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Immunosuppressive Therapy for the Prevention of Restenosis After Coronary Artery Stent Implantation (IMPRESS Study)

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OBJECTIVES This study tested the effect of oral prednisone on clinical and angiographic restenosis rate after successful stent implantation in patients with persistent elevation of systemic markers of inflammation after the procedure.

BACKGROUND Experimental studies have shown that corticosteroids have the potential to reduce the inflammatory response associated with stent implantation.

METHODS Eighty-three patients undergoing successful stenting with C-reactive protein (CRP) levels >0.5 mg/dl 72 h after the procedure were randomized to receive oral prednisone or placebo for 45 days. The primary clinical end point was 12-month event-free survival rate (defined as freedom from death, from myocardial infarction, and from recurrence of symptoms requiring additional revascularization). The angiographic end points were restenosis rate and late loss at six months.

RESULTS Twelve-month event-free survival rates were 93% and 65% in patients treated with prednisone and placebo, respectively (relative risk [RR] 0.18, 95% confidence intervals [CI], 0.05 to 0.61, p = 0.0063). Six-month restenosis rate and late loss were lower in prednisone-treated than in placebo-treated patients (7% vs. 33%, p = 0.001, and 0.39 ± 0.6 mm vs. 0.85 ± 0.6 mm, p = 0.001, respectively).

CONCLUSIONS In patients with persistently high CRP levels after successful coronary artery stent implantation, oral immunosuppressive therapy with prednisone results in a striking reduction of clinical events and angiographic restenosis rate. (J Am Coll Cardiol 2002;40:1935–42)

Successful treatment of patients with stenotic coronary arteries by percutaneous transluminal coronary angioplasty (PTCA) with stent implantation is associated with restenosis in approximately 10% to 50% of cases (1–4). Restenosis after stent implantation is mainly caused by neointimal proliferation through the stent struts (5–7). Experimental studies indicate a marked activation of inflammatory cells at the site of stent struts, which is likely to play a key role in the process of neointimal proliferation and restenosis (8–12). Indeed, interleukin-1 and -6, secreted by activated macrophages, are powerful stimuli for smooth muscle cell proliferation. Of note, interleukin-1 and -6 are also hepatocyte-stimulating factors inducing the production of acute-phase proteins including C-reactive protein (CRP) (13–16). Accordingly, preprocedural high plasma levels of CRP and a persistent elevation of plasma levels of CRP following successful stent implantation have been found to predict the risk of restenosis (17,18).

Although the powerful anti-inflammatory effects of corticosteroids are well known (19), previous studies in humans failed to demonstrate a significant reduction of restenosis rate after successful PTCA in unselected populations of anginal patients (20–22). However, the data presently available regarding the use of corticosteroids in patients undergoing coronary artery stent implantation are meager.

We carried out a double-blind, randomized, placebo-controlled study to assess the effects of oral prednisone on restenosis rate after successful stent implantation in patients with persistently high plasma levels of CRP after the procedure and, therefore, more likely to be susceptible to the anti-inflammatory effects of treatment.

METHODS

Patient selection. The study population consisted of patients enrolled from two centers with the following characteristics: typical angina pectoris, documented myocardial ischemia, or both; one-vessel or multiple-vessel disease (defined as a reduction ≥50% of the luminal diameter, as measured by quantitative computerized angiography) undergoing successful implantation of a single stent of a length <19 mm; CRP ≤0.5 mg/dl before stenting and >0.5 mg/dl 72 h after the procedure. The reason only one lesion was treated in patients with multivessel disease was because the other lesions were localized in a totally occluded vessel, in

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Abbreviations and Acronyms

CCS = Canadian Cardiovascular Society
CK = creatine kinase
CRP = C-reactive protein
MI = myocardial infarction
MLD = minimal lumen diameter
PTCA = percutaneous transluminal coronary angioplasty
TIMI = Thrombolysis In Myocardial Infarction
WHO = World Health Organization

vessels not susceptible to be treated percutaneously or surgically, or in vessels supplying infarcted myocardial regions with no evidence of residual ischemia. Exclusion criteria were unstable angina (Braunwald class III); previous myocardial infarction (MI) in the last six weeks; treatment of restenotic lesions or vein graft stenosis; total occlusions; connective tissue diseases; renal failure; left ventricular ejection fraction <40%; New York Heart Association functional class >II; steroid therapy within the preceding 30 days; contraindication to steroid use including active infective diseases, active peptic ulcer, diabetes treated with medical therapy, uncontrolled severe hypertension, pregnancy. The study protocol was approved by the Institutional Ethics Committee in each center, and written informed consent was obtained for all patients.

Study design. After eligibility, patients were randomly assigned to either placebo or prednisone group. In a double-blind fashion, either prednisone (Deltacortene, Bruno Farmaceutici, Rome, Italy) or placebo was given orally 72 h after the procedure according to the following protocol: 1 mg/kg for the first 10 days; 0.5 mg/kg from day 11 to day 30; 0.25 mg/kg from day 31 to day 45. The dosage of prednisone was chosen according to the standardized immunosuppressive protocol utilized for heart transplantation (23).

Clinical evaluation. Exertional angina was classified according to the system of the Canadian Cardiovascular Society (CCS) (24). Patients were classified as having unstable angina according to Braunwald's criteria (25). Patients were classified as having had an MI according to World Health Organization (WHO) criteria (26). Conventional risk factors were examined by direct questioning of patients and by a review of hospital records, as previously described (27).

Stent implantation. Three days before the procedure all patients were treated with aspirin 325 mg once daily and ticlopidine 250 mg twice daily. A bolus of 100 U/kg of heparin was administered after sheath insertion, and supplemental doses were then given to maintain an activated clotting time >300 s. The stent type, the need for predilation, and the final size of the balloon for stent implantation were chosen by the operator to obtain a close to zero angiographic residual stenosis. Only balloon-expandable, stainless steel tubular stents with multicellular design were used. After the procedure, arterial sheath was removed when the activated clotting time was ≤150 s.

Patients continued to receive aspirin 325 mg once daily indefinitely, ticlopidine 250 mg twice daily for four weeks, and pantoprazole 40 mg once daily for 45 days.

Laboratory assessment. Venous blood samples were obtained on admission to the hospital and 72 h after the procedure. Plasma samples for CRP concentration were analyzed by an immunoturbidimetric method (Roche Unimate 3 CP, Milan, Italy). The normal upper reference value for CRP with this method is 0.5 mg/dl. For total creatine kinase (CK), the MB isoform of creatine kinase (CK-MB), and for cardiac troponin I, venous blood samples were obtained immediately before the procedure and 6, 24, and 48 h after the procedure. Plasma samples were analyzed for CK and CK-MB with commercially available immunochemical tests and cardiac troponin I by an immunoenzymatic "sandwich" assay. Non–Q-wave MI was defined as post-procedural CK-MB elevations ≥3 times the upper normal limit.

Clinical and angiographic assessment. Patients were seen in outpatient clinic at 1, 3, 6, and 12 months. Follow-up coronary angiography was performed six months after the initial procedure or earlier if symptoms suggestive of coronary restenosis developed before that time. The angiographic end points were restenosis rate (defined as an in-stent stenosis ≥50% at follow-up coronary angiography) and late loss (defined as the minimal luminal diameter [MLD] after the procedure minus the value at six-month follow-up).

The clinical end point was 12-month event-free survival rate, defined as freedom from death, from MI, or from recurrence of symptoms requiring additional revascularization.

Angiography was performed in two orthogonal views after intracoronary administration of 200 μg of nitroglycerin. Angiographic variables were assessed before the procedure, immediately after, and at follow-up; the same two orthogonal views were always obtained. All angiograms were analyzed in an independent centralized core laboratory (European Imaging Laboratory, Rome, Italy). Quantitative angiography analysis was done by use of the automated edge-detection system CMS (Medis Medical Imaging Systems) (28) by experienced technicians who were unaware of the study protocol. Both high accuracy and precision for this system have been previously demonstrated (28). Nonetheless, 40 randomly selected measurements were reanalyzed by a blinded observer. Results were reproducible. The mean of the difference between measurements was 0.05 ± 0.2 mm ($p = 0.45$) for MLD and 0.09 ± 0.35 mm ($p = 0.40$) for diameter stenosis.

An independent Data and Safety Monitoring Board was instructed to verify the incidence of clinical events and to review patient records.

Statistical analysis. Patients were randomized according to a computer-generated random code. We calculated the size

Table 1. Baseline Clinical Characteristics of the 83 Patients

Characteristic	Prednisone Group (n = 41)	Placebo Group (n = 42)	p Value
Age (yrs)	63 ± 9	65 ± 9	0.15
Male gender, n (%)*	32 (83)	37 (88)	0.23
Risk factors, n (%)			
Current smoker	12 (29)	11 (26)	0.38
Diabetes mellitus	0 (0)	0 (0)	
Hypercholesterolemia†	18 (44)	18 (43)	0.46
Hypertension	16 (39)	15 (35)	0.38
Family history	13 (32)	10 (24)	0.21
Obesity*‡	2 (5)	3 (7)	0.78
Exertional angina (CCS class), n (%)*§			
I	6 (15)	10 (24)	
II	14 (34)	11 (26)	0.17
III	14 (34)	13 (30)	
IV	2 (5)	4 (10)	
Unstable angina (Braunwald class <III)*	5 (12)	4 (10)	0.9
Medical treatment, n (%)			
Aspirin	34 (83)	36 (86)	0.37
Beta-blockers	16 (39)	15 (36)	0.38
Calcium antagonists	18 (44)	17 (40)	0.38
Nitrates	16 (39)	20 (48)	0.22
Statins*	6 (15)	4 (10)	0.51
ACE inhibitors	14 (34)	13 (31)	0.38

Plus-minus values are means ± SD. *Fisher exact test was used. †Total cholesterol ≥200 mg/dl. ‡Body mass index ≥27.8 in men and ≥27.3 in women. §According to the classification system of the Canadian Cardiovascular Society (CCS).
ACE = angiotensin-converting enzyme.

of the sample necessary to achieve 80% statistical power at a two-sided significance level of 0.05. The calculated sample size was based on a previous report of about 24% of clinical restenosis at 12 months in stable patients with levels of CRP >0.5 mg/dl 72 h after stent implantation (17). Because clinical restenosis rate underestimates at about 10% the incidence of in-stent restenosis, we assumed that the restenosis rate in this subset of high-risk patients was 35%. To justify a pharmacotherapeutic intervention with a high dose of prednisone, we required a reduction of restenosis rate to 5%. Assuming a 20% drop-out rate, we set a goal of 83 patients for the study. The end points of the study were the event-free survival at 12 months and the occurrence of in-stent restenosis at 6 months. All end-point analyses were performed on an intention-to-treat basis, with all randomized patients included in the analyses.

Continuous variables are expressed as mean ± SD and compared by unpaired Student *t* test; nominal variables are expressed as proportions and compared by chi-squared test or the Fisher exact test as appropriate. Event-free survival curves were obtained by the Kaplan-Meier method and compared by log-rank test. The association of drug therapy with the end point of the study was assessed by Cox proportional hazard regression analysis. Univariate analysis was also applied to assess the association of other clinical and angiographic variables with the end point of the study. Stepwise multivariate Cox regression analysis was used to assess the independent association of drug therapy with the end point, by adjusting for other significant variables. To this aim, all variables with a p value ≤0.1 at univariate analysis were considered in the regression model. Variables were inserted in the model in decreasing order, according to univariate statistical significance.

For purposes of Cox analysis some continuous variables were dichotomized as follows: 1) anginal classification at presentation: stable vs. unstable angina; 2) Thrombolysis In Myocardial Infarction (TIMI) flow grade before and after the procedure (TIMI flow grade 3 vs. TIMI flow grade <3). A two-tailed p value <0.05 was always requested for statistical significance. All statistical analyses were performed with Statview (version 5.0) for Windows 8.0 (SAS Institute).

RESULTS

Clinical and angiographic characteristics of the patients. Between January 1999 and March 2001, a total of 527 consecutive patients with normal basal levels of CRP underwent successful stent implantation in the participating centers, of whom 137 had CRP levels persistently higher than 0.5 mg/dl 72 h after the procedure. Of these, 50 patients did not meet the inclusion criteria, 4 did not give consent, and 83 (71 men; mean age 64 ± 9 years; range, 40 to 80 years) were enrolled in the study. Forty-one patients were randomly assigned to receive prednisone and 42 to receive placebo. No significant differences existed in clinical or angiographic characteristics between the two groups (Tables 1 and 2).

Drop-out and collateral effects. Two patients assigned to placebo treatment dropped out of the study after randomization because they withdrew their consent to repeat angiography at six months. Systemic therapy with pred-

Table 2. Baseline Angiographic and Procedural Characteristics

Characteristic	Prednisone Group (n = 41)	Placebo Group (n = 42)	p Value
Ejection fraction (%)	57 ± 10	56 ± 7	0.84
Artery affected, n (%)			
Left anterior descending coronary	22 (53)	21 (50)	
Right coronary	8 (20)	11 (26)	0.76
Circumflex coronary	11 (27)	10 (24)	
Type of lesion, (%)*†			
A	10	10	
B1	51	57	
B2	29	26	0.7
C	10	7	
Reference diameter (mm)	3.06 ± 0.47	3.13 ± 0.62	0.61
Percent stenosis (%)	71 ± 9	70 ± 11	0.53
Maximal inflation pressure (atm)	11 ± 2.0	11 ± 3.0	0.66
Total duration of inflation (s)	44 ± 18	46 ± 15	0.69
Balloon diameter (mm)	3.43 ± 0.38	3.43 ± 0.45	0.98
Final stenosis (%)	14 ± 9	15 ± 9	0.91
Minimal luminal diameter (mm)	2.75 ± 0.4	2.73 ± 0.5	0.81
Vessel disease, n (%)*			
One vessel	23 (56)	25 (59)	
Two vessels	14 (34)	12 (29)	0.84
Three vessels	4 (10)	5 (12)	

Plus-minus values are means ± SD. *Fisher exact test was used. †Lesions classified according to the system of the American College of Cardiology–American Heart Association Task Force.

nisone was well tolerated: one patient randomized to prednisone complained of severe gastric pain five days after randomization and stopped the therapy. Two patients with moderate hypertension controlled by drug treatment before stent implantation needed upgrading of antihypertensive treatment during the study period. One patient exhibited transient glucose intolerance, which normalized after the study period. One patient randomized to placebo complained of gastric pain.

In-hospital clinical outcome. In-hospital outcome was similar between the two groups (Table 3). No patient had subacute thrombosis and/or non–Q-wave MI after stent implantation procedure. Post-procedural CK, CK-MB, and troponin I levels were always within normal range (Table 4).

Table 3. Clinical Outcome in the Hospital and During Follow-Up

Event	Prednisone Group (n = 41)	Placebo Group (n = 42)	p Value
In hospital, n (%)			
Procedural success	41 (100)	42 (100)	
Procedural failure	0	0	
Vascular complications	0	0	
Non–Q-wave MI	0	0	
Subacute thrombosis	0	0	
At 12 months, n (%)			
Event-free survival	38 (93)	27 (65)	0.0063
Death	0 (0)	1 (2)	0.16
Nonfatal infarction	0 (0)	1 (2)	0.16
Additional revascularization*	3 (7)	14 (33)	0.001
Any event	3 (7)	15 (35)	0.0063

*All additional interventions were target vessel revascularizations.
MI = myocardial infarction.

Clinical outcome at 12 months. Planned clinical follow-up data were available for all randomized patients. Clinical events at 12 months are detailed in Table 3. A primary clinical end point was reached by 3 of the 41 patients randomly assigned to prednisone group (7%), as compared with 15 of the 42 patients randomly assigned to placebo group (35%). All these patients had documented restenosis of the target vessel, which resulted in an acute MI

Table 4. Levels of CK, CK-MB, and Troponin I Before and 6, 24, 48 h After the Procedure; Levels of CRP Before and 72 h After the Procedure

	Prednisone Group (n = 41)	Placebo Group (n = 42)	p Value
Basal			
CK (U/l)	75 ± 34	70 ± 32	0.24
CK-MB (U/l)	8 ± 7	9 ± 5	0.40
Troponin I, ng/ml	0.05 ± 0.03	0.05 ± 0.02	0.42
CRP, mg/l	3.0 ± 0.6	3.0 ± 0.8	0.95
6 h after the procedure			
CK (U/l)	80 ± 37	76 ± 39	0.55
CK-MB (U/l)	9 ± 6	8 ± 7	0.49
Troponin I, ng/ml	0.07 ± 0.03	0.05 ± 0.04	0.63
24 h after the procedure			
CK (U/l)	82 ± 44	81 ± 36	0.70
CK-MB (U/l)	12 ± 6	13 ± 7	0.59
Troponin I, ng/ml	0.08 ± 0.04	0.07 ± 0.06	0.59
48 h after the procedure			
CK (U/l)	90 ± 43	87 ± 46	0.61
CK-MB (U/l)	13 ± 5	14 ± 9	0.41
Troponin I, ng/ml	0.04 ± 0.03	0.06 ± 0.04	0.39
72 h after the procedure			
CRP, mg/l	18.4 ± 11	17.2 ± 11.7	0.21

CK = creatine kinase; CRP = C-reactive protein.

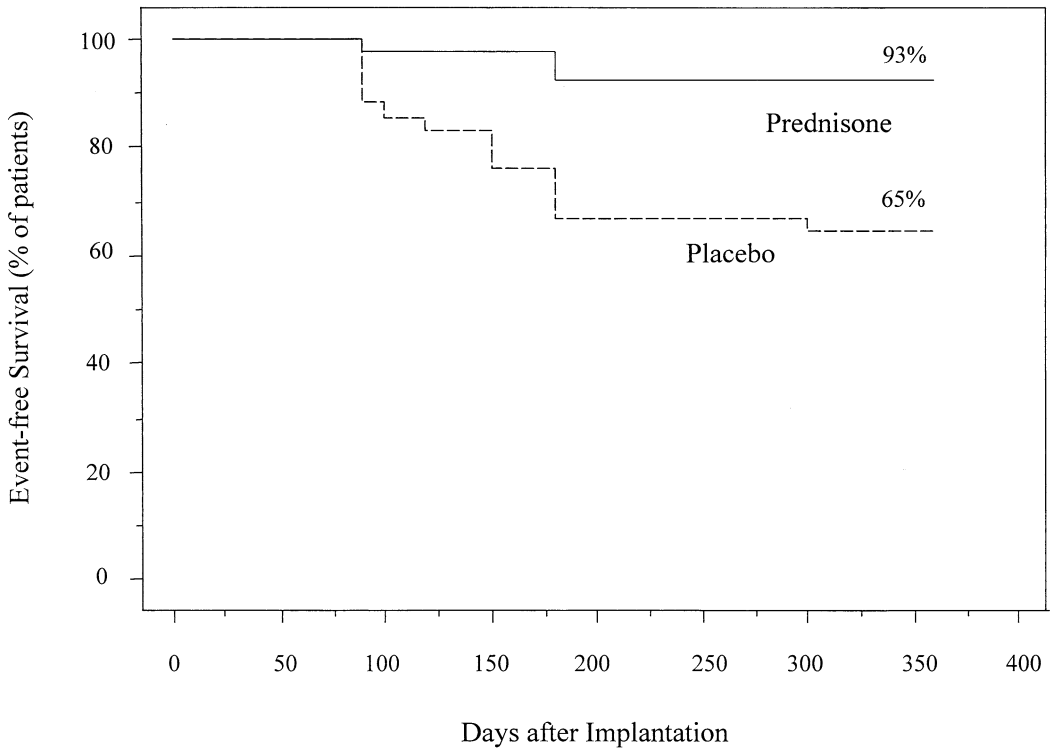

Figure 1. Event-free survival (death, myocardial infarction, recurrence of symptoms requiring additional revascularization) curves of the two study groups at 12-month follow-up. The rate of event-free survival was significantly higher in the prednisone group than in the placebo group ($p < 0.0016$ by Cox proportional hazards regression analysis).

in one patient in the placebo arm. One patient died in the placebo arm.

Log-rank test showed a highly significant statistical difference between event-free survival curves of the two study groups ($p = 0.0016$, Fig. 1). Compared with placebo, the relative risk (RR) reduction of events with prednisone was 0.18 (95% confidence intervals [CI]: 0.05 to 0.61, $p = 0.0063$). Stepwise multivariate Cox regression analysis showed that prednisone therapy was independently associated with the occurrence of events, when adjusted for possible confounding variables (RR: 0.15; 95% CI: 0.04 to 0.59; $p = 0.007$). Other covariates, which resulted in being predictors of the primary end point at univariate analysis, included presentation with stable angina (RR: 0.26; 95% CI: 0.08 to 0.80, $p = 0.018$); TIMI flow grade 3 after coronary stenting (RR: 0.23, 95% CI: 0.07 to 0.80, $p = 0.02$); and beta-blocking therapy (RR: 0.17, 95% CI: 0.04 to 0.76, $p = 0.02$).

Angiographic outcome at six months. Angiographic follow-up data were obtained for 98% of the eligible patients (Table 5). Restenosis at six-month follow-up occurred in 17 patients (20.5%). Of note, three patients (21%) in the placebo group and one patient (33%) in the treatment group who had angiographic restenosis at six months were completely asymptomatic. Restenosis rates were 7% and 33% in the treatment group and control group ($p = 0.001$), respectively. Late loss and MLD at follow-up were strikingly less in the treatment group than in the control group (0.39 ± 0.6 vs. 0.85 ± 0.6, $p = 0.001$, and 2.36 ± 0.7 vs. 1.88 ± 0.7 mm, $p = 0.003$, respectively). Frequency distribution curves for postprocedure and follow-up percent diameter stenosis of both populations are shown in Figure 2.

DISCUSSION

In this trial, immunosuppressive therapy with prednisone for 45 days in patients with persistently high CRP levels after coronary stent implantation was associated with a striking reduction of 12-month clinical events and 6-month restenosis rate. Indeed, immunosuppressive therapy resulted in a 28% absolute reduction of clinical events and in 26% absolute reduction of restenosis rate.

The key role played by inflammation in neointimal

Table 5. Angiographic Outcome at 6 Months

	Prednisone Group (n = 41)	Placebo Group (n = 42)	p Value
Reference diameter (mm)	3.18 ± 0.5	3.15 ± 0.5	0.79
Restenosis, n (%)	3 (7)	14 (33)	0.001
Degree of stenosis (%)*	26 ± 19	41 ± 18	0.0008
Minimal luminal diameter (mm)*	2.36 ± 0.7	1.88 ± 0.7	0.003
Late loss (mm)*	0.39 ± 0.6	0.85 ± 0.6	0.001
Net gain (mm)*	1.48 ± 0.7	0.92 ± 0.7	0.001

Plus-minus values are means ± SD. Late loss was calculated as the minimal luminal diameter after the procedure minus the value at follow-up, and net gain as the minimal luminal diameter at follow-up minus the value before the procedure. *Refers to 81 patients who completed angiographic follow-up.

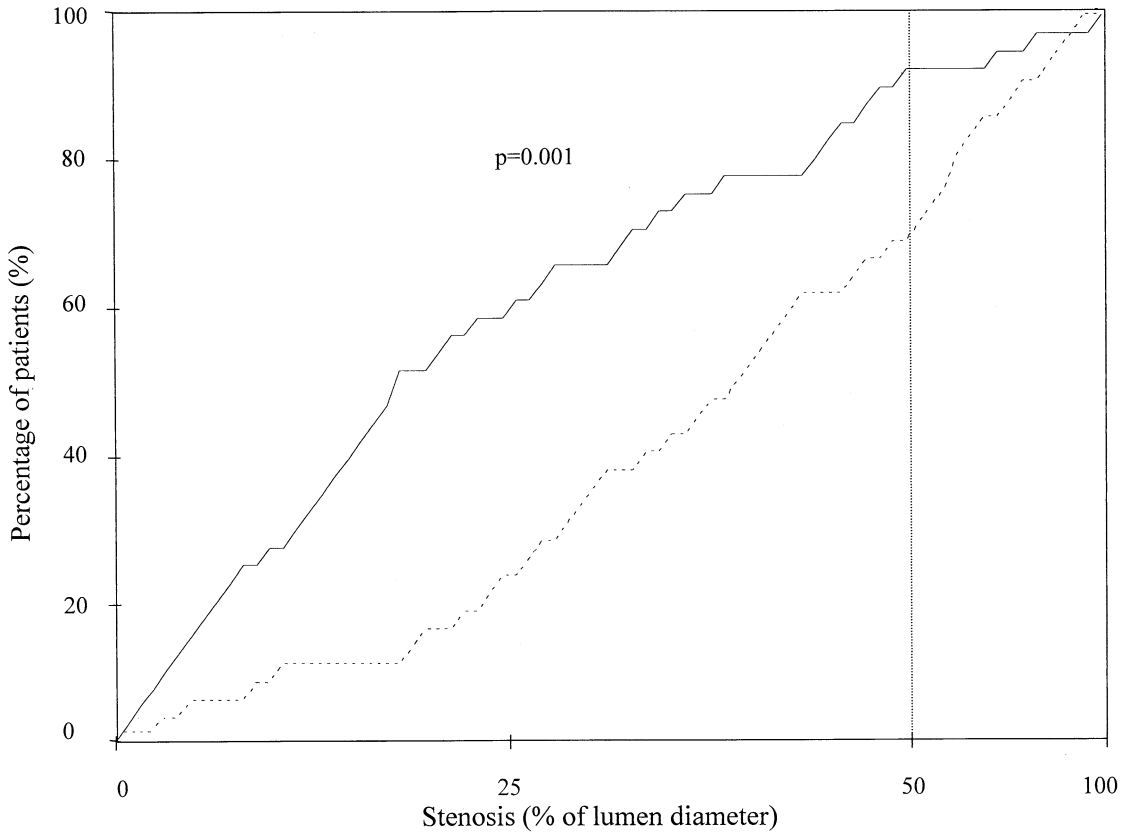

Figure 2. Cumulative frequency distribution curves showing the percentage of stenosis measured at six-month angiographic follow-up. The **vertical broken line** indicates the percentage of patients with (right of the line, 33% vs. 7% in placebo [**dashed line**] and prednisone [**solid line**] groups, respectively) and without restenosis (left of the line, 67% vs. 93% in placebo and prednisone groups, respectively).

proliferation after stent implantation has well been documented in several experimental studies (12) and in a postmortem study in humans (29), and has recently been confirmed in several clinical studies showing that elevated systemic levels of inflammatory markers before or after percutaneous coronary interventions are associated with a higher risk of restenosis (17,18,30,31). In particular, findings indicate that a high level of CRP 72 h after successful coronary stenting is predictive of a worse prognosis at 12 months (17). The high systemic inflammatory response may be due to a further activation of the inflammatory process within the plaque itself as well as to injury during coronary stenting.

Corticosteroids exert a profound inhibitory effect on the inflammatory processes and influence platelet function, smooth muscle cell proliferation, and collagen synthesis (19). Continuous infusion of hydrocortisone over a two-week period in rabbits subjected to aortic balloon injury was found to markedly reduce neointimal hyperplasia (12), yet in previous clinical studies systemic corticosteroid administration failed to reduce restenosis after balloon angioplasty. Stone et al. (20) randomized 102 patients with restenosis after a first PTCA to receive an intramuscular injection of 125 mg of methylprednisolone immediately before and after repeat PTCA, followed by 60 mg of oral prednisone for one week, or placebo. Angiographic follow-up was limited to 53% of patients, and restenosis rate was slightly lower in corticosteroid-treated patients than in placebo-treated patients (36% vs. 40%), although this difference did not reach statistical significance. The randomized, placebo-controlled M-Heart study (21) confirmed in a larger population that a single fixed dose of methylprednisolone before PTCA does not reduce restenosis rate. More recently, in a randomized, placebo-controlled study, Lee et al. (22) found that a single fixed dose of methylprednisolone prior to stent implantation failed to reduce clinical and angiographic restenosis rate.

In this study, treatment with oral prednisone for 45 days after successful stent implantation in selected high-risk patients with persistent systemic signs of inflammation after the procedure was associated with a striking reduction of clinical and angiographic restenosis rate. Several possible explanations may account for the different results between this and previous trials. First, in previous studies steroids were utilized for short periods often after the procedure. Conversely, in our study, prednisone was administered for 45 days, with the highest dosage during the first 10 days (20–22). Indeed, complete neointimal coating of stents is unlikely to be completed earlier than 28 days after the procedure, and in this time period exposure of the metal strut of the stent may trigger a persistent inflammatory

response to a "foreign body" in susceptible patients. Second, in some studies steroids were utilized after balloon angioplasty (20,21) rather than after stenting. It is unlikely that steroids might be helpful in the prevention of recoil and remodeling, which are the main mechanisms of restenosis after balloon angioplasty. Finally, previous studies utilized steroids in unselected populations of patients (20–22) rather than selectively in high-risk patients with evidence of enhanced inflammatory response.

Study limitations. The present study has some limitations. The number of patients enrolled is rather small, although the sample size, determined on the basis of an expected 80% reduction of restenosis rate in the treatment group, had a sufficient power (80% at an alpha level of 0.05) to detect a significant difference between groups. Nonetheless, because of the relatively small sample size, it cannot be ruled out that our results might be false positive, possibly due to chance or differences in unmeasured variables. Thus, a larger randomized trial with prednisone is warranted.

Another limitation is that our study population represents 15% of coronary patients referred to our centers for percutaneous coronary interventions. Indeed, for the purpose of this study, high-risk patients only were enrolled with persistent elevation of CRP after coronary artery stent implantation and without clinical contraindication to prednisone therapy. Of note, patients with diabetes, which represents a major cause of stent restenosis, were excluded because of the harmful effect of steroid therapy in this subset of high-risk patients. However, by studying highly selected patients we could exclude confounding factors due to heterogeneity of patients with coronary artery disease.

C-reactive protein values were assessed by an immunoturbidimetric method and not with the recently recommended high-sensitive CRP assay. However, a recent report comparing the two assays revealed a close correlation and indicated that CRP levels >0.5 mg/dl can be reliably detected using the less expensive immunoturbidimetric method (18).

Six-month angiographic follow-up might have caused an underestimation of restenosis, which, in turn, could have been simply delayed by prednisone. However, this seems unlikely as 12-month event-free survival rate confirmed the angiographic results obtained at 6 months. A practical drawback of this study is the need to measure CRP levels 72 h following the procedure to decide whether to initiate steroid therapy or not. However, it should be noted that CRP measurement does not require hospitalization, and blood sampling may be performed in the outpatient clinic.

Finally, our findings should be evaluated in the context of the newly developed medicated stents, which have been shown to be very effective in the prevention of in-stent restenosis (32). If initial positive results obtained with medicated stents will be confirmed, systemic therapy with prednisone might, however, serve as an adjunctive therapy in selected high-risk patients with persistent evidence of systemic inflammation after coronary stent implantation, or even a convenient alternative to expensive drug-eluting stents. In this context, comparative studies are needed to define the subgroup of patients who will most benefit from either therapy.

Conclusions. Our study shows that in patients with persistent systemic inflammatory response after coronary artery stent implantation, oral therapy with prednisone results in a striking reduction of 6-month restenosis and 12-month clinical events. Therapy with prednisone is generally well tolerated, although it should be carefully monitored to prevent mild side effects. If our results are confirmed in larger trials, prednisone therapy may represent a novel, powerful, and inexpensive treatment for the prevention of in-stent restenosis in selected patients.

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