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Clinical and Angiographic Factors Associated With Asymptomatic Restenosis After Percutaneous Coronary Intervention

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Background—Angiographic restenosis after percutaneous coronary interventional procedures is more common than recurrent angina. Clinical and angiographic factors associated with asymptomatic versus symptomatic restenosis after percutaneous coronary intervention were compared.

Methods and Results—All patients with angiographic restenosis from the BENESTENT I, BENESTENT II pilot, BENESTENT II, MUSIC, WEST 1, DUET, FINESS 2, FLARE, SOPHOS, and ROSE studies were analyzed. Multivariate analysis evaluated 46 clinical and angiographic variables, comparing those with and without angina. The 10 studies recruited 2690 patients who underwent percutaneous revascularization and 6-month follow-up angiography (86% of those eligible). Restenosis (≥50% diameter stenosis) occurred in 607 patients and was clinically silent in 335 (55%). Male sex ($P=0.008$), absence of antianginal therapy with nitrates ($P=0.0002$) and calcium channel blockers ($P=0.02$) at 6 months, greater reference diameter after the procedure ($P=0.04$), greater reference diameter at follow-up ($P=0.004$), and lesser lesion severity (percent stenosis) at 6 months ($P=0.0004$) were univariate predictors of asymptomatic restenosis. By multivariate analysis, only male sex ($P=0.04$), greater reference diameter at follow-up ($P=0.002$), and lesser lesion severity at 6 months ($P=0.0001$) were associated with restenosis without angina.

Conclusions—Approximately half of patients with angiographic restenosis have no symptoms. The only multivariate predictors of silent restenosis at 6 months were male sex, greater reference diameter at follow-up, and lesser lesion severity on follow-up angiography. **(*Circulation*. 2001;104:2289-2294.)**

Key Words: angioplasty ■ restenosis ■ stents

Restenosis remains the major shortcoming after percutaneous intervention, with reported rates, in recent times, varying between 10% and 40%. A combination of patient factors, such as diabetes, lesion variables including length and vessel size, and type of revascularization device, all influence the likelihood of restenosis.[1–4] With the evolution of core laboratories, such as Cardialysis in Rotterdam, large databases of clinical and angiographic data provide a unique opportunity to identify factors that may influence the restenotic process.

One consistent observation of studies evaluating patient outcome after percutaneous coronary interventional procedures is the disparity between the incidence of restenosis in those patients undergoing systematic angiographic follow-up 6 months after the interventional procedure and the rate of repeat target lesion revascularization in those with clinical follow-up and symptom-driven repeat angiography.[5,6] The clinically driven repeat revascularization rate is often ≈50% the angiographic restenosis rate, and routine angiography 6 months after the intervention clearly influences the likelihood of reintervention.[7]

There is little information on the differences in patient or lesion characteristics between patients who develop restenosis with recurrent symptoms and those in whom restenosis is clinically silent. This study evaluates patients from 10 interventional coronary angioplasty or stent trials, each enrolling between 102 and 1054 patients, with planned 6-month follow-up angiography. Multivariate analysis was used to assess clinical or angiographic factors that might be associated with asymptomatic as opposed to symptomatic restenosis.

Methods

Patient Population

Patients enrolled in 10 percutaneous coronary interventional studies[5,6,8–15] undertaken over a period of 9 years who underwent planned 6-month angiographic follow-up were considered for analysis. Of these studies, 2 were randomized trials of stent deployment

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TABLE 1. Abbreviations and Acronyms

BENESTENT	Belgium and Netherlands stent study
MUSIC	Multicenter Ultrasound Stenting in Coronaries study
WEST	West European stent trial
SOPHOS	Study of Phosphorylcholine on stents
DUET	Evaluation of the ACS-Multilink DUET coronary stent system
FLARE	Fluvastatin angioplasty restenosis trial
FINESS 2	First International NIR Endovascular Stent Study
ROSE	Registry for optimal stent evaluation

versus balloon angioplasty (BENESTENT I, BENESTENT II), 6 were registries of newer stent designs (BENESTENT II pilot, DUET, FINESS 2, ROSE, SOPHOS, WEST I), 1 assessed the efficacy of intravascular ultrasound–guided stent implantation (MUSIC), and another studied the effect of a cholesterol-lowering agent on restenosis rates in patients undergoing balloon angioplasty (FLARE) (for abbreviations and acronyms see Table 1). The 10 studies are summarized in Table 2. Baseline characteristics of patients enrolled in these studies are shown in Table 3. All clinical information was monitored and forwarded to the core laboratory (Cardialysis, Rotterdam) and entered into the study databases. Studies were approved by institutional ethics committees, and written informed consent was obtained from all patients.

All patients who underwent 6-month angiographic follow-up and had complete clinical and angiographic data were analyzed. In the Benestent II and SOPHOS studies, only those assigned to angiographic follow-up were enrolled. Of interest were those who had no symptoms of angina at 6-month clinical follow-up and angiographic restenosis, defined as a ≥50% diameter stenosis at the treated site. Forty-six clinical and angiographic factors were entered into a univariate and multivariate analysis to establish whether any were predictive of asymptomatic or silent restenosis (Table 4).

Angiographic Analysis

All procedural and follow-up angiograms were sent to the core laboratory (Cardialysis) and analyzed by the Cardiovascular Angiography Analysis System, which was validated previously.[16,17] For each patient, several matched angiographic views were obtained after intracoronary administration of nitrates. Patients with an unsuccessful procedure or without angiographic follow-up were excluded from the analysis. For patients who had undergone multilesion coronary angioplasty, the most severe restenotic lesion at follow-up was entered into the analysis. The minimal luminal diameter (MLD) and reference diameter obtained by an interpolated method were determined on an end-diastolic frame.

TABLE 2. The 10 Percutaneous Interventional Studies With Angiographic Follow-Up

Study	No. of Patients	Nature of Study	Stent Type
BENESTENT I	516	Stent vs balloon	Palmaz-Schatz
BENESTENT II pilot	203	Stent registry	Heparin-coated PS
BENESTENT II	827	Stent vs balloon	Heparin-coated PS
DUET	210	Stent registry	Multilink
FINESS 2	156	Stent registry	NIR
FLARE	1054	Balloon + fluvastatin	
MUSIC	161	Stent (IVUS guided)	Heparin-coated PS
ROSE	120	Stent registry	BeStent
SOPHOS	425	Stent registry	Biodiv Ysio
WEST I	102	Stent registry	Multilink

IVUS indicates intravascular ultrasound.

Statistical Analysis

Statistical analysis was performed with the SAS version 6.12 software package (SAS Institute). Continuous variables were compared by Student's *t* test and the categorical variables by the Fisher's exact test. We performed a logistic regression on the dependent variable Y, where Y=1 for patients with asymptomatic restenosis and Y=0 for patients with symptomatic restenosis. As explanatory variables. We considered 46 clinical and angiographic variables. We executed a univariate logistic regression defined by the formula $\log[P(Y=1)/P(Y=0)]=A+B\times X$, where X is the explanatory variable, A the intercept, and B the regression parameter. Multivariate logistic regression defined by the formula $\log[P(Y=1)/P(Y=0)]=A+B(1)\times X(1)+B(2)\times X(2)+\ldots+B(n)\times X(n)$, with X(1),. . .,X(n) as the explanatory variables, A the intercept, and B(1),. . .,B(n) the regression parameters, was then performed. With the stepwise procedure, a group of explanatory variables was selected that as a group were multivariately significant. Logistic regression analysis was also performed for the patients treated with an intracoronary stent. A value of $P\leq 0.05$ was considered significant.

Results

In the 10 studies, 4013 lesions were treated in 3774 patients. In 2 studies (BENESTENT II and SOPHOS), patients were allocated to 6-month clinical and angiographic follow-up or clinical follow-up alone; thus, ≈50% of the patients from these studies were not included in our analysis. Nineteen percent of patients declined follow-up angiography, leaving 2690 patients with complete clinical and 6-month angiographic data. Of these patients, restenosis, defined as a ≥50% diameter stenosis, occurred in 607, giving a restenosis rate of 23%; in 335 patients (55%), this was not associated with symptoms of angina. Most patients had moderate restenosis; only 5% had ≥70% diameter stenosis.

The significant univariate predictors of silent as opposed to symptomatic restenosis (diameter stenosis ≥50%) were male sex, absence of nitrate and calcium channel blocker use at 6-month follow-up, reference diameter after the procedure, reference diameter at 6-month follow-up, and lesion severity at 6 months (MLD and percent diameter stenosis) (Table 4). The cumulative frequency curves for MLD and diameter stenosis comparing those with symptomatic and asymptomatic restenosis are depicted in the Figure. By multivariate analysis, only male sex ($P=0.04$, OR 1.65, 95% CI 1.02 to 2.70), greater reference diameter at follow-up ($P=0.002$, OR 1.73, 95% CI 1.22 to 2.48), and lesser lesion severity (percent stenosis) at 6-month follow-up angiography ($P=0.0001$, OR 0.93, 95% CI 0.91 to 0.96) were associated with silent restenosis.

Mean vessel caliber was smaller in women than men (reference diameter 2.74 versus 2.88 mm, $P=0.01$), and women also tended to have a smaller mean MLD than men at follow-up angiography (MLD 0.97 versus 1.02 mm, $P=0.27$). There was no difference between women and men in mean percent diameter stenosis (64.5% versus 64.2%, $P=0.87$).

An analysis was also performed on patients who were treated with an intracoronary stent. Of the 1469 patients who received stents from a variety of manufacturers, 242 developed restenosis (16%), of whom 58% were asymptomatic (as opposed to 53% in the balloon group, $P=0.317$). The univariate predictors of asymptomatic restenosis were unstable

TABLE 3. Patient Characteristics

	BENESTENT I	BENESTENT II pilot	BENESTENT II	DUET	FINESS 2	FLARE	MUSIC	ROSE	SOPHOS	WEST I
No. of patients	516	203	827	210	156	1054	161	120	425	102
Age, y										
Mean	57	58	58	60	60	60	59	58	59	61
Range	31–78	31–76	26–83	33–87	32–83	30–85	31–78	36–82	29–84	33–82
Male, %	81	84	79	80	81	82	82	80	74	81
Angina, %										
Stable	58	68	51	68	54	83	50	48	53	84
Unstable	42	30	42	29	40	5	30	44	41	15
Silent	0	2	6	3	6	12	20	8	6	1
Diabetes, %	6	8	12	14	21	2	11	15	13	11
Previous MI, %	19	23	26	42	43	35	26	36	32	33
Previous CABG, %	1	3	2	3	4	5	3	4	3	2
Previous PTCA, %	3	6	7	15	16	9	9	22	12	4

MI indicates myocardial infarction.

angina at screening ($P=0.019$), absence of calcium channel blocker ($P=0.023$) and nitrate ($P=0.0002$) use at 6-month follow-up, and presence of heparin use at the time of screening ($=0.0179$). By multivariate analysis, unstable angina at the time of screening ($P=0.03$) and absence of nitrate use at 6 months ($P=0.0001$) were associated with silent restenosis.

Discussion

Large studies of patients undergoing percutaneous coronary intervention with planned 6-month angiographic follow-up have identified the clinical and angiographic predictors of restenosis. These studies have also demonstrated that angiographic restenosis is more frequent than clinically driven repeat target lesion revascularization. This analysis demonstrates that >50% of patients with angiographic restenosis have no symptoms of angina 6 months after the intervention. Our finding that 55% of patients with restenosis were asymptomatic is similar to the 48% reported in the study by Hernandez et al,[18] which was a rigorous evaluation of 277 consecutive patients with restenosis after balloon angioplasty. Earlier studies reporting a lower proportion of asymptomatic restenosis have major design limitations, including small numbers of patients, incomplete angiographic follow-up, and variable time to follow-up angiography.[19–21]

In this series of patients enrolled in 10 percutaneous intervention studies, the overall restenosis was 23%; only 20% of those with restenosis had ≥70% diameter stenosis. Univariate predictors of asymptomatic restenosis were male sex and absence of antianginal medication use, greater reference diameter after the procedure, greater reference diameter at follow-up, and lesser lesion severity at 6-month follow-up. By multivariate analysis, only male sex, reference diameter at follow-up, and lesser lesion severity at 6 months were associated with asymptomatic restenosis. This suggests that there are more similarities between symptomatic and asymptomatic patients with restenosis than there are important differences.

Previous studies have demonstrated that the angiographic MLD rather than percent diameter stenosis predicts recurrent symptoms after coronary intervention, with a threshold of 1.35 to 1.50 mm.[22,23] This is consistent with our finding that men were more likely than women to have restenosis without symptoms, because the women in this study had smaller-caliber arteries than men, no difference in percent diameter stenosis, and a trend toward a smaller MLD.

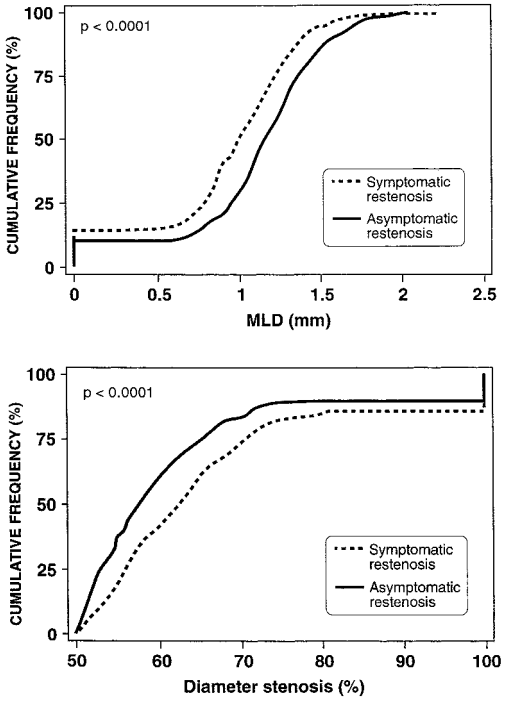
Other factors relating to attitude and perception of pain may also play a role. Several studies have documented a sex bias in referral for diagnostic procedures and treatment of patients with coronary artery disease.[24–27] The initial diagnosis of angina in women is made more slowly than in men, because chest pain is often attributed to other causes.[27] After intervention, however, men may experience less pain, may experience pain that they do not identify as a recurrence of angina, or may not admit to recurrent symptoms. Alternatively, women, once proven to have coronary artery disease, may present earlier with recurrent angina. A combination of these factors may contribute to the sex difference.

Absence of use of nitrates and calcium channel blockers at follow-up was a univariate predictor of asymptomatic restenosis. Although recurrent symptoms would be expected to precede the reinstitution of antianginal treatment, cause and effect are not self-evident. It is possible that those with a restenotic lesion of lesser severity had no symptoms and therefore did not receive medication, whereas those with a more severe progressive lesion may have been treated with escalating doses of antianginal agents. Although symptomatic patients may be on more medication, it is also plausible that patients on more treatment may have fewer symptoms. By multivariate analysis, lesser lesion severity was in fact a predictor of asymptomatic restenosis, suggesting that moderate restenosis (lesion severity 50% to 60%) may often be associated with no recurrent symptoms. Repeat intervention on such lesions may not be warranted, because they are associated with a good clinical outcome and may regress over the next 2 to 5 years.[28–30] Routine 6-month follow-up

TABLE 4. Forty-Six Clinical and Angiographic Variables Analyzed for Univariate Predictors of Silent as Opposed to Symptomatic Restenosis (≥50% Diameter Stenosis)

Variable	Asymptomatic	Symptomatic	OR	95% CI	*P*
Age, y	59.9	59.2			0.39
Male sex	86.6	78.3	1.79	1.17–2.75	0.008
Hypertension	36.4	40.8			0.27
Diabetes mellitus	11.9	14.0			0.46
Smoking					
Never	25.1	28.3			0.63
Ex-smoker	49.6	25.7			
Current	25.4	46.0			
Hypercholesterolemia	39.9	49.4			0.07
Family history of heart disease	33.3	35.2			0.67
Previous myocardial infarction	29.6	30.9			0.72
Pathological Q waves at screening	16.6	16.4			0.97
Previous PTCA	6.6	8.5			0.38
Previous CABG	1.5	3.7			0.095
Peripheral vascular disease	7.7	7.9			0.93
Multiple vessel disease	14.7	19.3			0.13
Angina status at screening					
Silent	8.7	3.7			0.49
Stable	62.4	75.4			
Unstable	29.0	21.0			
β-Blocker at screening	68.2	64.5			0.53
Nitrates at screening	64.2	66.4			0.72
Calcium channel blocker at screening	38.5	41.1			0.67
Aspirin at screening	93.2	91.2			0.57
Dipyridamole at screening	0.8	2.1			0.44
Heparin at screening	18.7	10.3			0.09
Coumarin/warfarin at screening	3.2	2.1			0.59
Diuretics at screening	5.8	8.8			0.36
ACE inhibitor at screening	18.7	27.5			0.11
Reference diameter preintervention, mm	2.83	2.76			0.07
Diameter stenosis preintervention, %	65.6	65.7			0.93
Preintervention MLD, mm	0.96	0.93			0.39
Left main lesion stenosis screening	0	1.1			0.99
LAD lesion stenosis screening	60.1	59.2			0.82
Circumflex lesion stenosis screening	25.5	31.5			0.11
RCA lesion stenosis screening	29.1	30.7			0.68
Reference diameter postintervention, mm	2.97	2.89	1.43	1.02–2.02	0.04
Pathological Q waves at discharge	16.8	16.2			0.87
Angina status at discharge					
None	86.8	91.6			0.72
Silent	12.5	5.3			
Stable	0	2.1			
Unstable	0.7	1.1			
β-Blocker at follow-up	50.0	61.3			0.17
Nitrates at follow-up	16.7	45.2	0.24	0.11–0.50	0.0002
Ca channel blocker at follow-up	26.0	43.6	0.46	0.23–0.90	0.02
Aspirin at follow-up	91.5	94.8			0.29
Dipyridamole at follow-up	41.9	40.5			0.82
Heparin at follow-up	0	1.9			0.99
Coumarin/warfarin at follow-up	7.0	5.8			0.78
Diuretics at follow-up	12.7	11.5			0.85
ACE inhibitor at follow-up	25.3	38.6			0.09
Pathological Q waves at follow-up	15.1	19.4			0.32
Reference diameter at follow-up, mm	2.91	2.77	1.61	1.17–2.240	0.004
Diameter stenosis at follow-up, %	62.4	66.6	0.98	0.97–0.99	0.0004
MLD at follow-up, mm	1.09	0.92	2.26	1.58–3.27	0.0001

LAD indicates left anterior descending coronary artery; RCA, right coronary artery. Values are percent except as given.



Cumulative frequency curves for MLD and diameter stenosis comparing symptomatic and asymptomatic patients with >50% stenosis at 6-month angiographic follow-up.

angiography and resultant higher rates of repeat intervention may be related to a lower 10-year mortality rate.[7,31]

The predictors of asymptomatic restenosis in the subgroup undergoing stent deployment were absence of the use of nitrates at 6-month follow-up and unstable angina at initial presentation. It is possible that stents may have a "plaque-stabilizing" effect in the relief of symptoms in acute coronary syndromes (as opposed to stable angina).

An unexpected finding was that diabetes was not a predictor of asymptomatic restenosis. Patients with diabetes are more likely than those without to have suffered a silent myocardial infarction and are less likely to have symptoms in association with myocardial ischemia during treadmill stress testing or Holter ECG, perhaps because of a sensory neuropathy.[32,33] Conversely, one reason that those with diabetes may have worse angina than those without is that diabetes is associated with reduced collateral development.[34] Such collateral formation may be particularly important in the prevention of angina when there is slow and progressive lesion development, as occurs with restenosis. Hence, a lack of collateral formation may offset a tendency toward reduced symptoms from diabetic neuropathy, with diabetes having no net effect on silent versus symptomatic restenosis.

Study Limitations

Although there was some standardization of clinical and angiographic data collection, only the data common to all 10 study databases were included in the analysis. Collateral vessel formation, which may have a significant bearing on the presence or absence of symptoms associated with restenosis, was not assessed in a standardized manner and thus could not be analyzed.

Exclusion criteria for coronary interventional studies mean that the study population is carefully selected and probably at lower risk for restenosis than an unselected population of patients. This may influence the rate of asymptomatic restenosis and its predictors.

Conclusions

Men are more likely than women to have recurrent symptoms if they develop restenosis after percutaneous coronary revascularization. The only other multivariate predictor of recurrent symptoms was greater lesion severity at 6-month follow-up angiography.

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