

Impaired Flow-Mediated Dilatation and Risk of Restenosis in Patients Undergoing Coronary Stent Implantation

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Background—Impaired endothelial function is a key event in the atherosclerosis process and predicts future cardiovascular events in subjects with and without coronary artery disease (CAD). We performed the first prospective study evaluating whether early measurement of brachial artery endothelium-dependent dilation (flow-mediated dilation [FMD]) after coronary stenting could predict occurrence of in-stent-restenosis.

Methods and Results—The study population included 136 patients with single-vessel CAD undergoing percutaneous coronary intervention (PCI) with stenting and at least 6 months of follow-up. All patients underwent ultrasound detection of brachial artery reactivity 30 days after PCI; FMD was investigated before and after 5 minutes of occlusion of the brachial artery, and nitroglycerin-mediated dilation was investigated before and after administration of sublingual nitrates. Clinical in-stent restenosis was demonstrated in 20 patients (15%), whereas 116 patients (85%) remained free of signs or symptoms of recurrent ischemia. FMD was significantly impaired in patients with restenosis versus those without restenosis (percent diameter variation $4.6 \pm 5.8\%$ versus $9.5 \pm 6.6\%$, $P=0.002$); moreover, 4% of patients with $FMD \geq 7\%$ (median value) developed in-stent restenosis versus 28% of those with $FMD < 7\%$ ($P=0.0001$). On multivariate analysis, FMD was the strongest predictor of restenosis (OR 4.5, 95% CI 2.4 to 12.0); conversely, nitroglycerin-mediated dilation did not independently predict the risk of restenosis (OR 2.4, 95% CI 0.8 to 6.3).

Conclusions—This is the first prospective study indicating that impaired FMD independently predicts occurrence of in-stent restenosis in patients undergoing PCI. Early evaluation of endothelial function after stenting may represent a useful screening tool to stratify patients according to future risk of restenosis. (*Circulation*. 2005;111:70-75.)

Key Words: endothelium ■ stents ■ restenosis

Impairment of endothelial function is an early event in the atherosclerotic process, and markers of endothelial dysfunction have been used as a surrogate of disease activity.¹⁻³ Abnormal endothelial function in the coronary circulation may precede development of angiographically evident coronary plaques,⁴ has been associated with a higher prevalence of coronary artery disease (CAD),⁵ and may be predictive of future cardiovascular events^{6,7}; however, direct assessment of coronary vasomotor response is invasive and cannot be widely applied in clinical practice. Endothelial dysfunction is considered a systemic process^{1,2}; therefore, endothelium-dependent vasomotion detected in peripheral arteries with noninvasive tests reflects coronary endothelial function. Ultrasound assessment of brachial artery flow-mediated dilation (FMD) is a sensitive test for quantifying endothelium-dependent vasomotion,⁸ and a close relationship has been demonstrated between this technique and coronary vasomotor responses to acetylcholine.⁹ Finally, FMD by brachial artery ultrasound imaging has been correlated with the occurrence of adverse events in patients with chest pain¹⁰ and after vascular surgery.¹¹ Percutaneous coronary

intervention (PCI) with stenting has now become an effective and widespread treatment modality for patients with CAD, but in-stent restenosis remains its main limitation; therefore, early identification of patients with higher risk of restenosis after PCI is the object of active investigation. In a small observational study,¹² forearm reactive hyperemia was impaired in patients with in-stent restenosis, but no prospective data are available on the predictive role of endothelial function assessment in patients undergoing coronary stent implantation. Thus, we prospectively investigated whether early evaluation after coronary stenting of FMD by brachial artery ultrasound imaging could predict in-stent-restenosis in a consecutive cohort of patients followed up for 6 months after the procedure.

See p 8

Methods

Study Population and Procedural Characteristics

This is a prospective study of consecutive patients with CAD treated with PCI at Campus Bio-Medico University of Rome (Rome, Italy)

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and followed up by protocol design for up to 6 months. Inclusion criteria consisted of patients who were symptomatic for myocardial ischemia and who were undergoing stent implantation for single-vessel significant CAD. Exclusion criteria were multivessel CAD, restenotic target lesions, stenoses of saphenous vein grafts, primary angioplasty for acute myocardial infarction, balloon angioplasty without stent deployment, and liver and renal failure with creatinine >3 mg/dL. Two-hundred twenty-six patients underwent elective PCI in our institution over the study period, and after evaluation of inclusion and exclusion criteria, 136 consecutive patients were enrolled and represent the study population; a total of 90 patients were excluded, most because of multivessel CAD or balloon angioplasty without stenting.

All patients had ≥ 1 significant de novo stenoses (reduction $\geq 50\%$ of the lumen diameter) on the same coronary vessel at angiography that was deemed responsible for the myocardial ischemia. Indications for coronary intervention were chronic stable angina (according to the Canadian Cardiovascular Society classification) with documented inducible myocardial ischemia in 32 patients, unstable angina (Braunwald class IIB or IIIB) in 31, and angina/ischemia after myocardial infarction in 73. Baseline demographic data and a complete clinical history that included cardiovascular risk factors (family history for CAD, diabetes mellitus, cigarette smoking, systemic hypertension, and hypercholesterolemia) were collected. In all patients, PCI was performed with conventional techniques by the femoral approach. Quantitative coronary angiography was done by electronic calipers. All patients received aspirin (100 mg/d) and ticlopidine 250 mg BID at least 3 days or clopidogrel 300 mg at least 6 hours before the procedure. Before intervention, patients received weight-adjusted intravenous heparin with a target activated clotting time of >300 seconds in the absence of glycoprotein IIb/IIIa inhibitor therapy and 200 to 300 seconds with glycoprotein IIb/IIIa, which was allowed at the operator's discretion. Procedural success was defined as reduction of stenosis to $<30\%$ residual narrowing, with improvement of ischemic symptoms and without major in-hospital complications: death, emergency bypass surgery, or myocardial infarction (defined as >2 times increase in creatine kinase-MB levels). Aspirin (100 mg/d) was given indefinitely; ticlopidine 250 mg BID or clopidogrel 75 mg QD was continued for at least 4 weeks after intervention (patients with unstable ischemic syndromes or treated with drug-eluting stents received clopidogrel for 9 months). Each patient provided written informed consent to the study.

Evaluation of Brachial Artery Reactivity

By protocol, all patients underwent ultrasound detection of brachial artery diameter variations during hyperemia 30 days after PCI. All vasoactive drugs (in particular nitrates, ACE inhibitors, angiotensin antagonists, and calcium antagonists) were discontinued for 48 hours before this measurement. Brachial artery reactivity was assessed at the time of the first follow-up visit, 30 days after the procedure, and after complete clinical stabilization to enable the safe withdrawal of vasoactive drugs. Because of circadian variations of peripheral vascular tone,¹³ detection of brachial artery vasomotion was performed in all patients between 9 and 9:30 AM in a quiet, temperature-controlled room (22°C to 24°C). Ultrasound evaluation was done on the dominant (usually right) forearm; patients were studied supine and were kept fasting and at rest for 5 minutes before the evaluation, and smoking and beverages that contained alcohol or caffeine were prohibited within the preceding 12 hours. 2D brachial artery imaging and measurements were obtained in all patients by the same operator with a 7.5-MHz linear-array transducer connected to a Hewlett Packard ultrasound machine (Sonos 5500). Straight segments of the artery (8 to 10 mm in length) were chosen above the antecubital fossa, perpendicular to the ultrasound beam and along its long axis. FMD due to shear-induced endothelial nitric oxide production was detected after occlusion of the forearm circulation. A longitudinal image was used to measure brachial artery diameter (first baseline value); a blood pressure cuff was inflated on the upper arm to 50 mm Hg above systolic pressure for 5 minutes and then deflated, and after 1 minute, a second longitudinal scan was obtained to

calculate the brachial artery diameter (postocclusion value). FMD was expressed as percent diameter variation (absolute diameter changes were also recorded). After 15 minutes of rest, a new detection of brachial artery diameter was performed (second baseline value) and repeated 3 minutes after administration of 0.5 mg of sublingual nitroglycerin (postnitrate value). Endothelium-independent dilation (nitroglycerin-mediated dilation [NMD]), due to the direct effect of nitroglycerin-derived nitric oxide, was then obtained and expressed as percent diameter variation. All brachial artery diameters were obtained from the near-to-far blood-wall interface (intima-media interfaces); measurements were performed at end diastole in the cardiac cycle (onset of the R wave) by ECG gating during image acquisition. Five cardiac cycles were analyzed and averaged for each scan. Twenty randomly selected images were reanalyzed to assess intraobserver variation; intraobserver variations for FMD and NMD were, respectively, $1.3 \pm 1\%$ and $2 \pm 1.6\%$ (coefficient of variation 5% and 7%, respectively).

Follow-Up Assessment

All patients underwent follow-up office visits 3 and 6 months after stent implantation by protocol; specifically, return of angina (according to the Canadian Cardiovascular Society classification of stable angina or the Braunwald classification of unstable angina) and the occurrence of cardiac death or myocardial infarction were evaluated, and physical examination and 12-lead ECGs were obtained. All patients underwent exercise tolerance test/myocardial scintigraphy 3 and 6 months after the procedure. The study end point was clinical recurrence, and reangiography was performed in the presence of signs or symptoms of myocardial ischemia. At reangiography, multiple views were obtained, and in-stent restenosis was defined as $\geq 50\%$ reduction of the luminal diameter by quantitative coronary angiography.

Statistical Analysis

In a previous prospective study,¹¹ the incidence of cardiovascular events in patients with impaired versus normal FMD was 32% versus 8%, respectively; thus, if we hypothesized a similar association with in-stent restenosis, a population of 106 patients would be needed to detect this difference with $\alpha=0.05$ and a power of 0.90. Results are expressed as mean \pm SD unless otherwise specified. Continuous variables were compared by 2-tailed independent *t* test for normally distributed values; otherwise, the Mann-Whitney *U* test was applied. Proportions were compared by χ^2 test or Fisher's exact test when appropriate. Correlations were assessed by Spearman's test. Independent predictors of in-stent restenosis were calculated by logistic regression. The following parameters were evaluated first in a univariate model: FMD, NMD, age, gender, clinical pattern, diabetes mellitus, systemic hypertension, hypercholesterolemia, cigarette smoking, left ventricular ejection fraction, type of target vessel (left anterior descending versus circumflex/right artery), type of lesion (A/B1 versus B2/C, according to the American College of Cardiology/American Heart Association classification), stent diameter, stented segment length, periprocedural use of glycoprotein IIb/IIIa inhibitors, and medical therapy on discharge. Variables with a probability value <0.15 were then entered into a multivariate logistic regression analysis. Event-free survival curves at 6 months in patients with lower versus higher FMD were obtained by the Kaplan-Meier method with a log-rank test. A probability value <0.05 (2-tailed) was considered significant. All calculations were performed with GB-STAT version 6 software.

Results

Clinical and Procedural Characteristics

In the study population, mean age was 63 ± 8 years, and prevalences of male gender and diabetes mellitus were 82% and 24%, respectively. Thirty-two patients underwent PCI for stable angina, 31 for unstable angina, and 73 for angina/ischemia after myocardial infarction. Procedural success was

TABLE 1. Clinical Features in Patients With FMD <7% and ≥7%

Characteristic	FMD <7% (n=61)	FMD ≥7% (n=75)	P
Male gender	49 (80)	62 (83)	0.89
Age, y	63±9	60±10	0.20
Family history	12 (20)	13 (17)	0.89
Diabetes mellitus	21 (34)	12 (16)	0.02
Systemic hypertension	40 (66)	34 (45)	0.03
Hypercholesterolemia	45 (74)	54 (72)	0.96
Smokers	17 (28)	24 (32)	0.74
Left ventricular ejection fraction, %	55±7	55±8	0.81
Clinical presentation			
Chronic stable angina	15 (25)	17 (23)	0.95
Unstable angina	18 (30)	13 (17)	0.14
Angina/ischemia after myocardial infarction	28 (45)	45 (60)	0.14
Drug therapy after intervention			
Aspirin	61 (100)	75 (100)	1
Ticlopidine/clopidogrel	61 (100)	75 (100)	1
β-Blockers	9 (15)	12 (16)	0.97
ACE inhibitors	53 (87)	64 (85)	0.99
Nitrates	55 (90)	64 (85)	0.56
Calcium antagonists	45 (74)	54 (72)	0.97
Statins	56 (92)	66 (88)	0.66
Hormone replacement therapy	1 (2)

Values are n (%) or mean±SD.

achieved in all 136 patients without major in-hospital complications. All patients underwent stent implantation (mean 1.3±0.7 stent/patient); no patient had significant side-branch closure during the procedure. One patient with no-reflow phenomenon was successfully treated with intracoronary adenosine and nitrates and infusion of glycoprotein IIb/IIIa inhibitor.

During 6 months of follow-up, 112 patients remained asymptomatic and without inducible myocardial ischemia; a positive stress test or recurrent ischemia/anginal symptoms occurred in 23 patients, who underwent repeat coronary angiography. In-stent restenosis was detected in 20 patients (15%), whereas 1 patient showed disease progression on a nontarget vessel; the remaining 2 patients had patent coronary arteries, without significant (≥50%) in-stent restenosis. Finally, 1 other patient was hospitalized for an acute myocardial infarction, and angiography showed total occlusion of a nontarget coronary artery. All 20 patients with in-stent restenosis underwent successful repeat angioplasty.

Brachial Artery Reactivity

Clinical and procedural variables in patients with FMD above or below the median value (7%) are shown in Table 1 and Table 2, respectively. The two groups were similar with regard to age, gender, family history, hypercholesterolemia, cigarette smoking, clinical presentation, and left ventricular function; coronary anatomy, lesion type, procedural characteristics, stent diameter, stented segment length, and IIb/IIIa inhibitor infusion were also similar. As expected, patients

with lower FMD had a significantly higher prevalence of diabetes mellitus and systemic hypertension. Baseline high-sensitivity C-reactive protein levels were available in the last 50 patients and were similar in patients with FMD <7% versus FMD ≥7% (0.66±1.12 versus 0.57±1.34 mg/L, $P=0.86$), and there was no significant correlation between C-reactive protein levels and FMD ($r=0.19$, $P=0.60$) in this subgroup; likewise, FMD was not significantly different in patients with C-reactive protein <3 mg/L versus those with levels ≥3 mg/L (10.1±7% versus 8.4±5.4%, $P=0.36$).

With the median value used as the cutoff point for FMD (7%), 3 (4%) of 75 patients with FMD ≥7% developed restenosis versus 17 (28%) of 61 patients with FMD <7% ($P=0.0001$; Figure 1). FMD ≥7% had a negative predictive value of 96% for occurrence of clinical restenosis. FMD 1 month after PCI was significantly impaired in patients who developed in-stent restenosis during follow-up versus those without recurrence (percent diameter variation: 4.6±5.8% versus 9.5±6.6%, $P=0.002$; Table 3; Figure 1). Conversely, NMD was not significantly different in the 2 groups of patients (percent diameter increase 10±14% versus 14±11%, $P=0.09$; Table 3; Figure 1). Actuarial survival analysis showed a significantly higher restenosis rate during 6-month follow-up in patients with FMD <7% ($P=0.0008$; Figure 2). At univariate (Table 4) and multivariate (Figure 3) logistic regression analysis, diabetes mellitus, stent diameter <3.0 mm, and FMD <7% were the only variables associated with a significantly higher risk of in-stent restenosis, whereas ACE inhibitor use was associated with a lower risk; specifically, FMD <7% was the strongest predictor of restenosis at 6 months (OR 4.5, 95% CI 2.4 to 12.0).

Discussion

This is the first prospective study demonstrating that impaired FMD is an independent predictor of in-stent restenosis in

TABLE 2. Procedural Features in Patients With FMD <7% and ≥7%

Characteristic	FMD <7% (n=61)	FMD ≥7% (n=75)	P
Vessel treated			
Left anterior descending (%)	31 (51)	37 (49)	1
Left circumflex (%)	12 (20)	15 (20)	0.87
Right coronary artery (%)	18 (30)	23 (31)	0.97
Multivessel coronary disease
Lesion type B2/C (%)	23 (38)	40 (53)	0.09
Total occlusions (%)	4 (7)	5 (7)	0.75
Bifurcations with kissing balloon (%)	3 (5)	4 (5)	0.78
No. of stents per patient	1.3±0.8	1.4±0.5	0.79
Stent diameter, mm	3.1±0.4	3.2±0.3	0.19
Total stent length, mm	17.1±6.8	17.2±7.1	0.69
Use of drug eluting stents, %	...	3 (4)	...
Direct stenting, %	23 (38)	25 (33)	0.73
Stent deployment pressure, atm	13.8±1.1	13.5±1.9	0.59
Glycoprotein IIb/IIIa inhibitor use	14 (23)	15 (20)	0.84

Values are n (%) or mean±SD.

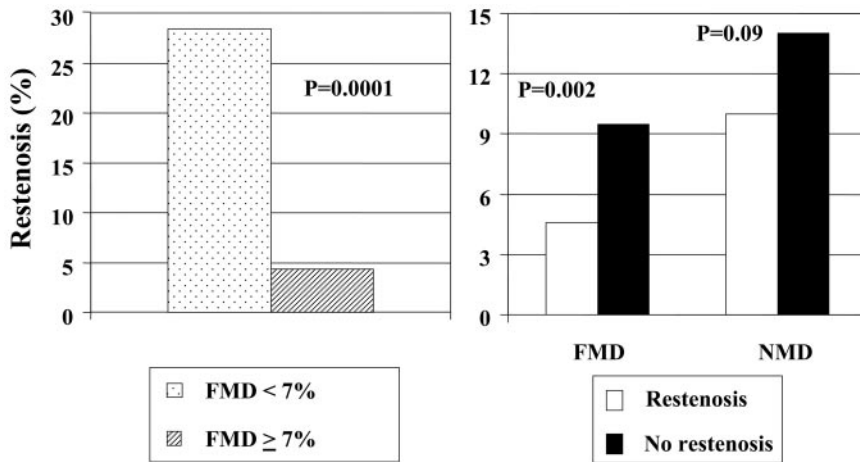


Figure 1. Left, Incidence of in-stent restenosis in patients with postprocedural FMD <7% vs \geq 7%. Right, Postprocedural FMD and NMD, expressed as percent diameter increase, in patients with and without in-stent restenosis during follow-up.

patients with single-vessel CAD undergoing PCI. Although there are several evidences of the close relationship between endothelial dysfunction and atherosclerosis,^{4,5,14,15} the role of endothelium in the process of restenosis after stent implantation is still unclear.¹² Previous studies have found an independent correlation between coronary endothelial function and risk of cardiovascular events,^{16,17} but there are no data on the possible association between endothelial dysfunction in the coronary circulation and risk of restenosis. FMD is a noninvasive technique that is easily applied in clinical practice, especially if repeated measurements are required.⁸ FMD depends largely on nitric oxide synthesis but may also reflect local release of other endothelium-derived factors (ie, prostacyclin and bradykinin).^{1,2} Furthermore, brachial artery FMD correlates well with coronary endothelial function,⁹ particularly that of conduit epicardial vessels.² In previous studies, impaired endothelial function by brachial artery FMD was associated with occurrence of future cardiovascular events in patients with chest pain who were undergoing coronary angiography¹⁰ and in those treated with vascular surgery¹¹; a large prospective trial on the role of brachial artery FMD in predicting cardiac events in a healthy population is ongoing.^{1,18}

In-stent restenosis due to intimal hyperplasia occurs after PCI with stent implantation in 10% to 40% of cases at 6 months, depending on various clinical, angiographic, and procedural features. Therefore, early stratification of patients according to the risk of development of in-stent restenosis

appears crucial after percutaneous revascularization and may influence clinical management. Mechanisms involved in the pathogenesis of in-stent restenosis include platelets and inflammatory cell activation due to procedural vascular injury with subsequent local release of cytokines and growth factors, leukocyte adherence, smooth muscle cell proliferation, and extracellular matrix synthesis.^{19,20} Previous studies have suggested that early deterioration of coronary microvascular function may be associated with restenosis in patients treated with balloon angioplasty²¹; moreover, in a retrospective study on a small number of patients,¹² comparison of endothelial function by venous occlusive plethysmography showed a significantly impaired forearm reactive hyperemia in patients with in-stent restenosis.

To date, no prospective study has evaluated the relationship between markers of endothelial function and outcome after PCI; thus, we investigated whether early ultrasound assessment of brachial artery FMD after PCI could predict occurrence of clinical in-stent restenosis. The present study, although it confirms the predictive role of known risk factors for restenosis, such as diabetes mellitus and lower stent diameter, demonstrates in a prospective fashion the strong association between signs of systemic endothelial dysfunction

TABLE 3. Brachial Artery Reactivity in Patients With and Without In-Stent Restenosis

	Restenosis	No Restenosis	P
FMD, mm			
First baseline value	4.26 \pm 0.5	4.14 \pm 0.5	0.73
Postocclusion value	4.45 \pm 0.47	4.53 \pm 0.58	0.66
Absolute diameter change	0.21 \pm 0.23	0.39 \pm 0.27	0.002
NMD, mm			
Second baseline value	4.48 \pm 0.55	4.16 \pm 0.75	0.07
Post-nitrates value	5.00 \pm 0.63	4.79 \pm 0.85	0.63
Absolute diameter change	0.45 \pm 0.52	0.63 \pm 0.40	0.09

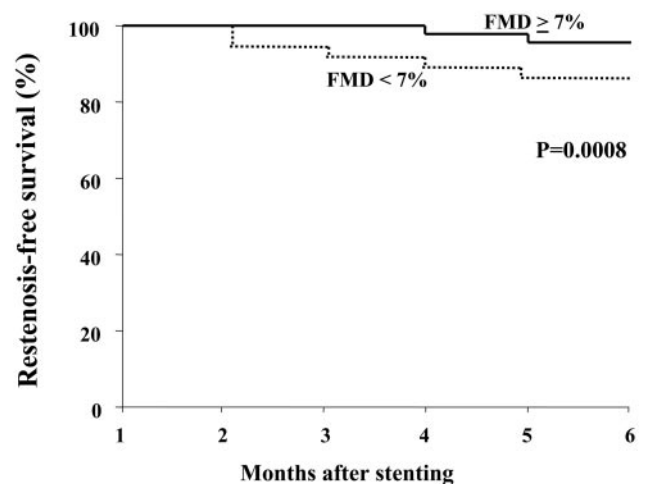


Figure 2. Actuarial survival curves in patients with FMD above or below median value (ie, FMD <7% vs FMD \geq 7%).

TABLE 4. Results of Univariate Logistic Regression Analysis According to Risk of In-Stent Restenosis

Variable	OR	95% CI	P
Male gender	1.3	0.4–4.9	0.67
Age >60 y	1.6	0.6–4.1	0.35
Family history	1.2	0.5–3.1	0.55
Diabetes mellitus	3.3	1.2–8.4	0.023
Systemic hypertension	1.3	0.5–3.4	0.59
Hypercholesterolemia	1.1	0.4–3.4	0.81
Smoking	0.5	0.2–1.7	0.29
Left ventricular ejection fraction <50%	1.0	0.4–3.1	0.94
Unstable angina	0.9	0.3–2.9	0.93
LAD vs left circumflex/RCA	1	0.4–2.6	1
Lesion type B2/C	0.6	0.2–1.6	0.28
Stent diameter <3.0 mm	3.6	1.2–10.5	0.018
Stented segment length >15 mm	1.2	0.5–3.2	0.67
Direct stenting	0.4	0.1–1.3	0.15
Glycoprotein IIb/IIIa inhibitor use	2.3	0.8–6.4	0.11
β -Blockers	2.9	0.9–8.7	0.06
ACE inhibitors	0.3	0.1–0.6	0.006
Calcium antagonists	0.5	0.2–1.3	0.17
Statins	0.6	0.2–2.3	0.46
FMD <7%	5.1	2.4–12.0	0.001
NMD <13.5%	2.4	0.8–6.3	0.09

LAD indicates left anterior descending coronary artery; RCA, right coronary artery.

tion assessed by brachial artery FMD and in-stent restenosis. With a cutoff value of 7% for FMD, ultrasound detection of preserved endothelial function had a negative predictive value of 96% for excluding restenosis, and brachial artery FMD remained the strongest independent predictor of in-stent restenosis even after adjustment for all other risk factors.

The results of the present study support the hypothesis that preserved endothelial function with release of molecules with antiinflammatory, antithrombotic, and antiproliferative effects (including nitric oxide, prostacyclin, and other hyperpolarizing factors) is crucial for the prevention of luminal

narrowing by neointimal thickening.^{22,23} Dysfunctional endothelium may release several substances, such as endothelin-1, angiotensin II, and growth factors (platelet-derived growth factor, macrophage colony stimulating factor, and transforming growth factor), that may induce or enhance migration of smooth muscle cells and intimal hyperplasia,² thus contributing to the in-stent restenosis process; local production by dysfunctional endothelium of proinflammatory cytokines, tumor necrosis factor, adhesion molecules, and chemotactic factors may also play a role via activation of local inflammatory pathways. Indeed, in vivo data demonstrate that impaired endothelial function may enhance intimal hyperplasia after balloon angioplasty.^{24,25} NMD was not an independent predictor of restenosis in the present study population, although there was a nonsignificant trend toward an association between impaired NMD and restenosis; however, NMD reflects function of smooth muscle cells (endothelium-independent dilation), which are directly involved in the process of restenosis. Overall, FMD was low in the present study population, but this finding is common in individuals with multiple cardiovascular risk factors and significant CAD. Whether aggressive therapy with drugs that improve endothelial function (such as ACE inhibitors, statins, and antioxidants) translates to a reduction of restenosis risk in patients with endothelial dysfunction should be tested in appropriate trials; interestingly, we found a significant association between use of ACE inhibitors and absence of in-stent restenosis.

The end point of the present study was clinical recurrence (ie, recurrence of ischemia associated with angiographic documentation of restenosis); this approach is only apparently a limitation of the study, because isolated angiographic restenosis defined by a binary quantitative measurement ($\pm 50\%$) in the absence of inducible ischemia may have dubious clinical significance. This study was performed with traditional bare-metal stents (only 3 patients received a drug-eluting stent); previous randomized trials showed that drug-eluting stents significantly reduce intimal hyperplasia and restenosis after stent implantation,²⁶ and thus, these data cannot be directly extrapolated to patients receiving drug-eluting stents. However, our results indicate that early evaluation of endothelial function by brachial artery ultrasound after PCI may represent a useful screening tool to stratify patients according to a higher or lower risk of future restenosis. Furthermore, the evidence that systemic endothelial dysfunction is associated with risk of in-stent restenosis gives more insights on the determinant role played by the endothelium both in the atherosclerotic process and in the restenosis process.

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Odds ratio for in-stent restenosis

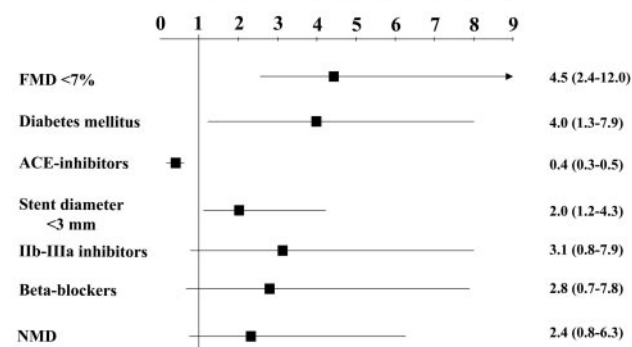


Figure 3. Multivariate logistic regression analysis showing that FMD, diabetes mellitus, and stent diameter <3 mm are independently associated with significantly increased risk of in-stent restenosis.

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Impaired Flow-Mediated Dilation and Risk of Restenosis in Patients Undergoing Coronary Stent Implantation

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