

Predictive value of plasma plasminogen activator inhibitor-1 for coronary restenosis: dependence on stent implantation and antithrombotic medication

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Summary. Background: The plasmin activation system is involved in the development of restenosis after percutaneous coronary interventions (PCI). Conflicting data exist concerning the role of plasminogen activator inhibitor-1 (PAI-1) and its predictive value for restenosis. **Objectives:** To evaluate the fibrinolytic response to injury after PCI with or without stent implantation on different antithrombotic medications and its relation to late restenosis. **Patients and methods:** Eighty consecutive patients with successful PCI without (balloon only; $n = 37$) or with stent implantation (stent; $n = 43$) on different antithrombotic regimes (balloon only, aspirin; stent, aspirin/coumadin/dipyridamole vs. aspirin/ticlopidine). Blood samples were taken at baseline and up to 7 days after PCI and PAI-1 active antigen and tissue plasminogen activator (t-PA) antigen were determined. Restenosis was angiographically determined after 6 months. **Results:** PCI increased both t-PA and PAI-1 levels ($P < 0.001$), with a significant prolonged and pronounced increase in stent vs. balloon-only patients ($P < 0.05$). Restenosis (stent 26%; balloon 38%) was significantly correlated to an attenuated PAI-1 increase after 24 h in the ticlopidine group ($P = 0.007$; restenosis, relative Δ PAI-1 $+ 50 \pm 28\%$; non-restenosis, $+ 139 \pm 50\%$), but not in the coumadin group. In the balloon-only group late restenosis (ISR) was associated with a trend for an augmented PAI-1 increase after 24 h. **Conclusions:** Coronary stent implantation significantly increases t-PA and PAI-1 plasma

levels up to 1 week compared with balloon angioplasty alone. ISR in ticlopidine-treated patients was associated with an attenuated early PAI-1 active antigen increase. A less than 50% increase 24 h after stent implantation under ticlopidine treatment may identify patients at risk for the development of ISR.

Keywords: coumadin, PAI-1, restenosis, ticlopidine.

Introduction

Restenosis after primary successful percutaneous coronary interventions (PCIs) with balloon angioplasty or conventional stent placement occurs in 20–50% of patients with coronary artery disease [1–3]. The leading pathological feature hereby is migration of smooth muscle cells (SMCs) into the intima with subsequent accumulation of extracellular matrix [4]. In addition, stent placement triggers a substantial early inflammatory response with macrophage invasion around the struts [5]. Several observations suggest that the fibrinolytic system plays an important role in this response to injury. Animal models have demonstrated the expression of tissue-type plasminogen activator (t-PA), urokinase-type plasminogen activator (u-PA), and plasminogen activator inhibitor type-1 (PAI-1), the primary physiological inhibitor of plasminogen activation in plasma and tissue, coinciding with SMC proliferation and neointima formation [6,7]. Studies in knock-out mice showed that PAI-1 deficiency accelerates the restenosis process whereas u-PA deficiency attenuates this response to injury [8,9].

Clinical studies investigating plasma levels of components of the plasmin activation system before and/or after PCI showed conflicting results (reviewed in [10]). Several studies demonstrated a positive correlation of increased PAI-1 levels

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or a lack of decreased PAI-1 activity with late restenosis, immediately after PCI (with or without stent implantation) [11], after balloon angioplasty alone [12–14] or coronary atherectomy [15]. Increased PAI-1 activity after balloon angioplasty has been reported to improve the predictive value of TI-201-scintigraphy for restenosis in asymptomatic patients [16]. In contrast, Strauss *et al.* [17] postulated low pre- and postprocedural PAI-1 antigen levels and increased u-PA levels to be associated with restenosis after stent placement and/or balloon angioplasty, but did not further differentiate between these groups or their medication.

The impact of various medication regimes on plasma levels of PAI-1 and t-PA post PCI is not known so far. Only in stroke patients have aspirin and ticlopidine been demonstrated to reduce PAI-1 plasma levels to a similar degree [18]. Standard adjuvant antithrombotic therapy after stent placement has made a significant change during recent years. Antiplatelet therapy with ADP receptor blockers (thienopyridines: ticlopidine and clopidogrel), in addition to aspirin, has been shown to reduce acute thrombotic events compared with previously used antithrombotic medication with coumadin [19] and represents standard of care nowadays, although potential beneficial effects of coumadin/aspirin combination therapy on long-term clinical endpoints after PCI are still suggested [20]. In patients with coronary artery disease, a recent review and meta-analysis still claims some benefit in decreasing recurrent cardiovascular events with coumadin/aspirin therapy [21].

We were interested whether these different antithrombotic regimes could affect (i) the expression of plasmin activation parameters after PCI with or without stent implantation, and (ii) the relation of these parameters to the development of late restenosis. Given the now well-established standard therapy with thienopyridines and aspirin post stent implantation, a contemporary randomized trial would not be acceptable to address this issue. Therefore plasmin activation parameters determined during a former study [22] were analyzed.

Methods

Patients

Plasmin activation markers in plasma samples of 80 consecutive patients with stable coronary artery disease who underwent elective and successful PCI on different antithrombotic regimes, collected and determined during the time course of a previous study [22], were analyzed. Exclusion criteria included any acute coronary syndrome within 3 months before the angioplasty, PCI for restenosis, concurrent severe illness (such as cancer, hepatic or renal disease or chronic infections) and unsuccessful procedure (i.e. $\geq 50\%$ diameter stenosis after the intervention). PCIs were performed according to standard techniques by experienced interventionists only. Stent implantation was left to the discretion of the operator. Angiographic restenosis was evaluated at 6 months' follow-up or earlier if clinically indicated and defined as $\geq 50\%$ diameter in-stent stenosis.

Antithrombotic therapy

All patients received aspirin (100 mg day^{-1}) throughout the study. Immediately before PCI, patients were treated with a bolus of unfractionated heparin (10 000 U), thereafter a continuous heparin infusion was adjusted to achieve a partial thromboplastin time of 60–80 s for 24 h. Starting on the day of PCI one group of stent patients received ticlopidine ($2 \times 250 \text{ mg day}^{-1}$) over 4 weeks, while the other group received coumadin (International Normalized Ratio 2.0–3.0) plus dipyridamole ($3 \times 160 \text{ mg day}^{-1}$) over 3 months. Patients in the balloon-only group received aspirin only.

Laboratory measurements

Venous blood was drawn from the antecubital vein with minimal tourniquet pressure into EDTA tubes (Vacutainer; Becton Dickinson, Rutherford, NJ, USA) at baseline (1 day before PCI), 24 h after PCI and serially thereafter on three consecutive days every 12 h and every 24 h up to 7 days after the intervention. After centrifugation (4°C ; $3000 \times g$ for 15 min) plasma samples were stored at -70°C until use. PAI-1 active antigen was determined by a functional immunological assay using a modified ELISA (Technoclone Inc., Vienna, Austria [23]). Briefly, an excess of active t-PA was immobilized on microtiter plates by an anti-t-PA monoclonal antibody. Active PAI-1 in the plasma samples was immunologically detected by using an anti-PAI-1 monoclonal antibody after complex formation with bound t-PA. t-PA antigen in plasma samples was determined by specific ELISA using monoclonal antibodies (Technoclone).

Statistical analysis

Data are presented as mean \pm SEM unless otherwise stated. After determination of the distribution pattern, statistical differences between groups were determined either by the Mann–Whitney *U*-test, or the unpaired *t*-test as well as χ^2 test for demographic parameters. Differences of fibrinolytic parameters after PCI over time were compared by analysis of variance (ANOVA) followed by Fisher's exact test. A value of $P < 0.05$ was considered statistically significant.

Results

Demographic data are presented in Table 1. There were no statistically significant differences in baseline characteristics of patients with or without restenosis.

Angiographic findings, restenosis data and interventional details are presented in Table 2. There were no statistically significant differences in lesion morphology (including lesion length, vessel diameter and target lesion location), percent diameter stenosis before and after intervention, or antithrombotic medication in patients with or without restenosis.

Table 1 Demographic data

	Restenosis (<i>n</i> = 25)		No restenosis (<i>n</i> = 55)		<i>P</i> *
	Balloon only (<i>n</i> = 14)	Stent (<i>n</i> = 11)	Balloon only (<i>n</i> = 23)	Stent (<i>n</i> = 32)	
Age (years)	61 ± 6	60 ± 8	58 ± 8	61 ± 7	ns
Sex (male/female)	11/3	9/2	18/5	25/7	ns
Smokers (<i>n</i>)	5	5	9	16	ns
Diabetics (<i>n</i>)	5	4	4	7	ns
Insulin/oral medication (<i>n</i>)	3/2	2/2	1/3	2/5	ns
Hypertension (<i>n</i>)	9	7	13	22	ns
ACE inhibitors (<i>n</i>)	5	4	7	12	ns
Prior MI (<i>n</i> /%)	6	4	8	14	ns
Body mass index (kg m ⁻²)	24.2 ± 0.9	25.3 ± 0.8	25.1 ± 0.8	24.8 ± 0.5	ns
Cholesterol (mg%)	220 ± 40	215 ± 31	210 ± 45	219 ± 51	ns
Triglycerides (mg%)	180 ± 51	170 ± 25	173 ± 29	165 ± 21	ns
Statins (<i>n</i>)	7	6	12	18	ns

Mean ± SD. *For all comparisons.

Table 2 Angiographic and interventional data

	Restenosis (<i>n</i> = 25)	No restenosis (<i>n</i> = 55)	<i>P</i>
Balloon only (<i>n</i>) (%)	14 (38%)	23 (62%)	–
Target lesion	3/0/11	5/1/17	ns
(prox.LAD/SVG/other)			
Lesion morphology (A/B/C)	5/5/4	5/14/4	ns
% Diameter stenosis			
Before PCI	75 ± 13	71 ± 12	ns
After PCI	21 ± 10	20 ± 11	
At follow-up	61 ± 18	26 ± 14	< 0.001
Balloon pressure (atm)	5.8 ± 2.0*	5.9 ± 1.5†	ns
Balloon inflations (<i>n</i>)	2.9 ± 2.1‡	2.6 ± 1.0§	ns
Intervention length (mm)	17.4 ± 4.4	16.9 ± 5.3	ns
Reference lumen diameter (mm)	3.3 ± 0.6	3.1 ± 0.4	ns
Stent (<i>n</i>) (%)	11 (26%)	32 (74%)	–
Target lesion (prox.LAD/SVG/other)	4/1/6	9/1/22	ns
Lesion morphology (A/B/C)	5/3/3	7/21/4	ns
% Diameter stenosis			
Before PCI	77 ± 14	73 ± 16	ns
After PCI	18 ± 9	17 ± 8	ns
At follow-up	59 ± 16	24 ± 16	< 0.001
Number of stents (<i>n</i>)	1.4 ± 0.9	1.2 ± 0.6	ns
Balloon pressure (atm)	10.6 ± 2.9	10.6 ± 2.2	ns
Balloon inflations (<i>n</i>)	1.5 ± 0.9	1.13 ± 0.4	ns
Intervention length (mm)	16.5 ± 3.3	16.0 ± 4.9	ns
Reference lumen diameter (mm)	3.1 ± 0.3	3.2 ± 0.5	ns
Medication			
Ticlopidine	7 (36.8%)	12	ns
Coumadin	4 (16.6%)	20	ns

mean ± SD; PCI = percutaneous coronary intervention, prox.LAD = proximal left anterior descendens, SVG = saphenous vein graft; **P* = 0004 vs. stent; †*P* < 0001 vs. stent; ‡*P* < 0,03 vs. stent; §*P* < 0001 vs. stent.

Influence of PCI on plasma levels of PAI active antigen and t-PA antigen (Fig. 1)

Coronary interventions led to an acute increase of both PAI-1 and t-PA plasma levels (*P* < 0.001). The fibrinolytic response to injury was significantly pronounced in the stent group compared with the balloon-only group. Patients with stent implantation showed a significantly prolonged increase in

PAI-1 active antigen and t-PA plasma levels compared with the balloon-only group (120 vs. 36 h, *P* < 0.05). The mean peak levels of PAI-1 active antigen were not significantly different between the groups (stent, 33 ± 2.8 ng mL⁻¹; balloon only, 31 ± 3.8 ng mL⁻¹; *P* = ns), whereas peak t-PA antigen levels were significantly higher after stent implantation compared with balloon-only interventions (33 ± 4.4 ng mL⁻¹ vs. 17 ± 1.2 ng mL⁻¹; *P* < 0.05).

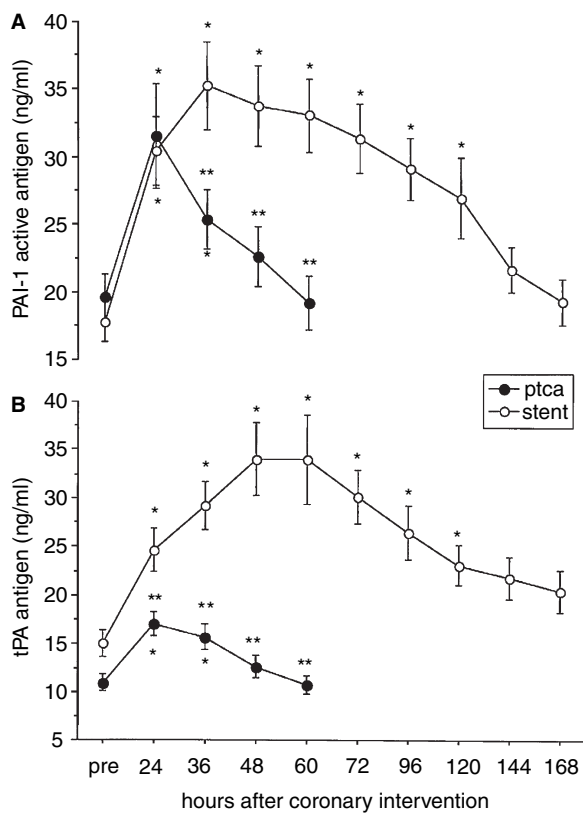


Fig. 1. Influence of coronary interventions on plasma levels of plasminogen activator inhibitor (PAI) active antigen and tissue-type plasminogen activator (t-PA) antigen: coronary interventions increased both (A) PAI-1 and (B) t-PA plasma levels. Stent (○) vs. balloon (●) group showed a significantly prolonged increase in PAI-1 levels and higher t-PA levels. * $P < 0.05$ within group; ** $P < 0.05$ between groups.

Influence of adjuvant antithrombotic medication after stent implantation on plasma levels of PAI active antigen and t-PA antigen (Fig. 2)

Ticlopidine treatment after stent placement led to a pronounced antifibrinolytic status during the first 5 days. Patients in the ticlopidine treatment group showed continuously higher PAI-1 levels within the first 120 h compared with the coumadin group, with statistically significant differences between 48 and 72 h (Fig. 2a). t-PA levels, in contrast, were lower in the ticlopidine group throughout the observation period with significant differences on days 1 and 3–7 ($P < 0.05$) compared with the coumadin group (Fig. 2b). No acute or subacute stent thrombosis occurred.

PAI-1 active-antigen increase 24 h after PCI and restenosis

Restenosis in the balloon-only group after 6 months was associated with a trend for an augmented increase of PAI-1 active antigen levels 24 h after PCI (Δ PAI-1) without reaching statistical significance (Table 3).

Late instent-restenosis (ISR) showed a different association to PAI-1 plasma levels after 24 h depending on the antithrombotic medication used (Fig. 3). Coumadin-treated stent patients with

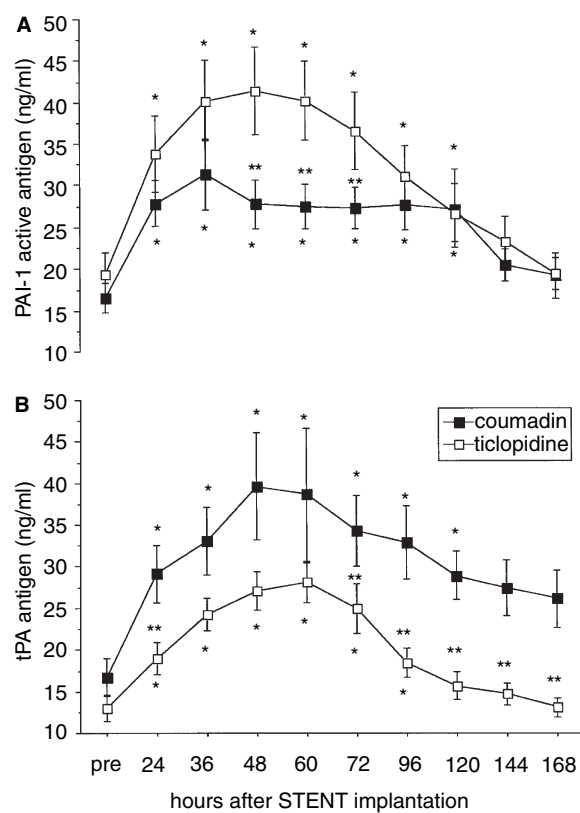


Fig. 2. Influence of adjuvant antithrombotic medication after stent implantation on plasma levels of plasminogen activator inhibitor (PAI) active antigen and tissue-type plasminogen activator (t-PA) antigen: ticlopidine (□) treatment increased (A) PAI-1 levels and decreased (B) t-PA levels during days 1–8 significantly ($P < 0.05$) compared with coumadin (■). No early stent thrombosis occurred. * $P < 0.05$ within group; ** $P < 0.05$ between groups.

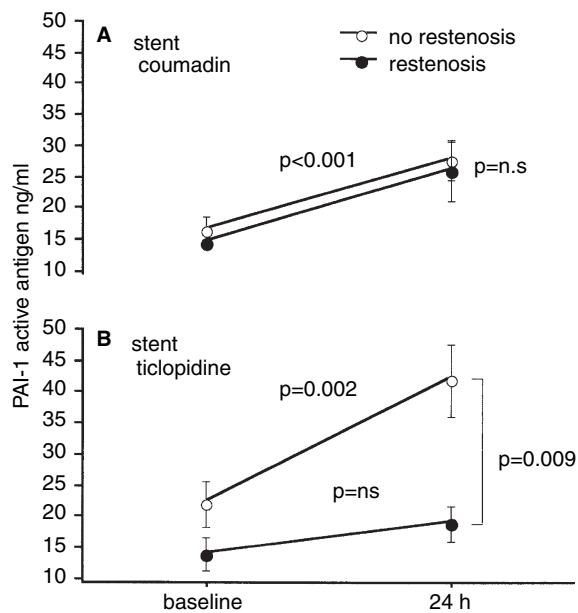
restenosis ($n = 4$, 16.6%) showed no differences in the baseline and 24 h post-PCI plasma levels of PAI-1 active antigen compared with non-restenosis patients (baseline: restenosis 14.8 ± 0.7 ng mL⁻¹, non-restenosis 16.8 ± 2.1 ng mL⁻¹; 24 h: restenosis 26.4 ± 4.8 ng mL⁻¹, non-restenosis 28.1 ± 3.2 ng mL⁻¹). Ticlopidine-treated stent patients with restenosis ($n = 7$, 36.8%) showed statistically non-significant lower baseline active antigen levels (restenosis 14.3 ± 2.6 ng mL⁻¹, non-restenosis 22.3 ± 3.6 ng mL⁻¹; $P = 0.13$) but highly significant lower levels 24 h post-PCI compared with non-restenosis patients (restenosis 19.2 ± 2.7 ng mL⁻¹, non-restenosis 42.3 ± 2.7 ng mL⁻¹; $P = 0.009$). These differences in Δ PAI-1 (Table 3) suggest a less than 50% relative PAI-1 active antigen increase 24 h after stent implantation to be predictive of late ISR under ticlopidine treatment.

T-PA antigen increase 24 h after PCI and restenosis

Restenosis after 6 months was not associated with significant differences in the increase of t-PA antigen levels 24 h after PCI, either in the balloon-only or the stent group (Δ t-PA) (Table 4). Stent patients with restenosis, however, showed lower Δ t-PA

Table 3 Plasminogen activator inhibitor (PAI)-1 active antigen (Δ PAI-1) 24 h after percutaneous coronary intervention

	Restenosis (n = 25)	No restenosis (n = 55)	P
Balloon only			
ng mL ⁻¹	15.3 \pm 6.6	9.9 \pm 2.4	ns
%	70 \pm 18	61 \pm 14	ns
Stent			
Ticlopidine			
ng mL ⁻¹	4.9 \pm 2.7	19.9 \pm 4.5	0.007
%	50 \pm 28	139 \pm 50	0.05
Coumadin			
ng mL ⁻¹	11.6 \pm 5.4	11.3 \pm 1.9	ns
%	83 \pm 43	73 \pm 11	ns

**Fig. 3.** Plasminogen activator inhibitor (PAI)-1 active antigen at baseline and 24 h after stent implantation. (A) Coumadin-treated patients with restenosis showed no differences in baseline and 24 h post percutaneous coronary intervention (PCI) PAI-1 active antigen levels compared with non-restenosis patients. (B) Ticlopidine-treated patients with restenosis showed statistically non-significant lower baseline PAI-1 active antigen levels and highly significantly lower levels 24 h post PCI compared with non-restenosis patients.**Table 4** Tissue-type plasminogen activator (t-PA) antigen (Δ t-PA) 24 h after percutaneous coronary intervention

	Restenosis (n = 25)	No restenosis (n = 55)	P
Balloon only			
ng mL ⁻¹	5.1 \pm 1.1	6.7 \pm 1.2	ns
%	57 \pm 12	81 \pm 13	ns
Stent			
Ticlopidine			
ng mL ⁻¹	1.5 \pm 3.6	8.7 \pm 2.8	ns
%	24 \pm 18	92 \pm 22	ns
Coumadin			
ng mL ⁻¹	7.7 \pm 3.0	13.3 \pm 3.4	ns
%	60 \pm 25	117 \pm 46	ns

values in both antithrombotic treatment groups, without reaching statistical significance.

Discussion

Plasmin activation primarily functions in dynamic equilibrium with the coagulation system to maintain vascular hemostasis, but also plays a crucial role in a wide variety of biological regulatory systems, including tissue remodeling after vascular injury [24,25]. The pathophysiological role hereby lies in the control of local proteolysis, cell migration and proliferation as well as inflammatory cell invasion [10].

In this present study of t-PA and PAI-1 plasma levels after PCIs, we could confirm at first previous findings concerning the induction of the plasmin activation system as a response to injury. By further comparison of coronary stent implantation with balloon angioplasty alone, major differences in the magnitude of plasmin activation were detectable. Although there were no significant differences in the extent of the underlying coronary vascular disease (i.e. distribution of lesion types in both groups), stent placement resulted in significant enhanced and prolonged increases of t-PA and PAI-1 plasma levels compared with balloon-only interventions. As the significantly lower balloon pressures used in the balloon-only group were counterbalanced by a significantly higher number of inflations (Table 2), the amount of mechanical injury might not be the major cause of these observed differences. These findings rather seem to reflect a different form of vessel wall injury with induction of a specific inflammatory response reaction caused by stent implantation. Compared with balloon-only intervention, stent implantation is known to cause an inflammatory response around stent struts [5]. The time course of macrophage invasion and intramural temperature rise post stent implantation [26] is paralleled by our observed rise in plasma levels of t-PA and PAI-1 within the first week.

Adjuvant antithrombotic therapy after stent implantation significantly altered the fibrinolytic response to injury, without influencing early outcome (i.e. acute stent thrombosis). Ticlopidine treatment led to a pronounced antifibrinolytic status during the first 5 days after PCI with higher PAI-1 and lower t-PA levels compared with coumadin, but no acute or subacute stent thrombosis occurred.

Late restenosis and its correlation to plasma levels of various components of the plasmin activation system has resulted in divergent results in the literature [10]. Depending on the time point of investigation (before or after PCI), increased PAI-1 but not t-PA values were related to restenosis in balloon-only patients [12–14]. Studies which also included stent patients showed different results: Strauss *et al.* [17] postulated lower baseline and decreased PAI-1 antigen levels immediately after PCI to be related to restenosis. No further analysis concerning the stent and balloon-only group or adjuvant antithrombotic medication was given. Prisco *et al.* [11] concluded that after elective PCI, both with and without stent application, the absence of a decrease in PAI-1 activity immediately after the procedure (i.e. within 60 min) represents a risk marker for

subsequent clinical recurrence due to restenosis. Also, no data on adjuvant antithrombotic medication were given.

In contrast, we were able to show in the present study that the early fibrinolytic response to injury (i.e. after 24 h) in relation to restenosis differs according to the PCI method used. In balloon-only patients the former demonstrated pattern of increased PAI-1 levels after PCI was weakly related to restenosis, whereas in stent patients a different relationship was found depending on the adjuvant antithrombotic medication: under coumadin treatment no significant association could be detected, whereas in ticlopidine-treated stent patients an attenuation of the early PAI-1 increase 24 h after PCI was related to late ISR.

Among the major reasons for the observed discrepancies, the different time points of PAI determination as well as the different assay methods used might be of most importance.

Our data not only point towards a different restenosis mechanism in stent patients, but also seem to confirm the hypothesis of the beneficial role of PAI-1 in controlling restenosis [10,27,28]. However, whether these findings reflect a primary interaction of ticlopidine with the inflammatory response to stent placement and secondary modification of the plasmin activation remains a subject of further investigation.

In summary, this study provides, first, evidence for differences in the induction of the plasmin activation system following stent placement vs. balloon-only angioplasty, supportive of differences in the response to injury pathomechanism. Second, an attenuation of early PAI-1 active antigen increase 24 h after stent implantation under ticlopidine treatment to less than 50% relative increase could be predictive of ISR after 6 months. Serial determination of PAI-1 active antigen before and 24 h after stent implantation might therefore identify patients at risk. Whether this finding can be extended to antithrombotic treatment with other thienopyridines (such as clopidogrel) seems likely but has yet to be proven.

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