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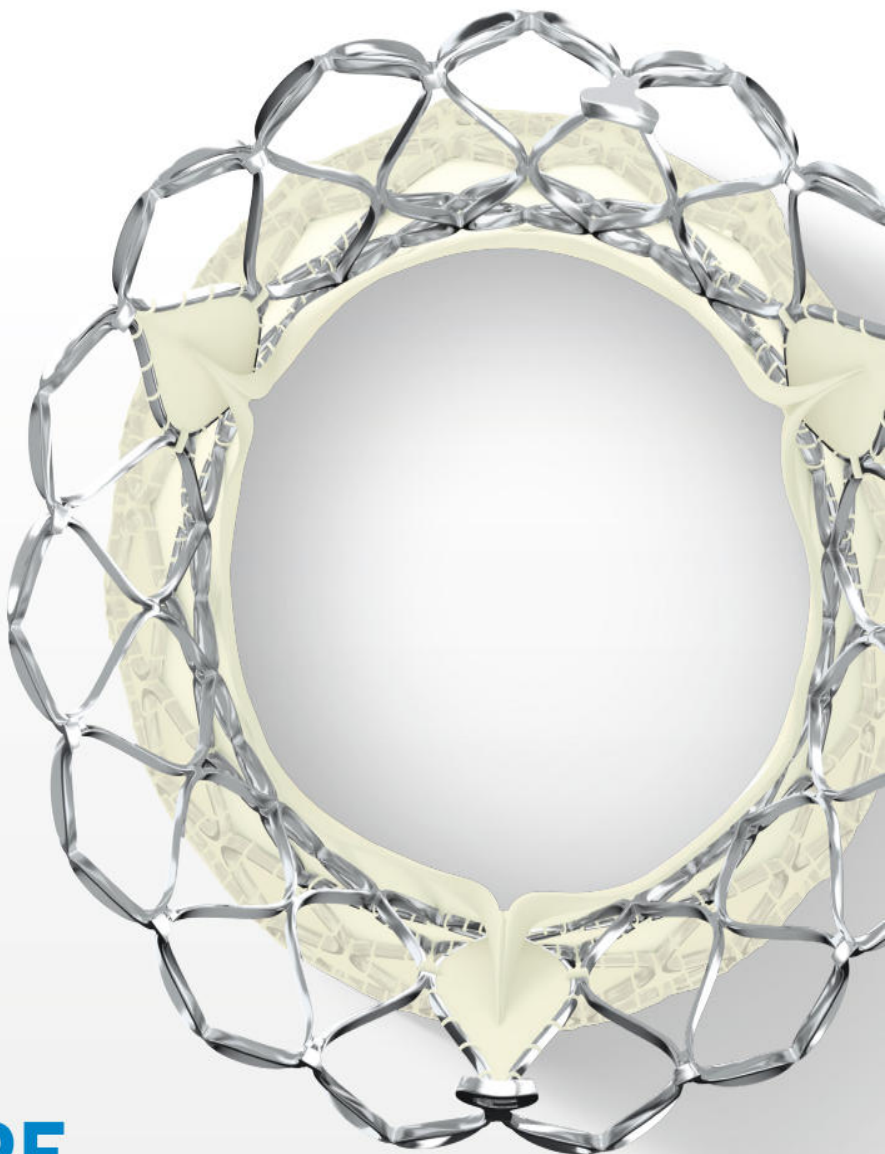

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Effects of Stent Coating on Platelets and Endothelial Cells after Intracoronary Stent Implantation

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Summary

Background: Adhesion molecules are known to be important in the regulation of endothelial cell and platelet functions. Increased platelets P-selectin expression is a marker of stent thrombosis after uncoated stent placement.

Hypothesis: The aim of this study was to compare the effects of intracoronary placement of phosphorylcholine (PC)-coated, versus heparin-coated, versus uncoated stents on platelets and endothelial activity.

Methods: Thirty patients (age 55 ± 10, 27 men) with significant proximal left anterior descending coronary artery stenoses were randomized to elective implantation of PC-coated, versus heparin-coated, versus uncoated stents. Following stent placement, intravenous heparin and aspirin plus ticlopidine were administered. Venous plasma soluble E-selectin, sP-selectin, and intercellular adhesion molecule-1 levels were measured before the procedure and 24 and 48 h thereafter as markers of platelet and endothelial cell activation. Patients were excluded if they had a disease known to influence platelet and endothelial cell function.

Results: Plasma sP-selectin levels decreased significantly after implantation of PC- and heparin-coated stents ($p = 0.04$), but remained unchanged in patients randomized to uncoated stents. Plasma sE-selectin levels increased significantly after uncoated stent placement ($p = 0.04$) and remained unchanged after coated stent implantation.

Conclusion: In patients treated with combined antiplatelet therapy, implantation of PC- and heparin-coated stents decreased platelet activity without activating endothelial cells, whereas placement of uncoated stents led to endothelial activation without changing platelet activity. These results suggest that PC-coated and heparin-coated stents may be advantageous in limiting thrombotic complications.

Key words: intracoronary stents, stent coating, adhesion molecules

Introduction

The use of intracoronary stents for the treatment of coronary artery disease has increased markedly in recent years. In selected patients, the elective implantation of intracoronary stents improves the early and long-term clinical success rates of percutaneous transluminal coronary angioplasty (PTCA).[1–3] The identification of platelet activation as a fundamental mechanism of stent thrombosis has prompted the systematic use of aspirin and other platelet aggregation inhibitors, such as ticlopidine and clopidogrel.[4–6]

Deep vessel injury caused by stent deployment in the diseased artery and a foreign body reaction caused by the implantation of an artificial surface lead to activation of platelets, endothelial cells (EC), leukocytes, and the coagulation system, and are probably important in the pathogenesis of stent thrombosis.[6–10] Since stents are metallic foreign bodies, hence thrombogenic, stent coating materials have been developed to increase their biocompatibility and thromboresistance.

Adhesion molecules play an important role in mediating the interaction of EC, leukocytes, and platelets in inflammation and thrombogenesis.[11–13] P-selectin is released from activated platelets, and intercellular adhesion molecule-1 (ICAM-1) and E-selectin are released from activated EC. Previous studies have shown that the expression of P-selectin is decreased or unchanged after intracoronary uncoated stent implantation in patients receiving combined aspirin and ticlopidine therapy.[5,14,15] Furthermore, an increase in P-selectin expression after coronary angioplasty predicted an increased risk of acute ischemic events after angioplasty and stent implantation.[16,17]

Changes in levels of soluble adhesion molecules after stent implantation, which may reflect the effects of stent coating on platelet function and endothelial cells after intracoronary stent implantation, have not been described. The present study was performed to examine and compare the effects of intracoronary placement of phosphorylcholine (PC)-coated, versus heparin-coated, versus uncoated stents on platelets

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and endothelial cells. Enzyme-linked immunosorbent assay (ELISA) was used to measure the changes in plasma soluble adhesion molecules released from activated EC and platelets.

Patient Population and Methods

Study Population

The study group consisted of 30 consecutive patients (27 men, 3 women, mean age 55 ± 10 years) scheduled to undergo elective PTCA and stent implantation limited to the left anterior descending coronary artery. Each patient gave written informed consent to participate. All patients had stable exertional angina and an abnormal exercise stress test attributable to a > 70% proximal left anterior descending coronary artery stenosis, classified as type A or B1 lesion. They were randomized to undergo elective implantation of heparin-coated (Jostent, JOMED Implantate GmbH, Rangendingen, Germany), versus PC (BioDivYsio, Biocompatibles Limited, Surrey, UK), versus uncoated (AVE stent, Arterial Vascular Engineering Inc, Santa Rosa, Calif., USA) stents. All stents were successfully implanted immediately after PTCA.

Patients with < 6 weeks old myocardial infarction, unstable angina, or coronary artery bypass graft performed within 6 months were excluded from randomization. In addition, patients with diseases known to influence adhesion molecule levels, including infections, diabetes mellitus, malignancy, chronic liver disease, renal insufficiency, connective tissue disease, and treatment with anti-inflammatory or anticoagulant drugs were also excluded from the study.

Stent Implantation and Postprocedural Management of Patients

Percutaneous transluminal coronary angioplasty was performed by standard procedures via the femoral approach. After coronary angiography, 10,000 IU of unfractionated heparin were given just before insertion of the catheter system. No patient developed abrupt or threatened vessel closure or coronary artery dissection during PTCA. After successful PTCA, 10 patients were randomized to heparin-coated, 10 to PC, and 10 to uncoated stents. Phosphorylcholine-coated stents were hand-crimped on the angioplasty balloon, whereas heparin-coated and uncoated stents were premounted.

After stent placement, intravenous heparin was infused for 24 h at a rate of approximately 1000 IU/h to maintain an activated partial thromboplastin time (APTT) between 80 and 100 s. All patients had been on a long-term treatment with aspirin before entering the study and received an additional oral dose of 300 mg on the morning of the procedure. Aspirin treatment was continued indefinitely. Ticlopidine treatment began on the day of intervention, just before the procedure, and continued at a dose of 250 mg twice daily for 1 month. No patient received other antithrombotic treatment, including glycoprotein IIb/IIIa inhibitors, during or after the procedure, and postinterventional therapy did not differ among the three treatment groups.

Blood Sampling

Blood samples for measurement of adhesion molecules were drawn from an antecubital vein before and 24 and 48 h after the procedure, separated by centrifugation, and immediately frozen and stored at −80°C. Concentrations of sE-selectin, sP-selectin, and sICAM-1 in stored plasma were measured with ELISA assay kits (R&D Systems, Abingdon, UK). The concentrations in plasma were expressed in ng/ml. Routine laboratory analyses were performed immediately by standard methods.

Statistical Analysis

The distribution of numeric variables was examined by the Kolmogorow-Smirnow (KS) test. Since the KS test confirmed a normal distribution of the variables studied, that is, E-selectin, P-selectin, and ICAM-1, parametric tests were used for the remainder of the statistical analysis. Time-dependent changes were tested by repeated measures analysis of variance (ANOVA). Significant results of repeated measures ANOVA were compared post hoc by paired samples *t*-test, with a significance level adjusted downward to 0.017, that is, the number of pairwise comparisons in three groups. Intergroup comparisons of numeric variables was performed by one-way ANOVA. Intergroup comparisons of nominal variables, such as gender distribution and previous history of risk factors, were made by chi-square test. Data were expressed as mean ± standard deviation for numeric variables, and as n (%) for nominal variables. Except for pairwise comparisons following repeated measures ANOVA, a p value of < 0.05 was considered statistically significant.

Results

The three patient groups were comparable with respect to several important baseline and preprocedural characteristics (Table I). All stent implantation procedures were completed successfully without angiographically detectable endovascular dissections. No patient developed chest pain, electrocardiographic changes, or cardiac enzyme elevation within 48 h of stent implantation. Exercise testing, performed 1 month after the procedure, was not consistent with myocardial ischemia in any patient, confirming that none had developed stent thrombosis within this 1-month observation period.

Among the three patient groups, no significant differences were found in preprocedural plasma soluble adhesion molecule levels or laboratory variables (Table II). Similarly, the three groups did not differ significantly with respect to procedural characteristics, including number of dilatations, maximum pressure of dilatations, total dilatation time, maximal duration of dilatations, and diameter of last inflated balloon (Table III).

Mean plasma sP-selectin and sICAM-1 levels, measured at 24 and 48 h, were not significantly different among the three stent groups. The sE-selectin level, however, was significantly

TABLE I Baseline clinical characteristics of study patients

	PC-coated stent group	Heparin-coated stent group	Uncoated stent group
No. of patients	10	10	10
Gender (M/F)	9/1	9/1	9/1
Age (mean ± SD)	56 ± 11	51 ± 6	58 ± 10
History of myocardial infarction (%)	30	10	30
Prior PTCA (%)	10	0	10
Coronary risk factors			
Hypertension (%)	50	40	50
Hypercholestrolemia (%)	30	20	40
Active smoking (%)	30	40	40
Family history (%)	50	40	30
Obesity (%)	10	0	10

Differences among groups are not statistically significant.

Abbreviations: M = male, F = female, SD = standard deviation, PTCA = percutaneous transluminal coronary angioplasty.

TABLE II Preprocedural laboratory measurements

	PC-coated stent group (n = 10)	Heparin-coated stent group (n = 10)	Uncoated-stent group (n = 10)
sP-selectin (ng/ml)	255.30 ± 96.15	242.60 ± 45.08	242.0 ± 98.88
sE-selectin (ng/ml)	29.10 ± 9.87	31.88 ± 14.04	30.40 ± 6.82
sICAM-1 (ng/ml)	216.30 ± 72.42	199.50 ± 10.64	213.90 ± 92.91
Total cholesterol (mg/dl)	188.90 ± 65.85	204.80 ± 18.41	223.0 ± 51.22
Triglycerides (mg/dl)	139.0 ± 55.43	187.70 ± 56.7	132.0 ± 65.67
HDL-C (mg/dl)	40.13 ± 5.38	41.8 ± 6.8	47.9 ± 11.9
LDL-C (mg/dl)	139.88 ± 29.92	125.78 ± 13.85	159.67 ± 40.88
BUN (mg/dl)	15.7 ± 3.37	15.5 ± 2.95	14.8 ± 2.78
Creatinine (mg/dl)	2.06 ± 2.8	0.95 ± 0.24	1.11 ± 019
AST (U/l)	19.8 ± 6.16	18.70 ± 4.76	20.70 ± 4.14
ALT (U/l)	19.8 ± 4.49	20.10 ± 3.7	22.40 ± 7.68
WBC ($\times 10^3/\mu l$)	7,100 ± 1,979	7,100 ± 1,576	7,640 ± 718
Hemoglobin (g/dl)	13.48 ± 1.29	14.4 ± 1.56	13.98 ± 2.04
Platelet ($\times 10^3/\mu l$)	211,000 ± 48,820	215,000 ± 51,699	207,922 ± 82,489

Differences among groups are not statistically significant.

Values are expressed as mean ± SD.

Abbreviations: WBC = white blood cells, HDL = high-density lipoprotein, LDL = low-density lipoprotein, AST = asparatate aminotransferase, ALT = alamine aminotransferase, BUN = blood area nitrogen, SD = standard deviation.

TABLE III Procedural characteristics among the three patient groups

	PC-coated stent group	Heparin-coated stent group	Uncoated stent group
Number of dilatations	3.4 ± 0.52	3.3 ± 0.67	3.7 ± 0.48
Max dilatation pressure (atm)	13.1 ± 1.85	12.6 ± 2.12	12.9 ± 1.20
Total dilatation time (s)	171.0 ± 28.3	165.5 ± 31.04	174.0 ± 16.12
Max dilatation duration (s)	64.44 ± 8.82	65.0 ± 10.8	62.5 ± 5.40
Last inflated balloon diameter (mm)	3.05 ± 0.16	3.0 ± 0.0	3.15 ± 0.24

Differences among the groups are not statistically significant.

Data are mean ± standard deviation.

TABLE IV Soluble adhesion molecules before and after stent placement

	Before procedure	24 h after stent placement	48 h after stent placement
PC-coated stent			
sP-selectin (ng/ml)	255.30 ± 96.15	196.0 ± 65.93[a]	178.0 ± 72[a]
sE-selectin (ng/ml)	29.10 ± 9.87	26.30 ± 8.94	27.50 ± 9.97
sICAM-1 (ng/ml)	216.30 ± 72.42	233.10 ± 59.78	232.8 ± 54.8
Heparin-coated stent			
sP-selectin (ng/ml)	242.60 ± 45.08	184.30 ± 64.73[a]	177.0 ± 77.36[a]
sE-selectin (ng/ml)	31.88 ± 14.04	38.83 ± 13.86	27.62 ± 19
sICAM-1 (ng/ml)	199.50 ± 10.64	208.80 ± 42.26	231.60 ± 84.16
Uncoated stent			
sP-selectin (ng/ml)	242.0 ± 98.88	205.50 ± 105.84	200.90 ± 122.3
sE-selectin (ng/ml)	30.40 ± 6.82	38.80 ± 16.97	43.8 ± 9.1[a]
sICAM-1 (ng/ml)	213.90 ± 92.91	228.50 ± 105.36	207.5 ± 108.7

[a] Significant change compared with baseline (see text for p value). Values are expressed as mean ± SD.
Abbreviations: PC = phosphorylcholine, sICAM = intercellular adhesion molecule 1, SD = standard deviation.

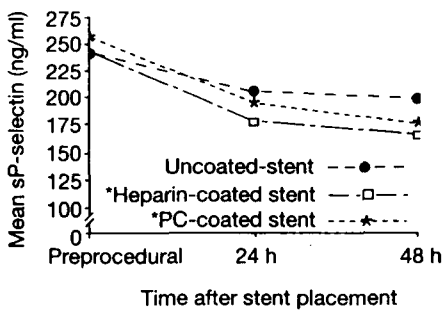

FIG. 1 Time course of plasma sP-selectin levels in patients undergoing implantation of intracoronary uncoated, PC-coated, and heparin-coated stents. (*p<0.05. vs. baseline). PC = phosphorylcholine.

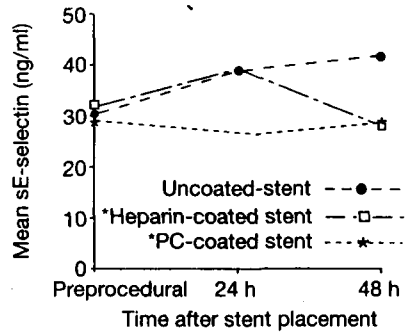

FIG. 2 Time course of plasma sE-selectin levels in patients undergoing implantation of intracoronary uncoated, PC-coated, and heparin-coated stents. (*p<0.05. vs. baseline). Abbreviation as in Figure 1.

higher in patients with uncoated stents than in those with PC- or heparin-coated stents at 48 h (p = 0.03).

Evolution of Soluble Adhesion Molecule Levels in the Phosphorylcholine-Coated Stent Group

Table IV shows the plasma sP-selectin, sE-selectin, and sICAM-1 levels before and after PC-coated stent implantation. A significant decrease in sP-selectin levels was measured between baseline and 24 h (p = 0.02) and 48 h (p = 0.01) after stent implantation (Fig. 1). In contrast, sE-selectin (Fig. 2) and sICAM-1 levels (Fig. 3) did not change significantly between baseline measurements and 24 h (p = 0.3 and p = 0.5, respectively), or 48 h (p = 0.6 and p = 0.2, respectively).

Evolution of Soluble Adhesion Molecule Levels in the Heparin-Coated Stent Group

Plasma sP-selectin, sE-selectin, and sICAM-1 levels before and after heparin-coated stent implantation are presented in Table IV. sP-selectin levels (Fig. 1) decreased significantly

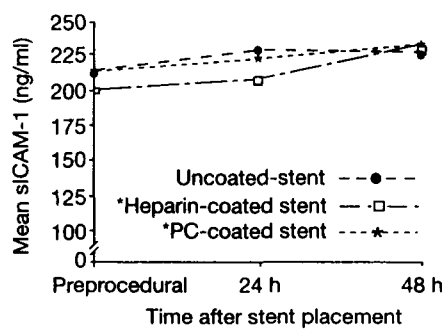

FIG. 3 Time course of plasma sICAM-1 levels in patients undergoing intracoronary implantation of uncoated, PC-coated, and heparin-coated stents. Abbreviations as in Table IV.

between baseline and 24 and 48 h after stent implantation (p = 0.03 and p = 0.02, respectively). sE-selectin levels (Fig. 2) measured at 24 h rose nonsignificantly from baseline, then decreased at 48 h (p = 0.2 and p = 0.08, respectively). No sig-

nificant changes in sICAM-1 levels (Fig. 3) were measured between 24 and 48 h after coronary stenting ($p = 0.7$ and $p = 0.3$, respectively).

Evolution of Soluble Adhesion Molecule Levels in the Uncoated Stent Group

Table IV shows the plasma sP-selectin, sE-selectin, and sICAM-1 levels before and after uncoated stent implantation. The sP-selectin levels (Fig. 1) remained unchanged from baseline 24 and 48 h after stent implantation ($p = 0.3$ and $p = 0.4$, respectively). sE-selectin levels (Fig. 2) rose within 24 h after uncoated stent placement ($p = 0.2$) and were significantly higher than at baseline at 48 h ($p = 0.04$). The sICAM-1 levels (Fig. 3) did not change significantly between baseline and 24 h and 48 h after coronary stenting ($p = 0.3$ and $p = 0.7$, respectively).

Relation between Soluble Adhesion Molecules and Stent Placement Procedures

No correlation was found in any of the patient groups between the soluble adhesion molecule levels measured 24 and 48 h after stent placement and procedural characteristics, such as number of dilatations, maximum pressure of dilatations, total dilatation time, maximal duration of dilatations, or diameter of last balloon inflated.

Discussion

To our knowledge, this study is the first that compares the effects of intracoronary placement of coated versus uncoated stents on platelets and EC. Its results indicate that the implantation of coated stents is associated with a more effective suppression of platelets and EC activation than that of uncoated stents in patients treated with combined antiplatelet therapy.

Neither plasma adhesion molecule levels nor the coagulation system are influenced by diagnostic heart catheterization.[8] Therefore, changes in concentrations of plasma soluble adhesion molecules after PTCA and stent placement must be the result of the latter interventions.

Mechanical disruption of the atherosclerotic plaque by the angioplasty balloon and the stent implantation may activate platelets, EC, leukocytes, and the coagulation system.[6,8–10,18] The foreign stent material itself may also contribute to alterations of platelet and EC function, as well as to activation of complement and coagulation systems, which may play important additional roles in the pathogenesis of stent thrombosis.[7,19] Biocompatible stent coating materials have been developed to prevent contact between flowing blood, EC, and stent surface, thereby increasing stent biocompatibility and thromboresistance. Recent studies have confirmed that the use of heparin and PC-coated stents effectively reduces the rate of stent thrombosis.[20–22]

Platelet activation has been observed after PTCA and stent implantation in patients treated with aspirin and intravenous heparin.[6,8–10,18] Recent studies have found no change or a decrease in the expression of P-selectin after uncoated Palmaz-Schatz stent placement in patients treated with aspirin and ticlopidine, a finding indicative of platelet deactivation.[5,14,15] In our study, plasma sP-selectin levels did not change significantly after the implantation of uncoated stents. On the other hand, sP-selectin levels decreased significantly 24 and 48 h after placement of PC- and heparin-coated stents, an observation consistent with platelet deactivation, confirming the biocompatibility of such stents described in previous studies.[21,23]

An increase in the expression of platelets P-selectin after PTCA and stent implantation may be a predictor of increased subsequent risk of acute ischemic events.[16,17] Although no patient developed stent thrombosis in our study, it appears legitimate to hypothesize that a decrease in sP-selectin levels may predict a lower risk of such complication after intracoronary stent implantation.

In previous studies, sE-selectin levels were either unchanged or they increased after PTCA in patients treated with aspirin and heparin.[8,24] In the present study, sE-selectin levels remained unchanged after PC- and heparin-coated stent implantation. In contrast, sE-selectin levels were increased after uncoated stent placement, a finding consistent with EC activation. It has been shown that ticlopidine suppresses endothelial cells functions, such as vasoreactivity and antiproliferative activity.[25,26] Since our patients were all treated with ticlopidine in addition to aspirin and heparin, EC were expected to be effectively suppressed. Since PC- and heparin-coated stents are biocompatible, they are not expected to stimulate EC. Indeed, in this study, sE-selectin levels remained unchanged after coated stent implantation. On the other hand, selectin levels increased in patients who received uncoated stents despite the suppression of endothelial cell function by ticlopidine, as the foreign stent material itself causes further EC activation. These results suggest that the stent coating characteristics are an important cause of the variable EC responses observed after stent placement.

No significant changes in sICAM-1 levels were measured in any of the three patient groups between baseline and up to 48 h after coronary stenting. This is consistent with the results of two previous studies. Kurz *et al.* found no changes in sICAM-1 levels after PTCA.[8] Siminiak *et al.* compared the levels of sICAM-1 in peripheral venous and coronary sinus blood sampled during and after PTCA and found an increase in sICAM-1 levels in the coronary sinus samples but not in the peripheral blood.[24] In our study, sICAM-1 levels were measured in the peripheral venous blood, which may not have been sensitive enough to detect the activation of endothelial cells lining the coronary arteries.

Clinical Implications

Stent thrombosis rates have been significantly reduced by technical and pharmacologic advances in the last few years,[1–3] although it continues to occur in 1–3% of patients.[7] Since coating of the stent improves its hemocompatibility, the incidence of thrombosis of PC- and heparin-coated stents has been lower than that of uncoated stents in clinical studies of patients treat-

ed with combined antiplatelet therapy.[20,27] This advantageous effect may allow a reduction in the periprocedural and postprocedural antithrombotic and antiplatelet regimens, as well as in associated vascular, hematologic, and bleeding complications.

Conclusion

Our study demonstrates that platelet deactivation occurs without influencing EC after the implantation of PC- or heparin-coated stents in patients treated with combined antiplatelet therapy. In contrast, implantation of uncoated stents causes EC activation without changing platelet activity. Thus, the different responses of platelets versus EC after coronary stent placement may be modified by the selection of coated versus uncoated stents, and the choice of PC- or heparin-coated stents could effectively decrease the rate of thrombotic complications.

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