

Relative Risk Analysis of Angiographic Predictors of Restenosis Within the Coronary Wallstent

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Background. Late angiographic narrowing has been observed following coronary implantation of the Wallstent[®]. To identify the angiographic variables that predict restenosis within the stented segment, a retrospective study of data from the European Wallstent core laboratory was performed.

Methods and Results. Follow-up angiograms (excluding patients with in-hospital occlusions) were analyzed for 214 lesions in 176 patients (78% restudy rate). The incidence of restenosis within the stented segment was 35% by lesion and 35% by patient for criterion 1 (≥ 0.72 mm loss in minimal luminal diameter) and 24% by lesion and 24% by patient for criterion 2 (diameter stenosis $\geq 50\%$ at follow-up). The association between 16 variables and restenosis was determined by a relative risk ratio assessment. Variables with significant risk ratios for restenosis with criterion 1 were use of multiple stents/lesion (relative risk, 1.56; 95% confidence interval [CI], 1.08–2.25) and oversized (unconstrained stent diameter exceeding reference diameter > 0.7 mm) stents (relative risk, 1.64; 95% CI, 1.10–2.45), and for criterion 2, oversizing by more than 0.70 mm (relative risk, 1.93; 95% CI, 1.13–3.31), bypass grafts (relative risk, 1.62; 95% CI, 0.98–2.66), use of multiple stents/lesion (relative risk, 1.61; 95% CI, 0.97–2.67) and residual diameter stenosis more than 20% post stenting (relative risk, 1.51; 95% CI, 0.91–2.50).

Conclusions. It is concluded that several angiographic variables are significantly associated with late angiographic narrowing after stenting in the coronary arteries. We suggest that stent operators avoid excessive oversizing in the selection of stent diameter and the use of multiple stents per lesion to lessen the risk of late restenosis. (*Circulation* 1991;84:1636–1643)

The implantation of stents in coronary arteries or saphenous vein bypass grafts as an adjunct or alternative to percutaneous transluminal coronary angioplasty (PTCA) was initially proposed to prevent late restenosis.¹ Since March 1986, the coronary Wallstent[®] has been the most intensively studied endovascular prosthesis in Europe. As a result of cooperation among the six participating European cen-

ters, a central core laboratory was set up in Rotterdam to objectively assess the follow-up of stents with quantitative coronary angiography. In our previous report on the initial 117 stents implanted in 105 patients, we observed that late angiographic narrowing occurs in a significant number of patients.² To further characterize the factors associated with angiographic restenosis within the stented segment, we retrospectively studied

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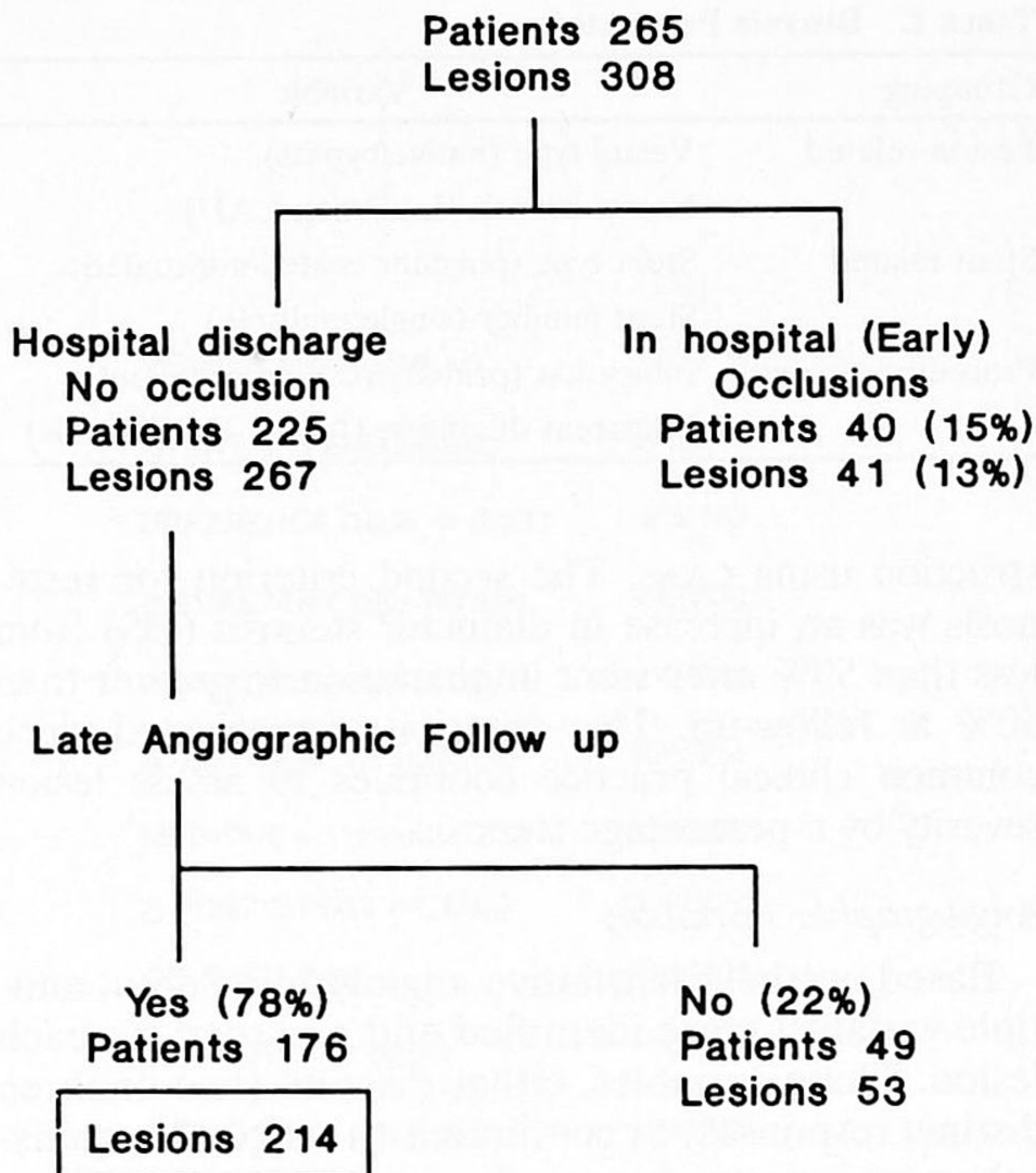


FIGURE 1. Flow diagram showing angiographic follow-up in 265 stented lesions. In-hospital (early) occlusions occurred in 40 patients (15%). In the remaining 225 patients discharged from hospital without known stent occlusion, 176 patients (78%) with 214 stented lesions had quantitative angiographic follow-up.

the predictive ability of several angiographic variables, based on our experience of 214 separate lesions implanted with the coronary Wallstent® in 176 patients. Since the core laboratory was set up only as an angiographic data bank, detailed clinical data were not available for this analysis.

Methods

Study Patients

Two hundred sixty-five patients were enrolled after informed consent was obtained between March 1986

and March 1990 at the six participating centers. The study group consisted of 222 men and 43 women with a mean age of 58 ± 11 years. Sixty-two percent of the stents were implanted in native vessels, and 38% were placed in bypass grafts. In the overall group, angiographic follow-up was obtained in 218 patients (82%). However, in-hospital occlusions (40 patients, 41 lesions) were excluded from this study since these were definite thrombotic events and the objective of this study was late angiographic narrowing. Follow-up angiograms were quantitatively analyzed in 176 patients (78%) of the 225 patients who were discharged from hospital without known occlusion (Figures 1 and 2). Patients could not be restudied for the following reasons: death ($n=10$), early bypass surgery as per protocol for the "bail-out" indication at one institution or due to contraindication to anticoagulation ($n=11$), angiograms that were technically inadequate for quantitative analysis ($n=3$), or refusal for restudy ($n=25$). The study group consisted of 176 patients who had a total of 259 stents implanted in 214 lesions. The mean length of angiographic follow-up in the study group was 6.6 ± 4.8 months.

In this trial, the endovascular prosthesis, Wallstent®, was provided by Medinvent SA, Lausanne, Switzerland. The method of implantation and description of this stent has previously been reported.^{1,2} This stent is a self-expandable stainless steel woven mesh prosthesis that can be positioned in the coronary artery using standard over-the-wire technique through an 8F or 9F guiding catheter. The device is constructed of 16 wire filaments, each 0.08 mm wide. It is constrained in an elongated configuration on a 1.57 mm diameter delivery catheter with the distal end covered by a removable plastic sleeve. As the sleeve is withdrawn, the constrained device returns to its original unconstrained larger diameter and becomes anchored against the vessel wall. Unconstrained stent diameter ranged from 2.5

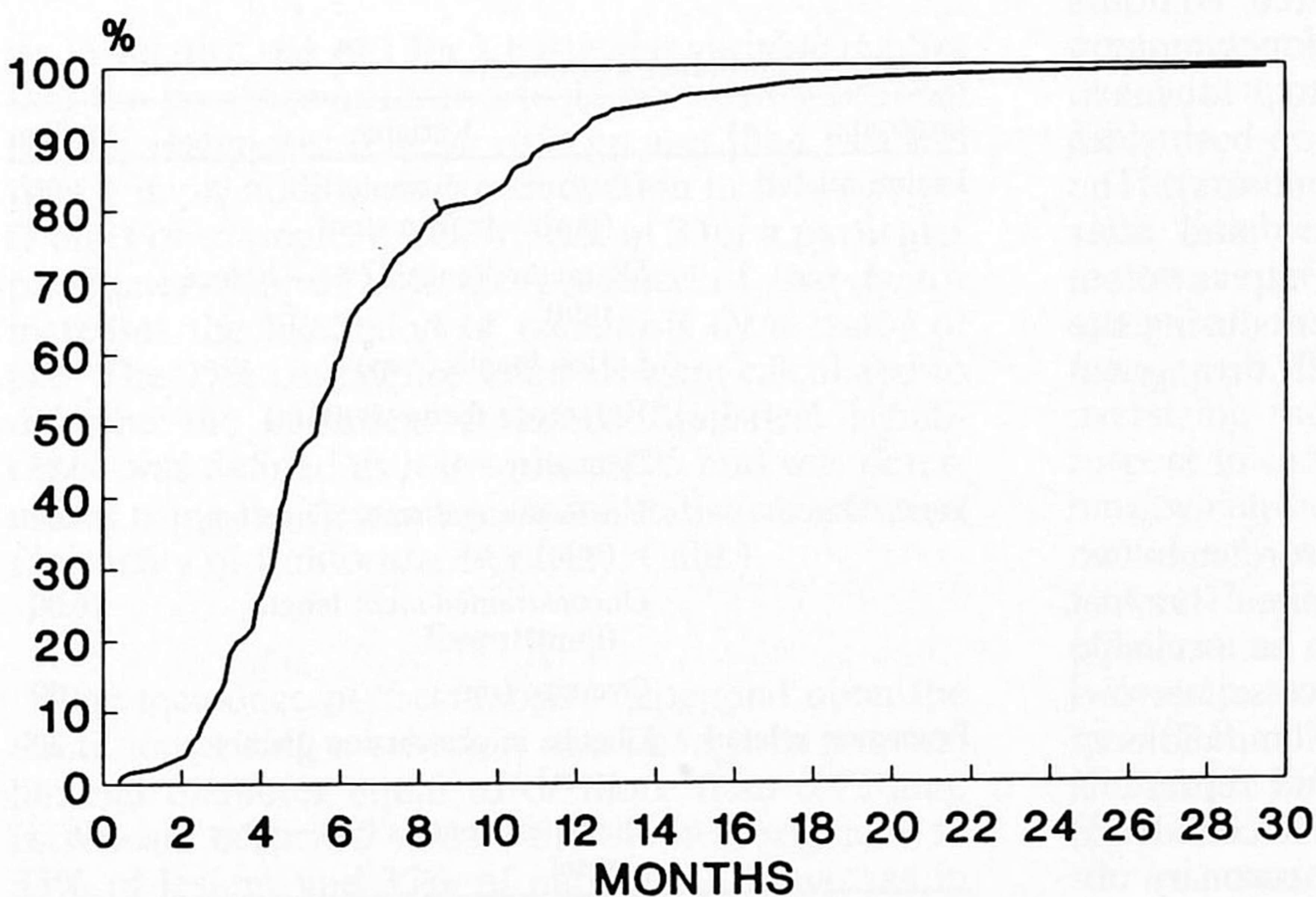


FIGURE 2. Timing of late angiographic follow-up after stent implantation. In this cumulative curve, interval (in months) between date of implantation and final angiographic follow-up is shown for the study group.

to 6 mm and was selected to be 0.50 mm larger than the stented vessel based on a visual estimate of the pre-stent angiogram by the investigator. In an effort to alleviate the problem of acute thrombosis, the stent design was changed in April 1989 with the introduction of a polymer-coated stent (Biogold®) for certain stent sizes. By August 1989, all manufactured stents contained this particular polymer coating.

Quantitative Coronary Arteriography

All cineangiograms were analyzed at the core laboratory in Rotterdam using the computer-assisted cardiovascular angiography analysis system (CAAS), which has previously been discussed in detail.^{3,4} The important steps will be briefly described. Selected areas of the cineframe encompassing the desired arterial segment (from side branch to side branch) are optically magnified, displayed in a video format, and then digitally converted. Vessel contour is determined automatically based on the weighted sum of the first and second derivative functions applied to the digitized brightness information. A computer-derived estimation of the original arterial dimension at the site of the obstruction is used to define interpolated reference diameter and area. The absolute diameter of the stenosis as well as the reference diameter are measured by the computer which uses the known guiding catheter diameter as a calibration factor, after correction for pincushion distortion. The percentage diameter of the narrowed segment is derived by comparing the observed stenosis dimensions to the reference values. The length of the lesion (mm) is determined from the diameter function on the basis of a curvature analysis. Using the reconstructed borders of the vessel, the computer can calculate a symmetry coefficient for the stenosis. Differences in distance between the actual and reconstructed vessel contours on both sides of the lesion are measured. Symmetry is determined by the ratio of these two differences with the largest distance between actual and reconstructed contours becoming the denominator. Values for symmetry range from 0 for extreme eccentricity to 1 for maximal symmetry (that is, equal distance on both sides between reconstructed and actual contours). The angiographic analysis was done before and after angioplasty, immediately after stent implantation, and at long-term follow-up in all patients using the average of multiple matched views with orthogonal projections wherever possible.

Restenosis

The restenosis rate was determined according to two criteria. We have found a loss in minimal luminal diameter (MLD) of 0.72 mm or more to be a reliable indicator of angiographic progression of vessel narrowing.^{3,4} This value takes into account the limitations of coronary angiographic measurements and represents twice the long-term variability (i.e. the 95% confidence interval) for repeat measurements of a coronary ob-

TABLE 1. Discrete Parameters

Grouping	Variable
Lesion related	Vessel type (native/bypass)
	Vessel branch (LAD/non-LAD)
Stent related	Stent type (polymer coated/noncoated)
	Stent number (single/multiple)
Procedure related	Indication (primary/restenosis/bailout)
	Intrastent dilatation ("Swiss Kiss"/no SK)

struction using CAAS. The second criterion for restenosis was an increase in diameter stenosis (DS) from less than 50% after stent implantation to greater than 50% at follow-up. This criterion was selected since common clinical practice continues to assess lesion severity by a percentage stenosis.

Angiographic Variables

Based on the quantitative angiographic data, multiple variables were identified and recorded for each lesion. These variables, either discrete (two or three distinct responses) or continuous (a range of responses), were grouped according to lesion, stent, or procedural factors (Tables 1 and 2). These particular variables were of a priori clinical interest on the basis of previously published PTCA and stent reports.⁵⁻¹¹

Statistical Methods

A relative risk analysis was performed for the aforementioned discrete and continuous variables.¹² The continuous variables were dichotomized for the risk ratio analysis. To avoid arbitrary subdivision of data in continuous variables, cutpoints were derived by dividing the data into two groups, each containing roughly 50% of the total population. This method of subdivision has the advantage of being consistent for all variables and thus avoids any bias in selection of subgroups that might be undertaken to emphasize a particular point. The incidence of restenosis in the two groups was compared using a relative risk analy-

TABLE 2. Continuous Parameters

Grouping	Variable	Median
Lesion related	Obstruction diameter (mm) — before stent	1.20
	Diameter stenosis (%) — before stent	60
	Lesion length (mm)	8.0
	Reference diameter (mm)	3.25
	Symmetry	0.85
Stent related	Unconstrained stent diameter (mm)	4.00
	Unconstrained stent length (mm)	20.00
	Oversize (mm)	0.70
Procedure related	Change in obstruction diameter (mm)	1.30
	Diameter stenosis (%) — after stent	20

TABLE 3. Restenosis Rates According to Criterion 1 (≥ 0.72 mm Loss in Minimal Luminal Diameter)

Variable		<i>n</i>	Restenosis rate
Stent number	Multiple	22/44	50%
	Single	53/165	32%
Stent oversize	>0.7 mm	40/90	44%
	≤ 0.7 mm	26/96	27%

95% CI, 0.91–2.50). The actual restenosis rates for these variables are included in Tables 3 and 4.

Discussion

Despite progress in techniques and equipment, the rate of late angiographic narrowing following PTCA, a process popularly termed restenosis, has not been altered since its clinical introduction 13 years ago. This failure has provided the impetus for the development of newer alternative forms of coronary revascularization such as stenting, atherectomy, and laser. However, the effectiveness of all forms of nonoperative coronary interventions remains limited by the restenosis process(es).

Restenosis is a complex process that is only partially understood. Pathological studies of patients who have died more than 1 month following angioplasty have demonstrated the presence of intimal hyperplasia, presumably due to proliferation and migration of medial smooth muscle cells into the intima, and associated production of extracellular matrix collagen and proteoglycans.^{13,14} It has been suggested by Liu et al¹⁵ that the two major factors that determine the absolute amount of intimal hyperplasia are 1) the depth of injury and 2) the regional flow characteristics (which are determined by the geometry of the dilated lumen of the lesion and blood flow velocity patterns across that lumen). Two separate PTCA follow-up reports support the concept that the greater the diameter change after PTCA (implying a greater degree of disruption to the vessel wall), the more extensive is the absolute amount of reactive hyperplasia.^{16,17} On the basis of several angiographic studies from the Thoraxcenter, immediate results following stent implantation are superior to angioplasty alone (mean minimal luminal diameter of 2.5 mm versus 2.0–2.1 mm) and thus favor a more aggressive proliferative response after procedure.^{2,4,18} The second factor is illustrated by the inverse relation between the level of wall shear stress and subsequent intimal thickening. In the presence

of a significant residual stenosis, the post-stenotic region is a site of flow separation and low wall shear stress. This may retard endothelial recovery and prolong the period of smooth muscle cell proliferation, which is partially dependent on restoration of regenerated endothelial barrier.¹⁹ Stenting appears to diminish the effect of post stenotic wall shear stress by significantly improving the hemodynamic effects of the stenosis (based on the calculated reductions in Poiseuille and turbulent contributions to flow resistance).²⁰

It is extremely difficult if not impossible to predict restenosis in the individual patient following PTCA.²¹ This problem can be partially understood when one considers that the two factors (i.e., depth of injury and regional flow characteristics) affecting the extent of intimal proliferation act in opposition to the other and thus make it hazardous to predict outcome of this interaction in a particular patient. In large population of patients, relative risk analyses following PTCA have identified several patient, lesion, and procedural variables that predict late restenosis. However, the situation following stenting may be different where the mean loss of minimal luminal diameter at late follow-up is twice that of PTCA alone (0.62 mm versus 0.31 mm).^{2,18} Therefore, this study was designed to identify factors that were associated with an increased risk of restenosis following stenting.

Lesion Factors

Stented bypass grafts had a greater risk of restenosis than native vessels (30% versus 19%), but this finding was restricted to the DS criterion. The increased susceptibility of bypass grafts to the restenosis process has previously been documented following PTCA.^{9,22–26} Although left anterior descending (LAD) lesions have been shown to be a risk factor in several PTCA studies,^{5,15,16} this was not evident in our study. The reference diameter of the vessel also had no relation to restenosis. Forty-three percent of the vessels had reference diameter between 3 and 4 mm, and 43% were 3 mm or less. Lesion length and the severity of the lesion, in absolute minimal luminal diameter or diameter stenosis, prior to the procedure have been cited by several authors as important risk factors for restenosis following angioplasty although our data did not show this association.^{6–9} Lesion length is probably not an important factor for restenosis if lesions can be covered by a single stent

TABLE 4. Restenosis Rates According to Criterion 2 ($>50\%$ Diameter Stenosis at Follow-Up)

Variable		<i>n</i>	Restenosis rate
Vessel type	Bypass	30/103	30%
	Native	20/111	19%
Stent oversize	>0.7 mm	29/90	32%
	≤ 0.7 mm	16/96	17%
Diameter stenosis after stent	$>20\%$	30/107	28%
	$\leq 20\%$	19/102	19%

(see below). We believe that this is due to a more uniform and optimal dilatation with stenting. Long lesions treated with angioplasty are frequently less successfully dilated along the entire length of the lesion and the ragged irregular surface of the vessel may predispose to rheological factors critically involved in restenosis. Total occlusions have been reported as an important predictor of restenosis in angioplasty studies. However, this accounted for only 4.5% of the lesions in our study, which was too few for this analysis. Although there was a trend for higher restenosis in more eccentric lesions, this was not statistically significant.

Stent Factors

Multiple stents (RR: MLD, 1.56 [1.08–2.25]; DS, 1.61 [0.97–2.67]) and unconstrained stent diameter exceeding reference diameter by more than 0.7 mm (RR: MLD, 1.64 [1.10–2.45]; DS, 1.93 [1.13–3.31]) significantly predicted restenosis with both criteria. Preliminary reports from four separate groups working with the Palmaz-Schatz stent have shown a similar relation between multiple stents/lesion and restenosis.^{27–30} In our study, multiple stents placed in tandem were overlapped at the extremities (so-called “telescoping”), which may be the reason for the observed increase in restenosis rates. The segment of the vessel that was covered by the overlapping stents was subjected to the dilating force of two separate stents as well as an increased density of metal. We have observed that restenosis commonly occurred at these sites of overlapping between extremities of stents. Since the length of the lesion and the absolute length of the stent required to cover a lesion were not significant predictors, it seems prudent to implant longer stents rather than two or more shorter stents in tandem.

Selecting an oversized stent (unconstrained diameter >0.7 mm larger than the reference diameter) was a particularly important stimulus for hyperplasia with the self-expanding Wallstent[®]. Schwartz et al³¹ have described an aggressive proliferative response in a porcine model as a result of severe stent oversizing (0.5–1.5 mm). This effect, which they attributed to penetration of the internal elastic lamina by the stent wires and subsequent deep medial injury, was much less pronounced when the stent diameter was matched more closely to the vessel diameter. Furthermore, due to its self-expanding property, the Wallstent[®] (and particularly when it is oversized) continues to expand the vessel wall for at least 24 hours after implantation.³² The vessel is subjected to increasingly higher wall stress than after implantation of a balloon expandable stent (which is maximally expanded at the time of implantation), a factor which may adversely stimulate the proliferative process. It may seem paradoxical that oversizing the stent by more than 0.7 mm would result in a higher restenosis rate with the 50% DS criterion. However, the diameter stenosis after stent was not different in the two groups despite the oversizing. The main effect of oversizing then was not particularly a

superior immediate result but rather a more aggressive “hyperplastic” reaction and a smaller MLD at follow-up than if less oversized stents were implanted. The absolute value of the unconstrained stent diameter and the addition of the polymer coating (Biogold[®]) had no significant relation to late restenosis.

Procedural Factors

No significant relative risk could be attributed to a particular indication for the procedure. Restenosis rates for primary cases were not significantly different than for bail-out or restenosis cases (MLD criterion: 37%, 42%, 33%; DS criterion: 24%, 27%, 24%), although an increased rate of restenosis has been described with the Palmaz-Schatz stent in patients with previous restenosis.³⁰ The absolute change in diameter from the prestent to the poststent result and dilatation within the stent after implantation (the so-called “Swiss Kiss”) did not appear to affect the late restenosis. This poststent dilatation was performed to dissipate a clot within the stent and to accelerate early expansion of the stent. A post stent diameter stenosis more than 20% tended to be predictive of a follow-up diameter stenosis more than 50% (RR, 1.51; 95% CI, 0.91–2.50) although not for the MLD criteria. The larger the residual stenosis following stenting (i.e., less optimal result), the less hyperplasia is required to reach a particular diameter stenosis at follow-up such as the 50% diameter stenosis criterion.

Limitations of Study

Several important limitations of this study must be mentioned. Although this study suggests several factors that may be predictive of restenosis following stenting, it does not address the actual mechanisms of restenosis in the stented vessel. By comparing the predictors of restenosis following stenting to angioplasty, we have assumed that the underlying mechanism(s) responsible for late angiographic narrowing are similar (i.e., primarily intimal hyperplasia). Although almost every stenting procedure was accompanied by balloon dilatation at some particular time during the procedure, several other mechanisms may be important. Elastic recoil, which in the first few days following the procedure may be a significant factor in causing renarrowing, may be less important in stented vessels than angioplasty alone due to the scaffolding function of the stent. Although organization of thrombus at the site of intimal damage following PTCA has been recognized as a cause for late restenosis, it has not been particularly regarded as an important factor based on late pathological studies following PTCA. However, this may be an extremely important cause of late restenosis after stenting. Although it is difficult to histologically discriminate thrombus organization from intimal hyperplasia, we have observed a disorganized layer of intimal thickening directly above the stent wire associated with remnants of thrombus in segments of several bypass grafts that have been surgically re-

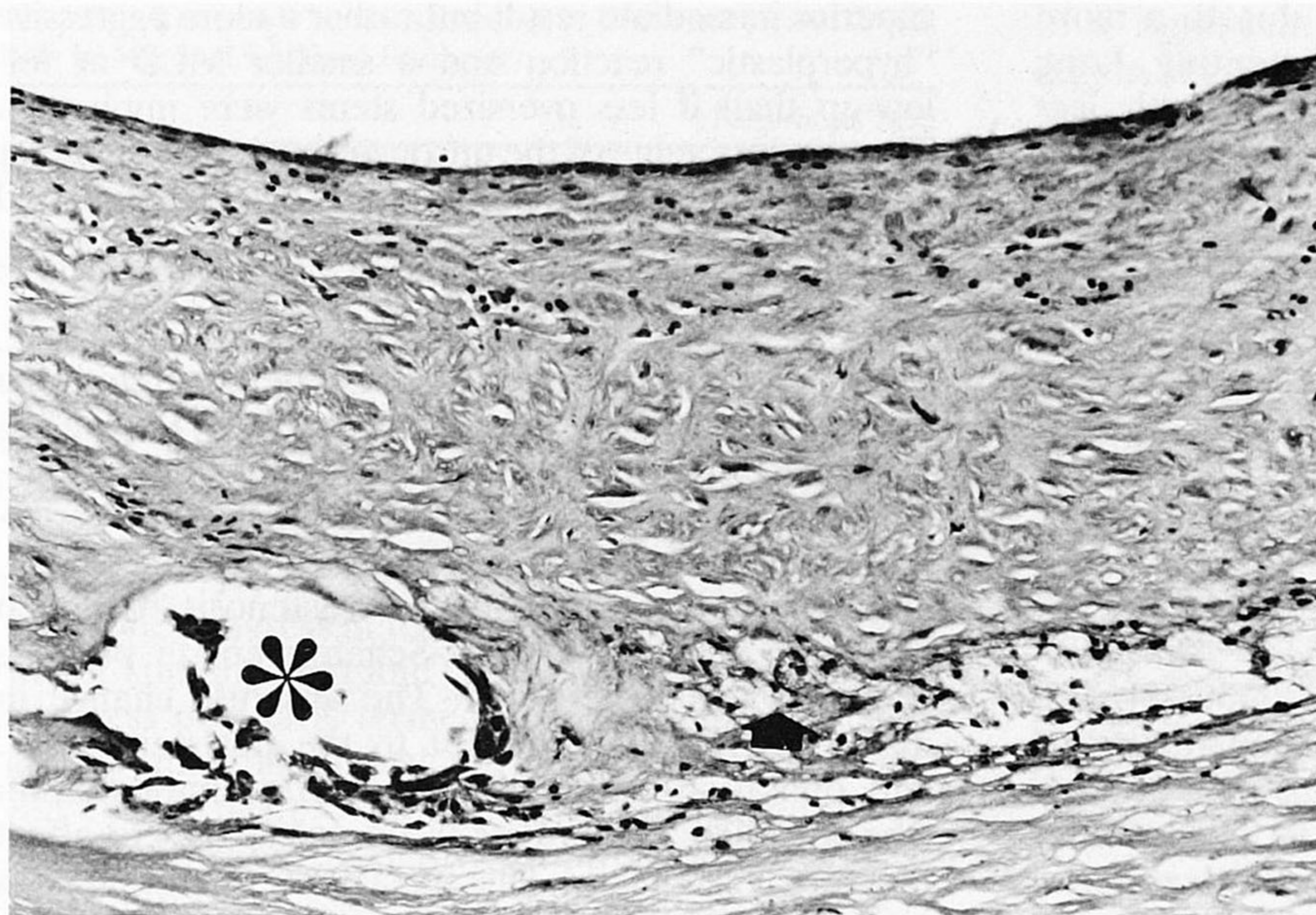


FIGURE 4. Light micrograph of stented bypass graft removed 10 months after stent implantation. The void (*) represents a 70 μm diameter stent wire. Immediately adjacent to the stent wire are cellular debris and foam cells (arrowhead). Directly above the stent wire is a layer of disorganized fibrointimal hyperplasia. (Courtesy of H.M.M. van Beusekom.)

trieved up to 10 months following stent implantation (Figure 4).^{33,34} Therefore, we consider organization of residual thrombus to be a potentially important cause of late angiographic narrowing in addition to the major occlusion problems early after stenting. This may partially explain why commonly regarded determinants of restenosis following PTCA (e.g., lesion length, LAD) do not appear to be significant in this analysis because different pathological processes may predominate. This also has important clinical implications since therapy to limit smooth muscle proliferation may be quite different than therapy to minimize thrombus formation. There are two statistical limitations to this study. Due to the relatively small sample size, we cannot rule out a significant beta error. Second, in performing multiple statistical comparisons, there is a risk that some of them may be significant by chance alone. Therefore, this data requires confirmation by other studies.

In conclusion, the European coronary Wallstent[®] experience has demonstrated that restenosis following stenting is increased in bypass grafts and in the presence of multiple stents and excessive oversizing of the stent (>0.7 mm) and less optimal results immediately post stenting (>20% diameter stenosis). Since some of these factors can be modified, we recommend against the use of multiple stents and excessive oversizing to reduce the probability of late restenosis.

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