	0.4 (0.1)*
Death (cardiac)	2 (3.5%)	0 (0%)	0.2	5 (6.0%)	3 (2.4%)	0.3 (0.1)*
TVR	16 (29.6%)	34 (27.2%)	0.8	32 (38.6%)	36 (29.0%)	0.17 (0.2)*
Primary combined endpoint (Target vessel MI, death, TVR)	18 (32.1%)	34 (27.2%)	0.4	39 (47%)	40 (32.3%)	0.03 (0.028)*

*p Value obtained from Kruskal-Wallis test for multiple comparisons (log-rank test $p = 0.012$); myocardial infarction (MI) end point consists of nonfatal and fatal MI. CRP = C-reactive protein; TVR = target vessel revascularization.

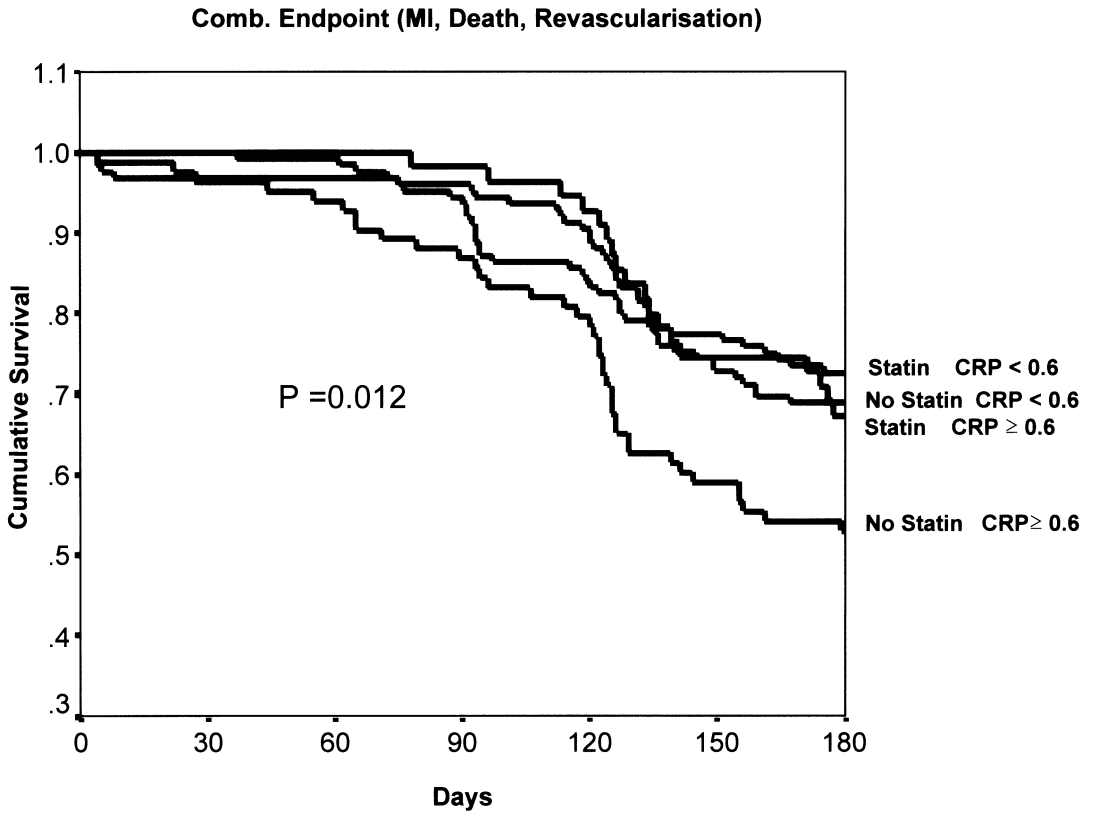

Figure 2. Cumulative survival curves for primary combined end point events (death, myocardial infarction [MI], target vessel revascularization) within six-month follow-up according to the presence or absence of elevated C-reactive protein (CRP) levels (above median value 0.6 mg/dl) or presence and absence of statin treatment in patients following coronary stent implantation. The p value was obtained from the log-rank test.

levels indicative of low-grade inflammation in patients undergoing coronary stent implantation. The data of the present study are highly reminiscent of a previously published report demonstrating that pravastatin attenuated the increased risk of recurrent coronary events among stable patients with a prior history of MI but with elevated CRP serum levels (9). However, in the present study, the beneficial effects of statin therapy were observed within a

Table 3. Quantitative Coronary Angiographic Analysis

	CRP < 0.6 mg/dl (n = 181)			CRP ≥ 0.6 mg/dl (n = 207)		
	No Statin (n = 56)	Statin (n = 125)	p Value	No Statin (n = 83)	Statin (n = 124)	p Value
Pre-PTCA						
Reference diameter (mm)	3.0 ± 0.6	2.9 ± 0.5	0.4	2.97 ± 0.6	3.1 ± 0.6	0.3
MLD (mm)	0.81 ± 0.6	0.82 ± 0.6	0.8	0.7 ± 0.6	0.75 ± 0.6	0.6
Percent stenosis	72 ± 17	72 ± 17	0.7	77 ± 17	76 ± 17	0.8
Post-stent						
Reference diameter (mm)	3.0 ± 0.5	3.0 ± 0.5	0.6	3.0 ± 0.5	3.0 ± 0.5	0.4
MLD (mm)	2.6 ± 0.5	2.57 ± 0.5	0.7	2.6 ± 0.5	2.65 ± 0.5	0.3
Percent stenosis	14 ± 12	15 ± 11	0.7	15 ± 13	15 ± 11	0.9
Acute gain (mm)	1.9 ± 0.6	1.9 ± 0.7	0.4	2.0 ± 0.7	2.0 ± 0.7	0.9
	No Statin (n = 44)	**Statin (n = 114)**	**p Value**	**No Statin (n = 66)**	**Statin (n = 113)**	**p Value**
Follow-up (n = 337)						
Reference diameter (mm)	2.96 ± 0.5	2.87 ± 0.85	0.4	3.0 ± 0.6	3.0 ± 0.6	0.6
MLD (mm)	1.7 ± 0.8	1.8 ± 0.8	0.4	1.57 ± 0.95	1.84 ± 0.87	0.07 (0.05)*
% stenosis	42 ± 24	36 ± 23	0.2	50 ± 26	40 ± 24	0.024 (0.008)*
Late loss	0.86 ± 0.7	0.7 ± 0.7	0.3	0.99 ± 0.88	0.63 ± 0.8	0.048 (0.06)*
Restenosis rate ≥50%	16 (38.0%)	25 (21.9%)	0.07	33 (50%)	39 (34.5%)	0.04 (0.003)†

*p Value from ANOVA. †p Value from Kruskal-Wallis test for multiple comparisons.
CRP = C-reactive protein; MLD = minimal lumen diameter; PTCA = percutaneous transluminal coronary angioplasty.

six-month follow-up period, whereas in the CARE study—as in the other lipid-lowering trials—approximately two years of treatment were required before a significant reduction in cardiovascular events could be discerned (11,15–17).

Recent data of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial (18) indicated that the beneficial effects of statin therapy also extend to patients experiencing an acute ischemic coronary event. However, in the MIRACL study a conservative treatment strategy for patients with acute coronary syndromes was anticipated (18). Results of the present study now indicate the potential role of statins to modify clinical outcome further in patients undergoing an aggressive interventional approach with coronary stent implantation.

Pathophysiologic mechanisms of statin effects. Systemic inflammatory reactions play a pivotal role for neointima formation within stents (19). Patients with elevated CRP serum levels exhibit a marked hyperresponsiveness of the inflammatory system to nonspecific stimuli like vessel wall traumatization by balloon angioplasty (20). In addition, elevated CRP levels are associated with a dramatically impaired endothelial vasodilator function (21). Finally, activation of inflammatory cells and cytokines can aggravate local thrombotic complications by increasing procoagulant or platelet activity or promoting thrombin generation (22). Thus, preprocedural activation of inflammatory cells appears to profoundly modify the vessel wall response to injury (23–25), leading to a significant increase in clinical complications and restenosis rates following coronary stent implantation, as observed in the present study.

Conversely, statins have been shown to exert beneficial physiologic effects within weeks. In conjunction with lowering lipid levels, statins have been shown to reduce vascular inflammation (26), improve endothelial function (27) and reduce platelet aggregability and thrombus formation (28). Thus, statins appear to interfere specifically with the pathophysiological mechanisms implicated in the dramatically accelerated progression of atherosclerotic disease in implanted stents in patients with low-grade systemic inflammation.

Study limitations. The lack of a placebo-controlled, randomized design might be regarded as a major limitation of the present study. However, statin therapy was initiated based on elevated serum cholesterol levels, but not on CRP serum levels. In fact, preprocedural CRP levels did not differ between patients with or without statin therapy. In addition, CRP levels did not correlate with serum cholesterol levels. C-reactive protein levels were not known either to the physician in charge of initiating statin therapy, nor to the operator at the time of reangiography, nor to the technician analyzing the coronary angiograms. Thus, it is highly unlikely that a selection bias might have contributed to the observed outcome.

Finally, glycoprotein IIb/IIIa receptor blockers were infrequently used in this patient population. Hence, we cannot comment on potentially additional effects of statins in patients with glycoprotein IIb/IIIa-receptor blockade.

Conclusions. Results of the present study demonstrate that statin therapy significantly attenuates the increased risk for major adverse cardiac events in patients with elevated CRP levels undergoing coronary stent implantation, suggesting that statin therapy interferes with the detrimental effects of inflammation on accelerated atherosclerotic disease progression following coronary stenting. Elevated CRP levels appear to be a powerful tool to target statin therapy to patients who are exposed to the highest risk for ischemic coronary events following coronary stent implantation.

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