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Increased Restenosis Rate After Implantation of Drug-Eluting Stents in Patients With Elevated Serum Activity of Matrix Metalloproteinase-2 and -9

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Objectives Our aim was to test whether serum levels of matrix metalloproteinase (MMP)-2 and -9 are associated with the development of in-stent restenosis (ISR) after implantation of drug-eluting stents (DES).

Background With the introduction of DES coronary ISR could be reduced dramatically. However, it still plays a significant role, particularly after treatment of multiple, complex lesions.

Methods We studied 85 patients who were treated with 159 DES. Blood samples for measurement of MMP-2 and -9 antigen and activity were taken directly before and 24 h after percutaneous coronary intervention (PCI). Restenosis was evaluated at 6 to 8 months by coronary angiography.

Results During the follow-up period, 2 patients (2.4%) died of cardiovascular causes, and 12 patients developed angiographic ISR. Patients with ISR showed significantly higher serum activity of MMP-9 at baseline ($p = 0.017$) and of MMP-2 ($p < 0.0001$) and MMP-9 ($p < 0.0001$) after the procedure. The PCI increased serum activity of MMP-2 ($p = 0.005$) and MMP-9 ($p = 0.008$) only in patients with ISR. The restenosis rates of patients in the highest quartile of MMP-2 after and MMP-9 before and after PCI were 40.0%, 38.9%, and 42.9% compared with 6.3%, 7.7%, and 4.0% in the lower quartiles, respectively. This was independent of clinical and procedural characteristics.

Conclusions Elevated serum activities of MMP-2 and -9 are associated with dramatically increased restenosis rates after PCI with implantation of DES. Determination of MMP levels might be useful for identification of patients who are at high risk for ISR despite implantation of DES. (J Am Coll Cardiol Intv 2010;3:90–7) © 2010 by the American College of Cardiology Foundation

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Despite possible safety issues, the implantation of drug-eluting stents (DES) is the most widely used method for coronary artery revascularization, and it has become the most powerful means to treat coronary artery stenosis. But overall in-stent restenosis (ISR) still remains a limitation for the long-term clinical outcome. A recently published article (1) suggests that in a real-world population the angiographic restenosis rate of DES could be up to 18%, particularly after treatment of multiple, complex lesions. Thus the question arises of whether known risk factors for ISR in bare-metal stents (BMS) are also playing a role in DES.

It is known that coronary interventions induce an inflammatory response by arterial wall damage, release of inflammatory and chemoattractant factors resulting in leukocyte and platelet activation (2). Migration and proliferation of neointimal smooth muscle cells together with the deposition of extracellular matrix might lead to the development of ISR. Previous studies have shown that mechanical injury (3–7) induces expression of matrix metalloproteinases (MMP) and increases gelatinase activity (3,8). Gelatinase A (MMP-2) and Gelatinase B (MMP-9) modulate matrix degradation and smooth muscle cell migration and might thereby play a role in the pathogenesis of restenosis. Increased MMP-9 serum levels were significantly associated with increased neointima formation (9), and serum levels of MMP-2 and -9 were found to be related with restenosis in BMS (10–12). However, not much is known about the role of MMPs in the pathogenesis of restenosis after implantation of paclitaxel-eluting stents (PES) (Taxus, Boston Scientific Corp., Natick, Massachusetts) and sirolimus-eluting stents (SES) (Cypher, Cordis Corp., Miami Lake, Florida), because these substances exert direct antimigratory and anti-inflammatory effects (13,14). Therefore, our aim was to evaluate the role of MMP-2 and -9 in the development of ISR after implantation of PES and SES.

Methods

Patients. Blood samples were taken prospectively from 544 consecutive patients with suspected stable coronary artery disease who were scheduled for elective PCI (Fig. 1). The PCIs were performed according to standard techniques by experienced interventionalists only. The type, number, length, and size of the stents implanted were left to the discretion of the interventionalist. All patients with DES only (n = 107) were asked to participate in this study, and we performed re-angiography in all 85 patients who gave their informed consent for follow-up angiography. The Taxus stents (PES) were implanted in 63 patients (75%); Cypher stents (SES) were used in 22 patients (25%). The study was approved by the institutional ethics committee for human subjects. Patients with acute coronary syndrome within 3 months before angioplasty were excluded. Exclusion criteria included also concurrent severe illness (such as cancer, hepatic or renal disease, or chronic infections), PCI for restenosis, and unsuccessful procedure (i.e., >50% diameter stenosis after the intervention). Aspirin and unfractionated heparin were administered per standard practice. Clopidogrel therapy was started either on the day before angiography or immediately after stent implantation with 4 tablets (300 mg). After the procedure, patients were maintained on aspirin 100 mg indefinitely, and clopidogrel 75 mg at least until follow-up angiography. Other medications such as beta-blockers, statins, and angiotensin-converting-enzyme inhibitors were given as appropriate. After enrollment, patients remained in the hospital for at least 48 h.

Blood samples. Two blood samples were taken under fasting conditions directly before PCI and 24 h after PCI. Therefore venous blood was drawn from the antecubital vein with minimal tourniquet pressure into serum separator tubes. Samples were allowed to clot for 30 min before centrifugation (4°C; 3,000 *g* for 15 min) and stored at −70°C until use.

Laboratory measurements. The MMP-2 and -9 antigens were measured with specific enzyme-linked immunosorbent assays (Amersham, GE Healthcare Bio-Sciences AB, Uppsala, Sweden). The MMP-2 and -9 activities have been determined with specific activity assays (Amersham).

Abbreviations and Acronyms

BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
ISR = in-stent restenosis
MMP = matrix metalloproteinase
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)

Angiographic definitions. The modified American College of Cardiology/American Heart Association grading system (type A, B1, B2, and C) was used to characterize lesion morphology. The off-line quantitative coronary angiographic analysis was performed with an automated edge-detection system (QCA-CMS Version 6.0, Medis, Medical Imaging Systems, Leiden, the Netherlands). The contrast-filled, nontapered catheter tip was used for calibration. The reference diameter was measured by interpolation. Minimal lumen diameter (before and after PCI) and diameter stenosis (before and after PCI) were measured within the stent and within the 5-mm proximal and distal edges of the stent. Furthermore, we measured vessel size, lesion length, and length of stented segment. All analyses were performed by the same investigator that was blinded to all laboratory results.

End points. The primary end point of the study was angiographic restenosis (diameter stenosis of at least 50% on the basis of in-segment analysis) at follow-up angiography, which was performed at 6 to 8 months' follow-up or earlier if clinically indicated. The secondary end points were in-stent late lumen loss and the need for target lesion revascularization due to restenosis in the presence of symptoms or objective signs of ischemia during the follow-up.

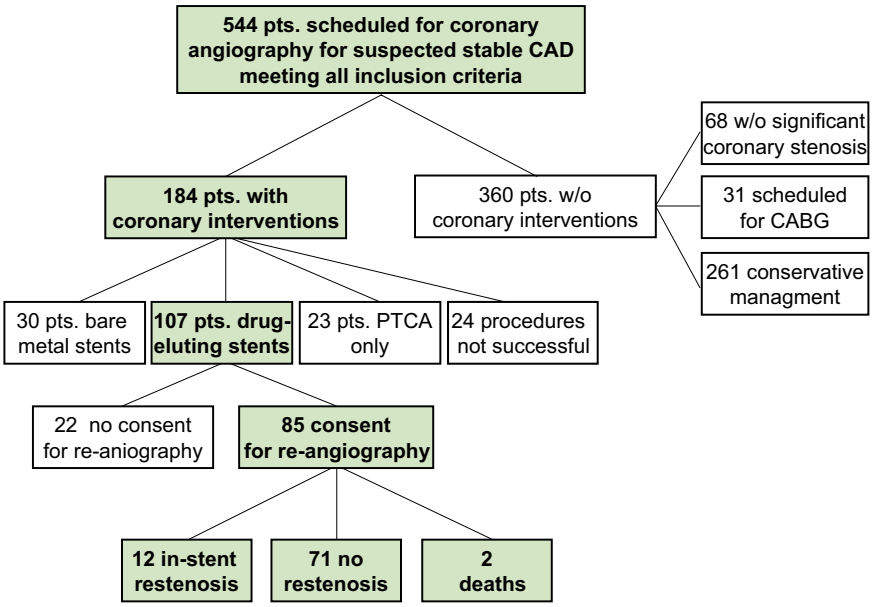

Figure 1. Study Flow Chart

Of 544 consecutive patients, 184 underwent percutaneous coronary intervention. Of 107 patients with drug-eluting stents, 85 gave their informed consent for follow-up angiography. CABG = coronary artery bypass graft; CAD = coronary artery disease; PTCA = percutaneous transluminal coronary angioplasty.

Statistical analysis. Sample size calculation was based on the hypothesis that MMP-2 and/or -9 activity before PCI show a difference of at least 50% in patients with and without ISR. Calculation of sample size revealed that, with an expected "real world" restenosis rate of 10%, 40 patients were needed to detect a 50% difference of MMP-2 activity, and 80 patients were needed to detect a 50% difference in MMP-9 activity before PCI between patients with and without ISR with a power of 80% and significance level (2-tailed) of 0.05 (15). For all additional comparisons (MMP antigen levels, post-procedure MMP levels, and increase of MMP levels upon PCI), we used the method according to Bonferroni-Holm to account for multiple testing. In patients with multiple lesion interventions, only the lesion with the highest late lumen loss was included. Continuous variables are expressed as mean ± SD. Demographic data of patients with and without restenosis were compared by the unpaired Student *t* test. Categorical variables are summarized as counts and percentages and were compared by the chi-square or by Fisher exact test. Serum levels of MMPs were compared by Mann-Whitney *U* test, and differences before and after PCI were determined by the Wilcoxon signed rank test for paired samples. Pearson's correlation was used to correlate MMP levels with late lumen loss after log10-transformation. Because a multivariable analysis was not feasible with only 12 ISR events, we adjusted only for that variable that was identified as the strongest confounding variable. As strongest confounder we selected that variable that implied the strongest modification of the odds ratio of the respective MMP level toward 1 among all bivariable models. A value of $p < 0.05$ (2-tailed) was considered statistically significant. All statistical analyses were performed with the statistical software package SPSS version 11.0 (SPSS, Inc., Chicago, Illinois). The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Thirty SES (Cypher) were used in 22 patients (25%), and 129 PES (Taxus) were implanted in 63 patients (75%). During follow-up 2 patients (2.4%) died of cardiovascular causes without evidence of stent thrombosis, and ISR occurred in 12 patients (14.5% of patients, 7.6% of stents). Target lesion revascularization was performed in all 12 patients. Patients with and without restenosis at follow-up angiography showed no significant differences in baseline clinical characteristics, cardiovascular risk factors, and medication (Table 1). There were also no significant differences in angiographic characteristics; however, the mean stent diameter was lower and the number of stents tended to be higher in patients with restenosis (Table 2).

Except MMP-2 antigen levels, which were higher in diabetic patients (799.58 ± 276.34 ng/ml vs. 667.82 ± 204.95 ng/ml; $p = 0.038$) and increased with age ($R = 0.258$; $p = 0.018$), MMP-2 and -9 antigen and activity levels at baseline were not associated with cardiovascular risk factors and demographic data, respectively. The MMP levels were also not associated with number of diseased vessel, lesion type, and size.

Table 1. Baseline Characteristics of Patients With and Without Restenosis

	Total (n = 85)	Restenosis (n = 12)	No Restenosis (n = 73)	p Value
Age (yrs)	64 ± 10.5	66.8 ± 7.3	63.6 ± 10.9	0.33
Sex (male)	66 (79.5)	9 (75)	57 (80.3)	0.70
Hypertension	63 (75.9)	7 (58.3)	56 (78.9)	0.12
Diabetes	25 (30.1)	3 (25)	22 (31)	0.48
Family history of coronary artery disease	46 (55.4)	7 (58.3)	39 (54.9)	0.54
Smoker	28 (33.7)	4 (33.3)	24 (33.8)	1.00
BMI (kg/m^2)	27.9 ± 3.7	26.6 ± 3.6	28.1 ± 3.7	0.20
Triglycerides (mg/dl)	174.6 ± 99.3	158.9 ± 70.2	177.2 ± 103.5	0.50
TC (mg/dl)	189.2 ± 43.5	186.4 ± 26.9	189.7 ± 45.8	0.81
HbA1c (%)	6.0 ± 0.7	6.1 ± 0.6	6.0 ± 0.8	0.83
CRP (mg/dl)	0.29 ± 0.28	0.28 ± 0.28	0.29 ± 0.28	0.87
Leukocytes (10^9/l)	6.7 ± 1.5	6.5 ± 1.8	6.7 ± 1.4	0.60
ACE inhibitor	35 (42.2)	7 (58.3)	28 (39.4)	0.34
ARB	10 (12)	1 (8.3)	9 (12.7)	1.00
Beta-blocker	44 (53)	8 (66.7)	36 (50.7)	0.36
Statin	64 (77.1)	9 (75)	55 (77.5)	1.00

Values are given as mean ± SD or n (%).
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CRP = C-reactive protein; HbA_{1c} = glycosylated hemoglobin; TC = total cholesterol.

Serum levels of MMP-2 and -9 at baseline in patients with and without restenosis. Patients with ISR at follow-up showed significantly higher MMP-9 activity levels before PCI (31.53 ± 16.9 ng/ml vs. 21.16 ± 10.87 ng/ml; p = 0.017). The MMP-2 activity levels as well as MMP-2 and MMP-9 antigen levels were not different in patients with and without ISR at baseline (Table 3).

Serum levels of MMP-2 and -9 24 h after PCI in patients with and without restenosis. In contrast to patients without ISR, in patients with ISR at follow-up angiography, the PCI procedure induced a significant increase of MMP-2 activity ($p < 0.0001$) and MMP-2 antigen ($p < 0.005$) as well as MMP-9 activity levels ($p < 0.0001$) (Table 3). Twenty-four hours after PCI, MMP-2 activity levels (44.20 ± 10.70 ng/ml vs. 29.23 ± 8.64 ng/ml, $p < 0.001$) as well as MMP-9 activity levels (54.25 ± 28.77 ng/ml vs. 24.75 ± 12.38 ng/ml, $p < 0.001$) were significantly higher in patients with ISR compared to patients without ISR (Fig. 2).

MMP activity predicts risk of restenosis after PCI. The restenosis rates of patients in the highest quartile of MMP-2 activity after PCI and MMP-9 activity before and after PCI were 40.0%, 38.9%, and 42.9% compared with a mean restenosis rate of 6.3%, 7.7%, and 4.0% in the 3 lower quartiles, respectively (Fig. 3). Whereas MMP-2 activity at baseline was no predictor for ISR, MMP-2 activity after PCI and MMP-9 activity before and after PCI predicted ISR independently from clinical, angiographic, and procedural risk factors as assessed by logistic regression model (Table 4).

Correlation of late lumen loss with MMP activity. In contrast to MMP-2 (R = 0.03, p = 0.81) and MMP-9 (R = 0.14, p = 0.21) activity at baseline, MMP-2 activity (R = 0.34, $p < 0.005$) and MMP-9 activity after the procedure (R = 0.53, $p < 0.000001$) were correlated with late lumen loss at follow-up (Fig. 4). Similar results were obtained when patients were stratified according to stent type. The MMP-9 activity showed a significant correlation with late lumen loss of PES (R = 0.52, $p < 0.00005$) and SES (R = 0.59, $p < 0.005$), respectively. The MMP-2 activity correlated significantly with late lumen loss of PES (R = 0.36, $p < 0.005$) but not of SES (R = 0.19, p = NS).

Discussion

The present study, which prospectively investigated angiographic outcome after implantation of DES, showed that elevated baseline serum activity of MMP-9 and increased post-procedural serum activities of MMP-2 and -9 were highly associated with the development of ISR. Multiple logistic regression demonstrated that MMP-2 and -9 activity levels independently predicted the occurrence of restenosis after implantation of DES.

Previous studies in patients with BMS suggested that antigen levels of MMP-2 and -9 might predict occurrence of restenosis (10,11), and it has been demonstrated retrospectively that patients with ISR in BMS showed increased MMP-9

Table 2. Angiographic and Procedural Characteristics of Patients With and Without Restenosis

	Restenosis (n = 12)	No Restenosis (n = 73)	p Value
Angiography			
CAD extent (1VD/2VD/3VD)	3/6/3	24/28/19	0.77
Target vessel			
LAD	7 (58.3)	41 (57.7)	0.69
LCx	1 (8.3)	12 (16.9)	
RCA	4 (33.3)	18 (25.4)	
Lesion type (A/B/C)	1/9/2	17/47/7	0.43
Vessel size (mm)	3.23 ± 0.39	3.26 ± 0.37	0.79
MLD (mm)	0.67 ± 0.21	0.67 ± 0.23	0.99
DS (%)	78.7 ± 7.04	80.03 ± 7.14	0.55
Intervention			
Number of stents/procedure	2.33 ± 1.37	1.79 ± 0.92	0.08
Number of stents/vessel	1.58 ± 0.8	1.29 ± 0.57	0.13
Type of stent			
Taxus	11 (91.7)	49 (69)	0.17
Cypher	1 (8.3)	22 (31)	
Stent diameter (mm)	2.77 ± 0.27	2.97 ± 0.33	0.03
Length of stented segment (mm)	22.42 ± 4.58	20.79 ± 6.38	0.40
MLD after procedure (mm)	2.63 ± 0.41	2.66 ± 0.35	0.78

Values are given as n or mean ± SD.
CAD = coronary artery disease; DS = diameter stenosis; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MLD = minimal lumen diameter; RCA = right coronary artery; 1VD/2VD/3VD = single-/double-/triple-vessel disease.

Table 3. MMP Serum Levels in Patients With and Without Restenosis

	Restenosis (n = 12)	No Restenosis (n = 73)	p Value	Corrected p Value*
Before procedure				
MMP-2 antigen (ng/ml)	645.28 ± 166.23	718.02 ± 244.13	0.407	1.0
MMP-2 activity (ng/ml)	27.68 ± 6.36	31.32 ± 8.44	0.221	0.221†
MMP-9 antigen (ng/ml)	855.83 ± 377.44	789.87 ± 395.15	0.729	0.729
MMP-9 activity (ng/ml)	31.53 ± 16.90	21.16 ± 10.87	0.017	0.017†
After procedure				
MMP-2 antigen (ng/ml)	1,080.93 ± 615.17	702.01 ± 221.26	0.017	0.09
MMP-2 activity (ng/ml)	44.20 ± 10.70	29.23 ± 8.64	<0.0001	<0.001
MMP-9 antigen (ng/ml)	1,124.31 ± 396.73	1,180.65 ± 449.83	0.623	1.0
MMP-9 activity (ng/ml)	54.25 ± 28.77	24.74 ± 12.38	<0.0001	<0.001
PCI-induced change				
MMP-2 antigen (ng/ml)	+435.66 ± 618.78	−16.01 ± 205.12	<0.005	<0.05
MMP-2 activity (ng/ml)	+16.52 ± 11.12	−2.03 ± 9.58	<0.0001	<0.0005
MMP-9 antigen (ng/ml)	+268.48 ± 481.49	+390.79 ± 523.60	0.561	1.0
MMP-9 activity (ng/ml)	+22.72 ± 25.40	+3.46 ± 13.27	<0.005	<0.05

Values are given as mean ± SD. *The p values corrected according to Bonferroni-Holm to account for multiple comparisons. †The p values for the primary hypothesis are not corrected to avoid type 2 error.

MMP = matrix metalloproteinase; PCI = percutaneous coronary intervention.

activity 1 year after the initial stent placement (12). Interestingly, in accordance with these studies and despite the anti-inflammatory and antimigratory effects of sirolimus and paclitaxel (13,14,16), this study provides evidence that gelatinase serum activity might also play a crucial role in the development of ISR after implantation of DES.

MMP-2 and -9 are produced by various cells like endothelial cells, macrophages, vascular smooth muscle cells, lymphocytes, and mast cells (17). MMP-2 and -9 expression might lead to basement membrane degradation that plays a key role in liberating contractile vascular smooth muscle cells to participate in repair after arterial injury. MMP-2 and -9 are crucial

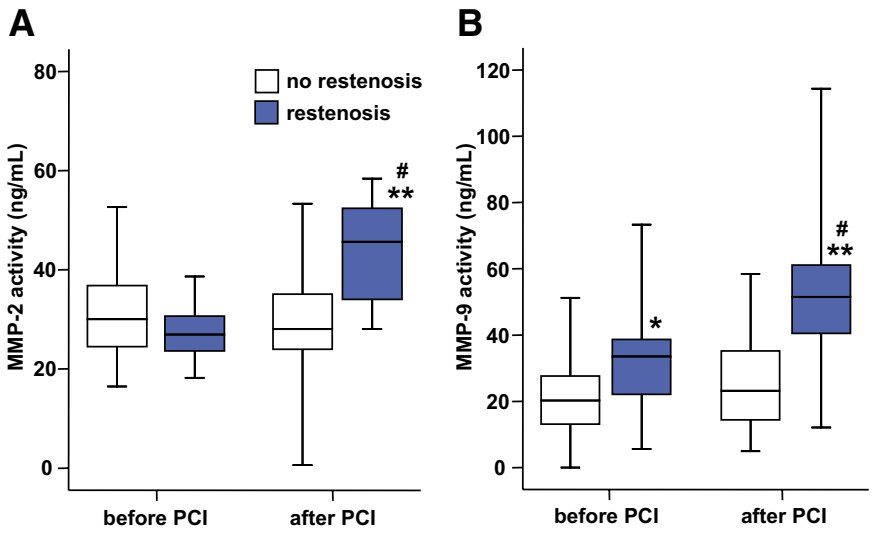

Figure 2. MMP Serum Activities in Patients With and Without In-Stent Restenosis

Serum activity of matrix metalloproteinase (MMP)-2 **(A)** and -9 **(B)** before and 24 h after percutaneous coronary intervention (PCI) with implantation of drug-eluting stents in patients without **(white boxes)** and with **(blue boxes)** angiographic in-stent restenosis. Box plots indicate median, interquartile range (range from the 25th to the 75th percentile), and total range. *$p < 0.05$ no restenosis versus restenosis; **$p < 0.001$ no restenosis versus restenosis; #$p < 0.01$ before versus 24 h after PCI.

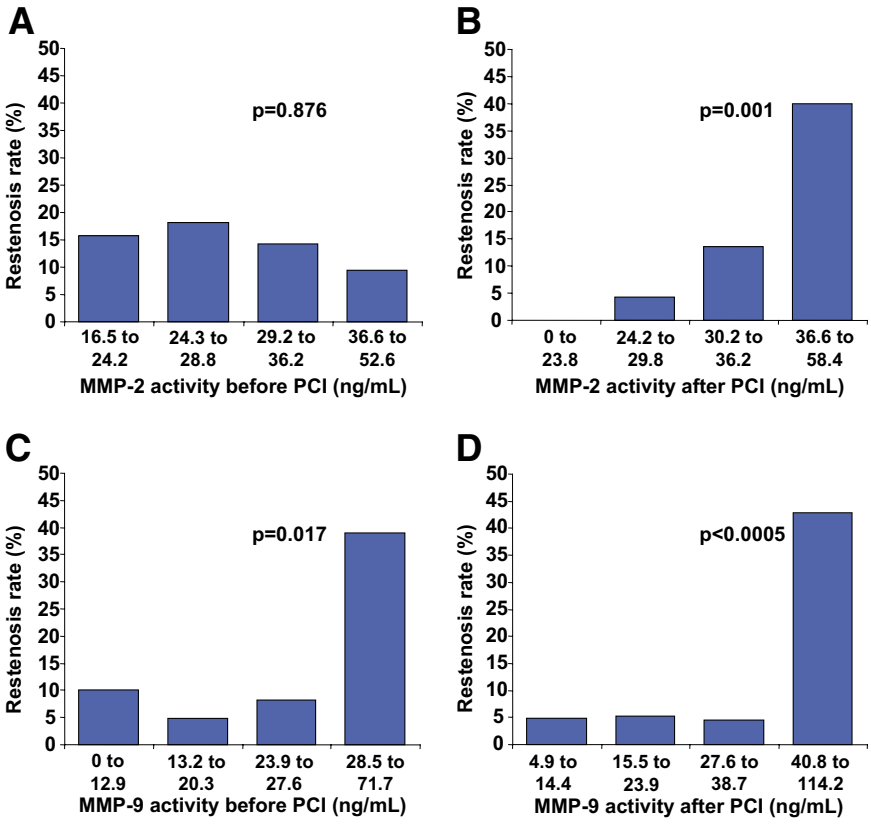

Figure 3. Restenosis Rates According to Quartiles of MMP Serum Activities

Restenosis rates according to quartiles of matrix metalloproteinase (MMP)-2 activity before percutaneous coronary intervention (PCI) **(A)**, MMP-2 activity after PCI **(B)**, MMP-9 activity before PCI **(C)**, and MMP-9 activity after PCI **(D)**.

for migration of vascular smooth muscle cells and matrix remodeling during wound healing (18). MMP-inhibition studies in animal models showed significant reductions in pathological remodeling (19–21). Although effects of MMP-inhibitors on the final intimal size are controversial (22–24), research on MMP-inhibitors as stent-coating material is ongoing (25).

Table 4. Logistic Regression Model Assessing the Risk for In-Stent Restenosis After Implantation of Drug-Eluting Stents

	Odds Ratio	95% Confidence Interval	p Value
MMP-2 activity after PCI	1.18	1.08–1.28	0.00012
MMP-9 activity baseline	1.07	1.01–1.12	0.015
MMP-9 activity after PCI	1.12	1.05–1.19	0.001
Adjusted for patient characteristics			
MMP-2 activity after PCI adjusted for hypertension*	1.17	1.08–1.27	0.0002
MMP-9 activity baseline adjusted for HDL*	1.07	1.01–1.13	0.024
MMP-9 activity after PCI adjusted for BMI*	1.11	1.04–1.19	0.001
Adjusted for angiographic and procedural characteristics			
MMP-2 activity after PCI adjusted for stent diameter†	1.17	1.08–1.27	0.0002
MMP-9 activity baseline adjusted for type of stent†	1.07	1.01–1.12	0.023
MMP-9 activity after PCI adjusted for type of stent†	1.11	1.04–1.18	0.001

*Strongest confounding variable, of hypertension, body mass index (BMI), high-density lipoprotein cholesterol (HDL), diabetes, and C-reactive protein (CRP).
†Strongest confounding variable, of vessel size, type of lesion, stent diameter, type of stent, number of stents, and total segment length.
MMP = matrix metalloproteinase; PCI = percutaneous coronary intervention.

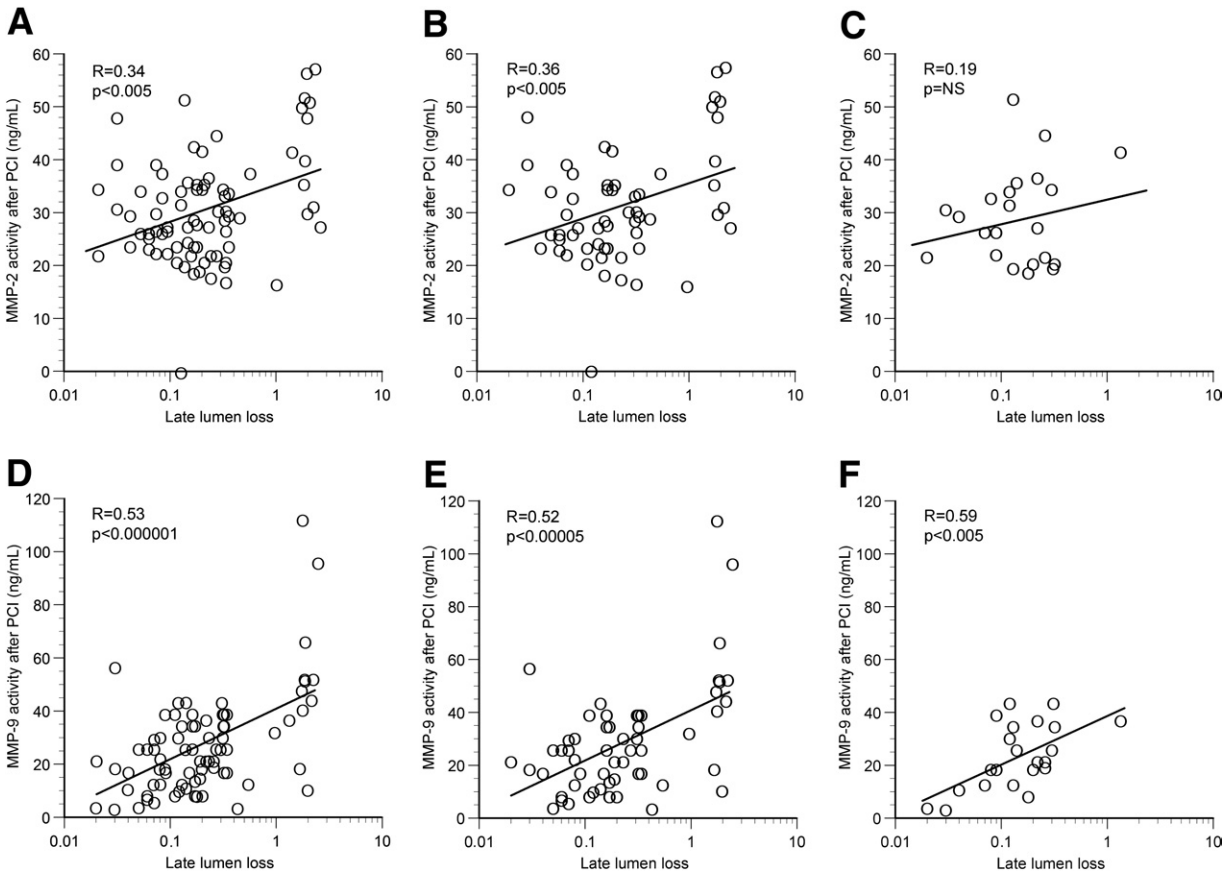

Figure 4. Correlation of MMP Serum Activities and Angiographic Late Lumen Loss

Correlation of serum activity of matrix metalloproteinase (MMP)-2 and -9 with angiographic late lumen loss of all patients **(A, D)**, patients with paclitaxel-eluting stents **(B, E)**, and patients with sirolimus-eluting stents **(C, F)**. In patients with multiple lesion interventions (n = 45), only the lesion with the highest late lumen loss is included.

In our study, the post-procedural activities of MMP-2 and -9 activity were correlated with angiographic late lumen loss. Surprisingly, despite the strong evidence that mechanical injury (3–7) and contact of peripheral blood monocytes with activated endothelial cells (26) rapidly increases gelatinase activity (3,8), patients who were free of ISR at follow-up angiography showed no or only minimal increases in serum activity of MMP-2 and -9 24 h after PCI. In contrast, patients with future ISR showed a significant increase in MMP-2 and -9 serum activity after the procedure.

Similar results were obtained for patients with PES and SES. The MMP-9 activity after PCI showed a strong correlation with late lumen loss of both stent types. The MMP-2 activity significantly correlated with late lumen loss of PES and showed only a trend to correlate with late lumen loss of SES. However, this might be explained by the smaller number and lower restenosis rate of SES in our study.

The PCI-induced increase of MMP-2 activity was associated with an increase of MMP-2 total antigen that was completely absent in patients without future ISR. In contrast, baseline levels of total antigen and the PCI-induced release of MMP-9 antigen was not different in both groups, suggesting an increased activation of pro–MMP-9 to its active form due to cleavage by plasmin and other MMPs in patients with future ISR.

Multiple logistic regression analysis showed that MMP-9 activity at baseline and MMP-2 and -9 activity after PCI predicted the occurrence of restenosis after implantation of DES independently of clinical risk factors as well as angiographic and procedural characteristics. We also included the acute phase protein C-reactive protein in the model and could demonstrate that the predictive value of MMP-2 and -9 was independent of this unspecific inflammatory marker.

In contrast to MMP-9 activity at baseline, MMP-2 activity before PCI did not predict the occurrence of ISR. In addition, MMP-2 and -9 activity before the intervention were not significantly associated with the grade of intimal hyperplasia.

However, post-procedural levels of MMPs might be useful for risk stratification, because patients with an increase of MMPs and a very high risk of restenosis could be monitored more closely (e.g., with stress test or re-angiography).

Study limitations. Some limitations of the present study have to be acknowledged. Because the primary end point of this study was angiographic restenosis, we included only patients who gave their informed consent for control angiography. However, we do not believe that selection bias plays a major role, because these patients did not differ with respect to baseline characteristics and outcome from the total cohort of patients who had PCI with implantation of DES. Furthermore, our study is necessarily of an observational nature. Accordingly, our results might be explained by unmeasured confounding factors. Therefore, we tried to control for baseline imbalances by multivariate modeling. The possibility of residual or undetected confounding is small but cannot be ruled out completely. Although the predictive value of MMP-2 and -9 was highly significant, this study was not powered for calculation of clinical cutoff values, due to the relatively low number of patients who develop ISR after implantation of DES. This needs to be further evaluated in larger, multicenter trials.

Conclusions

This study provides evidence that serum activity of MMP-2 and -9 might play a role in the pathogenesis of ISR after implantation of DES. An elevated baseline activity of MMP-9 and increased levels of MMP-2 and -9 activity after PCI with implantation of DES are associated with restenosis rates of 38.9% to 42.9%. In real world populations, ISR still plays a significant role after implantation of DES. Therefore, determination of MMP-2 and -9 activity might identify patients who are particularly at high risk for development of ISR.

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