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CLINICAL STUDIES

Restenosis After Coronary Angioplasty: The Paradox of Increased Lumen Diameter and Restenosis

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Restenosis after coronary angioplasty is the single complication that most limits this revascularization procedure in clinical practice. The process is largely unpredictable and the lesion-related factors predisposing to restenosis are poorly understood, with little consensus in published reports. In this study using detailed quantitative angiographic measurements to assess 490 lesions, the simple lesion characteristics associated with restenosis were defined and the relation to the restenosis process documented. Restenosis was defined as an absolute deterioration in the minimal lumen diameter by ≥0.72 mm, a criterion based on the 95% confidence intervals for repeat angiographic measurements. This was chosen in an attempt to separate spurious changes due to a poor angiographic result and the variability of angiographic measurements from significant changes due to the restenosis process.

The principal determinants of restenosis were found to be a large improvement in the minimal lumen diameter at the time of dilation (1.13 mm for the restenosis group compared with 0.86 mm for the no restenosis group [$p < 0.0001$]) and an optimal postangioplasty result (minimal lumen diameter 2.28 mm in the restenosis group compared with 2.05 mm [$p < 0.001$] in the no restenosis group, corresponding to a 25% and a 30% diameter stenosis, respectively [$p < 0.0001$]).

These observations reported for the first time suggest that the distinction needs to be made between a "clinical restenosis" of ≥50% diameter stenosis and the "restenosis process" as measured by the absolute changes occurring during and after angioplasty. They lend support to the hypothesis that the degree of mechanical stretch produced by the dilating balloon on the vessel wall may be important in stimulating the restenosis process. This is in contradiction to deductions obtained if restenosis is based on "clinical restenosis," which suggests that restenosis is associated primarily with a poor angioplasty result. More important, it indicates that there is potential for misinterpreting the results of restenosis studies if the observations are based solely on conventional restenosis criteria without knowledge of the absolute changes occurring during and after the angioplasty procedure.

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Restenosis after angioplasty is conventionally determined by the angiographic restenosis rate. Although this is known to be an inaccurate reflection of "clinical restenosis" (1–6), it is the most objective and reproducible form of assessment and consequently it remains the index by which the long-term success of angioplasty (7–9) as well as other nonsurgical revascularization procedures is judged.

This index, however, is significantly influenced not only by the definition of restenosis employed, but also by a host of other factors such as incomplete dilation, method of angiographic analysis, low follow-up rates and biased patient study groups. The failure to adopt a standard method of assessment has led to varying reports concerning the factors that influence the restenosis process.

The current lack of information means that the optimal angioplasty result necessary to achieve good long-term success is not known. Overdilation is associated with an increased incidence of acute dissection (10) and may stimulate the restenosis process by the extent of deep arterial injury, which in turn is associated with increased platelet activation (11). Alternatively, as suggested in the animal model (12), the injury due to stretching itself, independent of platelet accumulation, may be an important stimulant for restenosis. Conversely, underdilation may leave a significant residual stenosis, resulting in increased turbulence (5,13), increased platelet activation and subsequent restenosis by the same common pathway. More recently, the important association of residual stenosis, a positive stress test and their relation to "restenosis" have been reported (14).

In this study, simple lesion variables (minimal lumen diameter, reference diameter and percent diameter stenosis)

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Table 1. Clinical Characteristics of 424 Patients

No. of lesions	490
Lesions/patient	1.16
Patient age (mean) (yr)	57 ± 9 (range 31 to 79)
Male/female ratio	346/78
Time from angioplasty to follow-up (days)	94 ± 43 (range 3 to 226)
Vessels with CAD (no. of patients)	
1	288 (68%)
2	97 (23%)
3	39 (9%)
Previous CABG (no. of patients)	31 (7%)
Previous angioplasty (no. of patients)	176 (42%)
Previous MI (no. of patients)	44 (10%)
Dilated vessel (no. of patients)	
LAD	239 (57%)
LCx	80 (17%)
RCA	97 (20%)
Bypass graft	10 (2%)
No. of patients with more than one lesion dilated	63 (15%)

CABG = coronary artery bypass graft; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MI = myocardial infarction; RCA = right coronary artery.

were measured and the changes in each of these during and after the procedure assessed. The influence of the simple lesion morphology and changes occurring at angioplasty on the restenosis process have been determined and the distinction made between this process and "clinical restenosis" as assessed by more conventional restenosis criteria.

Methods

Study patients (Table 1). Five hundred consecutive patients who underwent successful angioplasty and agreed to have a follow-up angiogram were studied (7). Successful coronary angioplasty was defined as 1) <50% diameter stenosis on visual inspection of the postangioplasty coronary angiogram performed in multiple views; and 2) no in-hospital complications (namely, recurrence of angina, coronary bypass grafting, repeat percutaneous transluminal coronary angioplasty, acute myocardial infarction or death).

Patients with stable and unstable angina pectoris, as defined previously (15), were included. Patients with acute myocardial infarction receiving a thrombolytic agent who subsequently had immediate coronary angioplasty were excluded.

Patients were allocated at a predetermined time for follow-up angiography at the time of angioplasty. Of the 500 patients who met the inclusion criteria, 424 patients (with 490 lesions) had repeat angiograms suitable for quantitative analysis, with a mean time to follow-up angiography of 94 ± 43 days. The reasons for failure to complete the study were late death (2 patients), recatheterization contraindicated or refused (52 patients) and angiograms unsuitable for quantitative analysis (22 patients).

When clinically indicated (early recurrence of symptoms), patients were reinvestigated before the original preset time. Table 1 shows the baseline characteristics of the patients included in the study. Data concerning patients followed-up within 4 months of angioplasty have previously been published (7).

Coronary angioplasty. This was performed with a steerable, movable guide wire system by means of the femoral route. At the beginning of the angioplasty procedure, all patients received 10,000 IU of heparin and 500 mg of aspirin intravenously. After dilation, 10 mg of nifedipine was given orally every 2 h for the 1st 12 h and then 20 mg three times a day together with 500 mg of aspirin orally once a day until repeat angiography.

Quantitative coronary angiography. The quantitative analysis of the stenotic coronary segments was carried out with the computer-assisted Cardiovascular Angiography Analysis System (CAAS), which has been described in detail (16,17). Calibration of the diameter of the vessels in absolute values (mm) was achieved by using the guiding/diagnostic catheter as a scaling device (16).

A representative series of analyses, with the detected contours and the diameter functions superimposed on the original video image, are shown in Figure 1. To standardize the measurements and minimize potential errors, the "interpolated" reference diameter measurement was used whenever possible. This method has the advantage of eliminating the arbitrary choice of a reference diameter that will vary among individual observers and provides a smoothing effect for the segments adjacent to the stenosis so that extreme irregularities in the vessel will not artificially bias the reference diameter measurement. It also reduces the effect of the change in reference diameter at follow-up angiography that occurs as part of the restenosis process (18). The principle behind this technique has previously been described (19–21), as have the precision and overall accuracy of the system, the method of obtaining angiograms and precautions taken to reduce error (7).

Restenosis criteria. The restenosis group was defined as those patients with a deterioration in the minimal lumen diameter from postangioplasty to follow-up of ≥0.72 mm, a criterion based on the 95% confidence limits for determining a significant change using a quantitative angiographic system (CAAS) (7,16). The relevance of using this criterion and its comparison with the conventional cutoff criterion of ≥50% diameter stenosis at follow-up are addressed in the Discussion.

Data analysis. All angiographic and procedural variables were entered into a relational data base and statistical analysis was performed with use of BMDP statistical software (University of California, Berkeley, California, 1985). The tertile with the highest incidence of restenosis was identified for each variable, and the relative risk of restenosis in this group was compared with that in the remainder of the study group. An odds ratio for restenosis ≥2 with 95% confidence limits ≥1 was considered to have clinical relevance in this study group.

The variables selected for analysis in this study were all continuous with gaussian distributions. The determination

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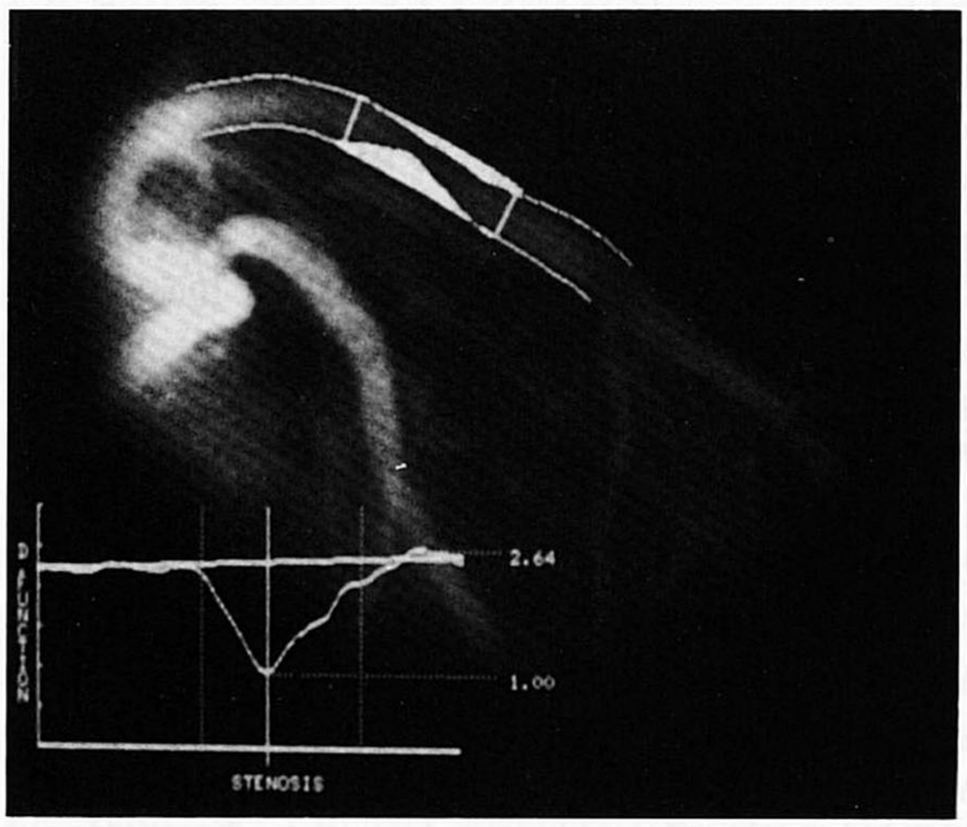
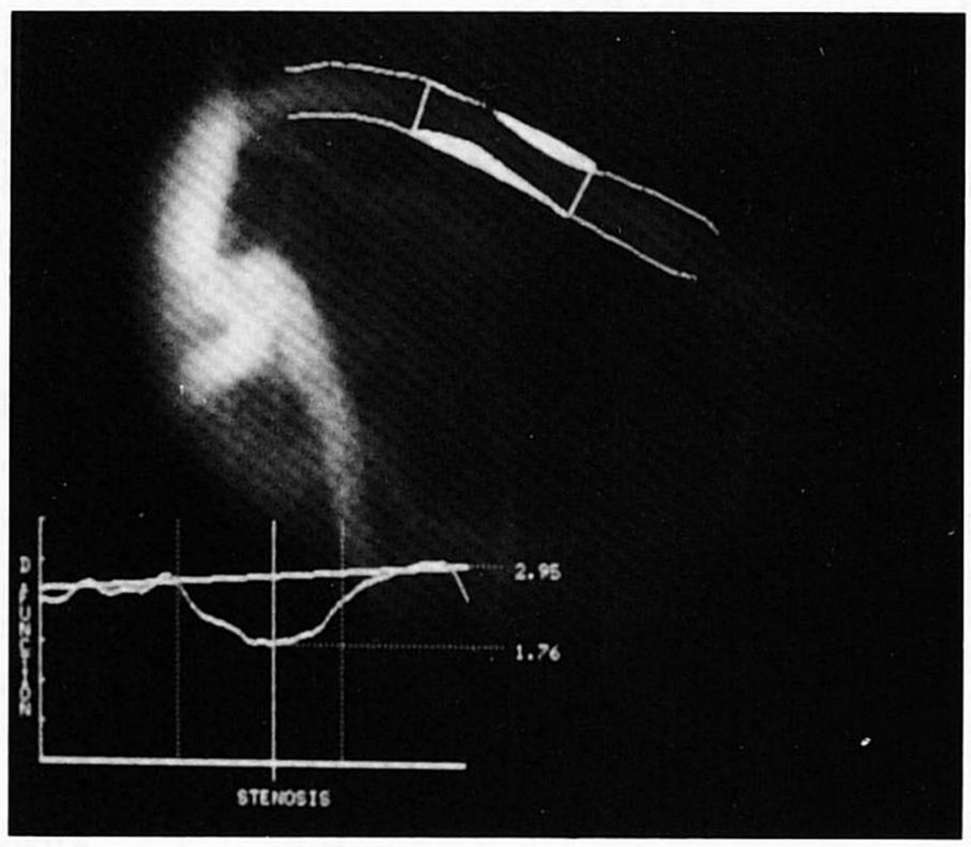




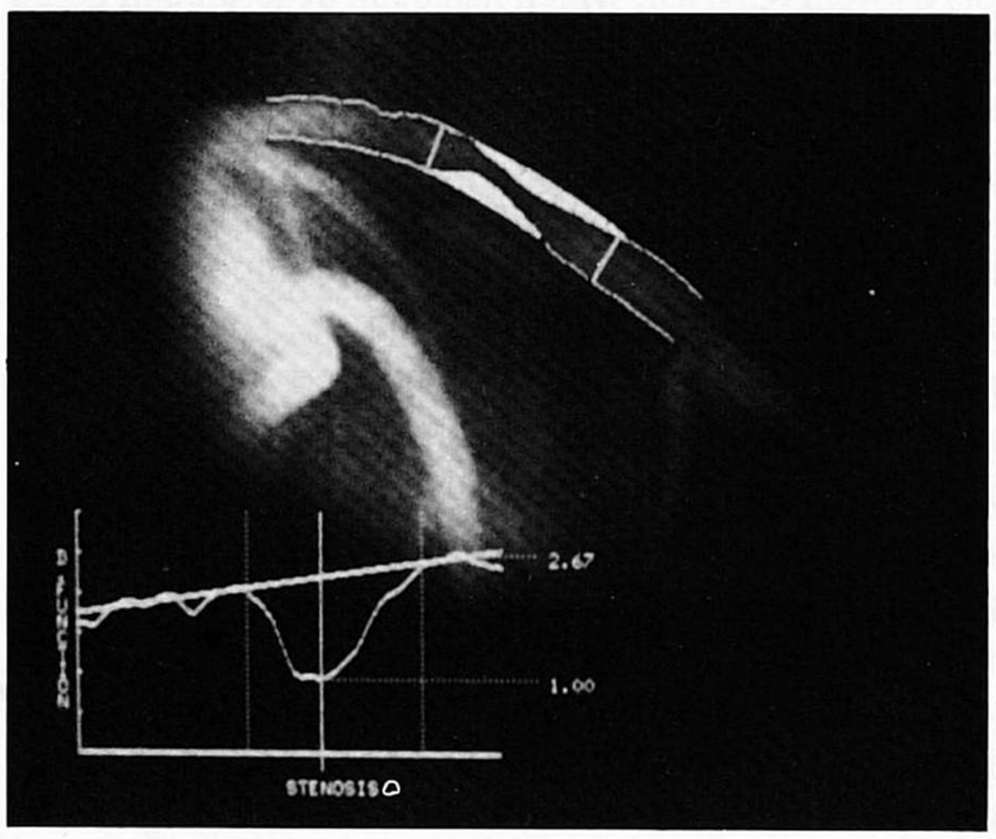


Figure 1. Single frame angiograms of a proximal left anterior descending artery stenosis before dilation (**top left**), after dilation (**top right**) and at follow-up angiography (**bottom**). Quantitative coronary analysis was performed using the Cardiovascular Angiography Analysis System. The arterial boundaries detected by the system are shown on the angiogram, and the diameter function curve derived from these contours is **below**. The example is chosen to illustrate a successfully dilated proximal left anterior artery lesion that undergoes a severe restenosis at 4 months.

of risk of restenosis for continuous variables is dependent on the arbitrary subdivision of data comparing the subgroup with the highest risk with the remainder of the study group. The risk may be artificially influenced by selecting small subgroups that vary from the population by chance and do not reflect the true nature of the population they are drawn from. To define the groups, the data were classified into three groups according to convenient cutoff points, so that each group contained one-third of the overall study patients and the group with the highest restenosis rate was identified. The two remaining groups were then combined to form the group considered to be at "normal risk" and the odds ratio of restenosis determined by comparing the third of the patients in the high risk group with this reference group (the remaining two-thirds of the study patients). (The identification of subgroups for postangioplasty percent diameter stenosis is illustrated in Fig. 2.) 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 95% confi-

Figure 2. Frequency histograms grouped by percent diameter stenosis after angioplasty showing how the group defined by the ≥0.72-mm criterion is divided to determine a relevant odds ratio. The **top line** shows the number of lesions in each third of the group with restenosis (NO WITH REST). The **vertical arrows** with the values beneath show the points of subdivision. POST-PTCA = after coronary angioplasty.

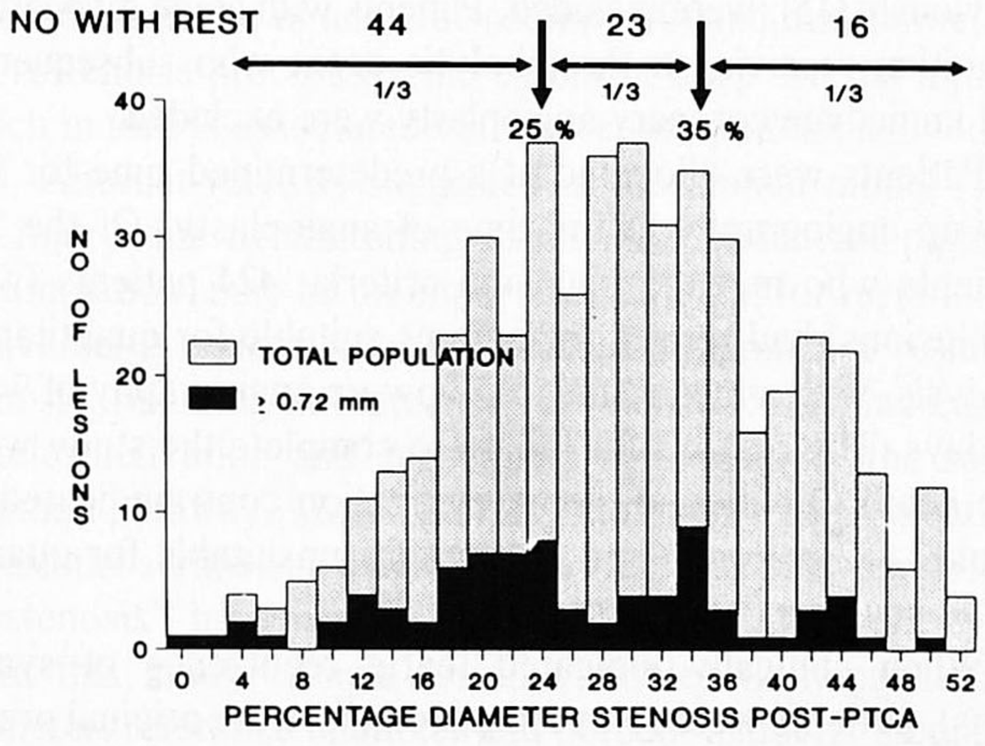


Table 2. Angiographic Variables of Restenosis Subgrouped According to Two Criteria

	≥50% Diameter Stenosis*			≥0.72 mm†		
	Restenosis	No Restenosis	p Value	Restenosis	No Restenosis	p Value
Minimal lumen diameter before angioplasty	1.18	1.21	NS	1.15	1.18	NS
Minimal lumen diameter after angioplasty	2.02	2.10	NS	2.28	2.05	<0.001
Minimal lumen diameter at follow-up	1.06	1.99	<0.0001	1.16	2.01	<0.0001
% diameter stenosis before angioplasty	62.6	57.7	<0.01	58.8	58.3	NS
% diameter stenosis after angioplasty	32.7	28.3	<0.005	24.8	29.7	<0.005
% diameter stenosis at follow-up	64	29.1	<0.0001	54.3	29.7	<0.0001
Normal vessel diameter before angioplasty	2.95	2.8	NS	2.86	2.85	NS
Normal vessel diameter after angioplasty	3.05	2.94	NS	3.06	2.93	NS
Normal vessel diameter at follow-up	2.92	2.81	NS	2.60	2.93	<0.001
Change in minimal lumen diameter at angioplasty (mm)	0.93	0.91	NS	1.13	0.86	<0.0001
Change in % diameter stenosis at angioplasty	30	29.4	NS	34	28.6	<0.01
Change in minimal lumen diameter at follow-up (mm)	0.97	0.10	<0.0001	1.12	0.04	<0.0001
Change in % diameter stenosis at follow-up	31.2	0.77	<0.0001	29.7	0.07	<0.0001

*Criterion of ≥50% diameter stenosis at follow-up angiography. †Deterioration in minimal lumen diameter by ≥0.72 mm after angioplasty to follow-up.

dence intervals then provide an index of the degree of certainty for the result obtained.

Results

Pre- and postangioplasty coronary stenosis measurements. For the total study group, the mean minimal lumen diameter was 1.18 mm before angioplasty, 2.09 mm after angioplasty and 1.85 mm at follow-up. The corresponding mean reference diameters were 2.85, 2.96 and 2.83 mm, giving rise to a percent diameter stenosis of 58.4% before angioplasty, 28.9% after angioplasty and 33.9% at follow-up.

The mean values for the angiographic variables subgrouped according to the ≥0.72-mm criterion and the ≥50% diameter stenosis criterion are shown in Table 2, emphasizing the differences between the two criteria. The grouping of the data for statistical analysis, showing the numbers in each group and the odds ratio for restenosis, are shown in Tables 3 to 5, again comparing the values obtained using the ≥0.72-mm criterion with the ≥50% diameter stenosis criterion.

Preangioplasty variables predictive of restenosis (Table 3). None of the preangioplasty variables were found to be associated with restenosis. A severe >65% diameter stenosis before angioplasty was the most relevant factor, with an odds ratio of 1.63 and confidence intervals from 0.85 to 3.31.

Table 3. Angiographic Variables Before Angioplasty

Grouped by ≥0.72-mm Change Criterion				Grouped by ≥50% Diameter Stenosis			
Minimal Lumen Diameter Before Angioplasty							
	≤1 mm	>1 mm	Total		≤1 mm	>1 mm	Total
No restenosis	129 (85)	278 (82)	407 (83)	No restenosis	128 (85)	295 (87)	423 (86)
Restenosis	22 (15)	61 (18)	83 (17)	Restenosis	23 (15)	44 (13)	67 (13)
Total	151	339	490	Total	151	339	490
Odds ratio = 1.29 (0.76–2.19)				Odds ratio = 1.21 (0.70–2.08)			
% Diameter Stenosis Before Angioplasty							
	≤65%	>65%	Total		≤65%	>65%	Total
No restenosis	312 (85)	94 (78)	407 (83)	No restenosis	328 (89)	95 (79)	423 (86)
Restenosis	57 (16)	26 (22)	83 (17)	Restenosis	42 (11)	25 (21)	67 (14)
Total	370	120	490	Total	370	120	490
Odds ratio = 1.63 (0.85–3.13)				Odds ratio = 1.42 (0.82–2.54)			
Normal Diameter Before Angioplasty							
	≤3.2 mm	>3.2 mm	Total		≤3.2 mm	>3.2 mm	Total
No restenosis	289 (84)	107 (82)	396 (83)	No restenosis	301 (87)	111 (85)	412 (87)
Restenosis	57 (16)	23 (18)	80 (17)	Restenosis	45 (13)	19 (15)	64 (13)
Total	346	130	476	Total	346	130	476
Odds ratio = 1.09 (0.64–1.86)				Odds ratio = 1.15 (0.64–2.04)			

Table 4. Angiographic Variables After Angioplasty

Grouped by ≥0.72-mm Change Criterion				Grouped by ≥50% Diameter Stenosis Criterion			
Minimal Lumen Diameter After Angioplasty							
	≤2.3 mm	>2.3 mm	Total		<2.3 mm	>2.3 mm	Total
No restenosis	304 (86)	103 (72)	107 (83)	No restenosis	285 (71)	77 (89)	362 (74)
Restenosis	42 (14)	41 (28)	83 (17)	Restenosis	119 (29)	9 (11)	128 (26)
Total	346	144	490	Total	404	86	490
Odds ratio = 2.88 (1.77–4.68)				Odds ratio = 0.28 (0.13–0.60)			
% Diameter Stenosis After Angioplasty							
	≤25%	>25%	Total		≤25%	>25%	Total
No restenosis	139 (75)	288 (89)	407 (83)	No restenosis	168 (81)	254 (80)	422 (86)
Restenosis	47 (25)	36 (11)	83 (17)	Restenosis	17 (9)	50 (20)	67 (14)
Total	186	324	490	Total	185	304	490
Odds ratio = 2.60 (1.40–4.82)				Odds ratio = 0.51 (0.28–0.95)			
Normal Diameter After Angioplasty							
	≤3.2 mm	>3.2 mm	Total		≤3.2 mm	>3.2 mm	Total
No restenosis	295 (86)	112 (76)	407 (83)	No restenosis	301 (88)	122 (83)	423 (86)
Restenosis	47 (14)	36 (24)	83 (17)	Restenosis	41 (12)	26 (18)	67 (14)
Total	342	148	490	Total	342	148	490
Odds ratio = 2.04 (1.25–3.31)				Odds ratio = 1.58 (0.92–2.69)			

Postangioplasty variables predictive of restenosis (Table 4). The restenosis group had a significantly better postangioplasty result as judged by minimal lumen diameter (2.28 mm) and percent diameter stenosis (24.8%) compared with the no restenosis group (2.05 mm and 29.7%; $p < 0.001$ and $p < 0.0001$, respectively). A postangioplasty minimal lumen diameter >2.3 mm was significantly associated with restenosis (odds ratio = 2.88) as was a postangioplasty percent diameter stenosis ≤25% (odds ratio = 2.60). A vessel ≥3.2 mm in diameter was less clearly predisposed to restenosis according to the ≥0.72-mm criterion with an odds ratio of 2.04.

Changes at angioplasty (Table 5). The factor most associated with restenosis was a large change in the minimal lumen diameter at angioplasty: 1.13 mm for the restenosis group and 0.86 mm for the no restenosis group ($p < 0.0001$), which corresponds to a change in percent diameter stenosis of 34% and 28.6%, respectively. The risk associated with a large improvement in the stenosis in terms of descending order of magnitude were: minimal lumen diameter ≥1.14 mm, minimal lumen diameter adjusted for vessel size ≥0.35 mm and percent diameter stenosis ≥35%, giving odds ratios of 3.30, 2.98 and 2.20, respectively. There was also a trend for a large change in reference diameter >0.36 mm to be associated with an increased risk of restenosis (≥0.72-mm criterion) with an odds ratio of 1.83.

Discussion

Criteria for postangioplasty restenosis. Soon after the introduction of coronary angioplasty as a revascularization procedure, it became clear that restenosis after the procedure was a significant limitation (22,23) and with the improvement in acute results over the years, this limitation has assumed increasing significance. Despite intensive investigation, there is as yet no known intervention that is able to reduce the incidence of restenosis. The reported risk factors associated with restenosis are unsatisfactorily documented, with little agreement among the various studies. These differences are primarily due to the failure of investigators to adopt a suitable standardized methodology with a uniformly accepted definition of restenosis that is relevant to the restenosis process. It has frequently been pointed out that different restenosis criteria give rise to similar restenosis rates (5,24). Although this is true, these similar restenosis rates do not define the same groups of patients (with sometimes as little as 50% overlap) and therefore risk factors may well be very different for different restenosis criteria (7). Figure 3 illustrates the distribution of the two restenosis groups in relation to the total number of lesions studied. Of the 104 lesions fulfilling at least one of the two criteria (21% of the total group of 490 lesions) <50% fulfilled both criteria, and 24% and 33%, respectively, fulfilled the ≥50% diameter stenosis and the ≥0.72-mm criteria.

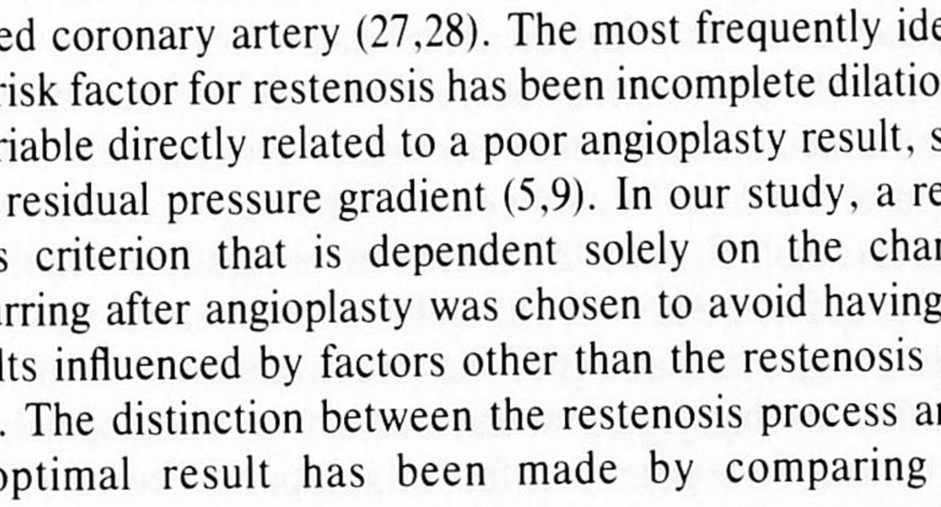
Risk factors for restenosis. There are as yet no prospective studies using quantitative coronary angiography that report on the risk factors for restenosis in large numbers of patients. However, a small number of factors relating to the restenosis process have been identified and confirmed in more than one study. These include dilation of a proximal left anterior descending coronary artery stenosis (5,25), a totally occluded vessel before angioplasty (26) and the presence of collateral vessels supplying the distal part of the

Table 5. Angiographic Variables: Change at Angioplasty

Grouped by ≥0.72-mm Change Criterion				Grouped by ≥50% Diameter Stenosis Criterion			
Change in Minimal Lumen Diameter at Angioplasty							
	≤1.14	>1.14	Total		≤1.14	>1.14	Total
No restenosis	314 (88)	93 (69)	407 (83)	No restenosis	308 (85)	115 (86)	423 (86)
Restenosis	42 (12)	41 (31)	83 (17)	Restenosis	48 (15)	19 (14)	67 (14)
Total	366	134	490	Total	356	134	490
Odds ratio = 3.30 (2.02–5.37)				Odds ratio = 1.06 (0.60–1.88)			
Adjusted Change in Minimal Lumen Diameter at Angioplasty							
	≤0.35	>0.35	Total		≤0.35	>0.35	Total
No restenosis	260 (89)	147 (74)	407 (83)	No restenosis	115 (89)	243 (86)	358 (86)
Restenosis	31 (11)	52 (26)	83 (17)	Restenosis	23 (14)	44 (14)	67 (14)
Total	291	199	490	Total	178	284	490
Odds ratio = 2.98 (1.82–4.84)				Odds ratio = 0.40 (0.22–0.76)			
Change in Diameter Stenosis at Angioplasty							
	≤35%	>35	Total		≤35%	>35%	Total
No restenosis	290 (75)	117 (75)	407 (83)	No restenosis	288 (75)	135 (87)	423 (86)
Restenosis	44 (25)	39 (25)	83 (17)	Restenosis	46 (25)	21 (13)	67 (14)
Total	234	156	490	Total	334	156	490
Odds ratio = 2.20 (1.36–3.56)				Odds ratio = 0.98 (0.67–1.70)			
Differences in Reference Diameter at Angioplasty							
	≤0.36	>0.36	Total		≤0.36	>0.36	Total
No restenosis	320 (85)	75 (76)	395 (83)	No restenosis	327 (87)	84 (84)	411 (86)
Restenosis	56 (15)	24 (24)	80 (17)	Restenosis	49 (13)	15 (15)	64 (14)
Total	376	99	475	Total	376	99	475
Odds ratio = 1.83 (1.07–3.14)				Odds ratio = 1.19 (0.64–2.23)			

dilated coronary artery (27,28). The most frequently identified risk factor for restenosis has been incomplete dilation or a variable directly related to a poor angioplasty result, such as a residual pressure gradient (5,9). In our study, a restenosis criterion that is dependent solely on the changes occurring after angioplasty was chosen to avoid having the results influenced by factors other than the restenosis process. The distinction between the restenosis process and a suboptimal result has been made by comparing the ≥0.72-mm criterion with that of ≥50% diameter stenosis. The analysis has been limited to the simple pre- and postangioplasty morphology (minimal lumen diameter, reference diameter and percent diameter stenosis) and the changes occurring during the procedure. Analysis of data in this form represents a significant change from the convention and gives rise to conclusions that are at odds with some of those previously published.

Figure 3. Of the 490 lesions analyzed, 386 were free of restenosis and 104 lesions (21%) had restenosis by either of the two criteria for restenosis. The column (**right**) illustrates how each criterion is associated with a substantial proportion of lesions that are exclusive to that criterion, with <50% of the lesions (43%) fulfilling both criteria. A similar lack of correlation exists with other conventionally used restenosis criteria. DS = diameter stenosis.



Predilation variables. Of the predilation variables analyzed, only the severity of the initial lesion has previously been reported (9) to be associated with restenosis although many studies have failed to find this association. Other predilation variables not analyzed in this study, such as eccentricity, bend point location and proximal left anterior descending artery stenosis, presence of collateral vessels and a totally occluded artery, have also been implicated (5,24,29).

The initial stenosis severity (Fig. 4) was not found to be associated with an increased risk as assessed with either of the two criteria: odds ratios = 1.29 and 1.21 when using the ≥0.72-mm criterion and the ≥50% diameter stenosis criterion, respectively. Likewise, if the severity of the initial stenosis is expressed as a percent of the normal diameter, a severe initial stenosis >65% was not significantly associated with an increased risk and this observation is in broad agreement with most published reports.

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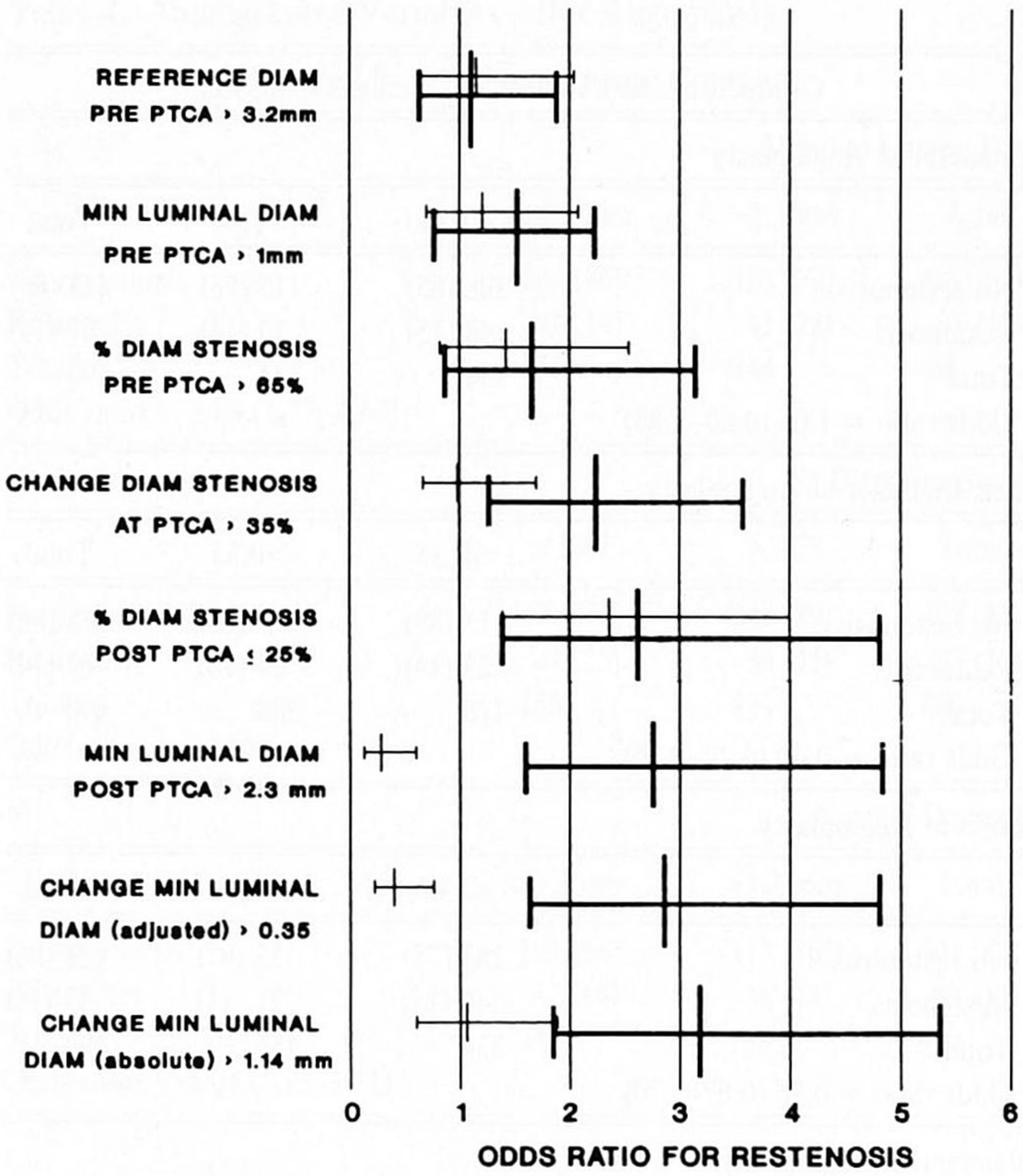

Figure 4. Odds ratios and 95% confidence intervals for restenosis in the third of the study group at highest risk are shown for the ≥0.72-mm criterion (**bold lines**) and for comparison the corresponding group according to the ≥50% diameter stenosis (**fine lines**). The cutoff point defining the relevant group at highest risk is indicated. CHANGE MIN LUMINAL DIAM (adjusted) = change in minimal lumen diameter divided by normal diameter of vessel; DIAM = diameter; MIN = minimal; other abbreviations as in Figure 2.

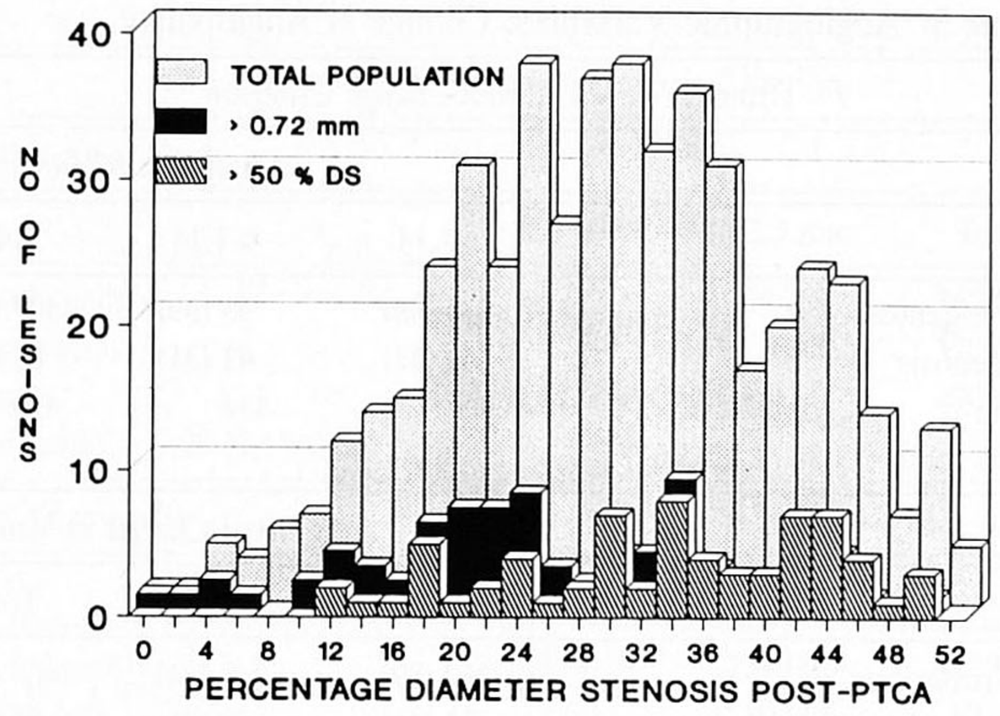

Figure 5. Frequency histogram of 490 lesions after successful angioplasty (POST-PTCA) grouped according to the postangioplasty percent diameter stenosis (DS). The distribution for the total study group is "normal" about a mean value of 29%. The lesions fulfilling each of the two criteria are also shown and the discrepancy between their distributions is clearly demonstrated: The group defined by the ≥0.72-mm criterion is distributed around a mean value of 25% and the group defined by the ≥50% diameter stenosis criterion is distributed around a mean value of 32%.

Postdilation variables. A poor postangioplasty result (or incomplete dilation) and factors associated with incomplete dilation such as a residual pressure gradient are most frequently reported to be associated with restenosis. The data from this study show that the associated risk is highly dependent on the restenosis criterion employed: essentially a good result (<25% diameter stenosis) is associated with restenosis if the ≥0.72-mm criterion is used and, conversely, a suboptimal result (>35% diameter stenosis) is a risk factor if ≥50% diameter stenosis is used (Fig. 4).

It is, perhaps, not surprising that incomplete dilation should be identified as a risk factor if the criterion for restenosis is a ≥50% diameter stenosis. However, the question remains as to whether a more severe residual stenosis actually induces the restenosis process or whether it reflects the use of a restenosis criterion that preselects lesions with less than optimal results. The answer to this question is crucial because some theories addressing the cause of restenosis incorporate this concept but, more important, if this question is not critically addressed, studies that are designed to determine the effect of therapeutic interventions on restenosis may be falsely interpreted.

Our study suggests that the latter of these two possibilities is the more likely and the frequency histogram (Fig. 5) illustrates why the discrepancy occurs, showing the distribution of the two restenosis groups. The lesions with restenosis (≥50% diameter stenosis criterion) tend to lie near the 50% threshold immediately after the procedure. It seems that if a "cut-off" criterion is used to define restenosis, it will preselect those lesions that lie close to the cut-off value and this appears to be the most relevant factor for the ≥50% diameter stenosis criterion. The reason for this is twofold. First, it should be remembered that the variability of the measurement using a quantitative measuring system is in the region of 6.5% (95% confidence limits ± 13%) (16), which suggests that if a ≥50% criterion is used, a significant number of lesions will be defined as restenosis due to methodologic limitations of the measurement system, when in reality no change has taken place between angioplasty and follow-up. The potential for this type of error will be magnified many times if visual estimates for stenosis severity are used. Lesions with a better postangioplasty result will fall outside this error of measurement and therefore will not be falsely defined as restenosis due to methodologic limitations. Second, after angioplasty, most lesions deteriorate to some extent (30), with the patients showing a normal distribution around a mean deterioration of −0.22 mm; thus, if a deterioration in the lumen diameter is an integral part of the healing process, any "cut-off" criterion that lies in the direction of population shift can be expected to choose preferentially those lesions near to the "cut-off" point. Conversely, the lesions that meet the ≥0.72-mm criterion tend to be distributed at the opposite end of the histogram and as a group have a much better result than those selected by the ≥50% diameter stenosis criterion. The mean postangioplasty percent diameter stenosis in this study was 25% for

those lesions fulfilling the ≥0.72-mm criterion and 32% for the ≥50% diameter stenosis criterion.

Variables of change at angioplasty. The factors found to be associated with an increased risk according to the ≥0.72-mm criterion in ascending order were change in reference diameter, change in diameter stenosis, change in minimal lumen diameter and change in minimal lumen diameter adjusted for vessel size by dividing by the normal diameter of the vessel (Fig. 4). It is clear that the more the lesion is improved at the time of the angioplasty procedure, the greater the subsequent deterioration in the months after the procedure. As one might expect, lesions that are improved less than the norm tended to have a greater residual stenosis after angioplasty. These lesions, although likely to meet the ≥50% diameter stenosis criterion because they lie close to it after angioplasty, undergo less deterioration than lesions that have a better result. The distinction should therefore be made between the postangioplasty result and the change in lumen diameter at angioplasty. Although the postangioplasty result is highly relevant to the long-term outcome, it is the change occurring at angioplasty that is the strongest predictor of subsequent deterioration between angioplasty and follow-up. This observation, which previously has not been generally recognized, is not entirely without rationale (10–14).

Substantial improvements in lumen diameter during angioplasty (from a severe stenosis to an optimal result) imply dispersion of large amounts of plaque into the vessel wall or alternatively a deeper dissection into the arterial wall to achieve the same effect. In either case, the degree of improvement is likely to correlate with the degree of trauma to the vessel wall. If the restenosis process is influenced by the degree of trauma, then the greater and deeper the trauma, the more the restenosis process will be stimulated. These results suggest that those lesions that are likely to experience the largest deterioration after dilation are those severe initial lesions that have the optimal postangioplasty result. The frequency histogram (Fig. 6) of change in minimal lumen diameter for the total study group and for those with restenosis according to the two criteria illustrates the discrepancy and relevance of the two criteria.

Implications for clinical practice. There seems to be a consensus among clinicians that the better the result at angioplasty, the less chance there is of restenosis. This premise is not supported by hard experimental evidence, although clearly if the lesion is not effectively dilated, the long-term result cannot be expected to be good. The data from this study suggest that there may well be a compromise result somewhere between a 20% and 30% postangioplasty diameter stenosis that has a good chance of a satisfactory long-term result and may avoid the increased risk of acute dissection and occlusion (9) incurred by using an oversized balloon to achieve an optimal result.

Perhaps more important, the postangioplasty result has implications for clinical restenosis studies, particularly when assessing the affect of pharmacologic interventions. If the

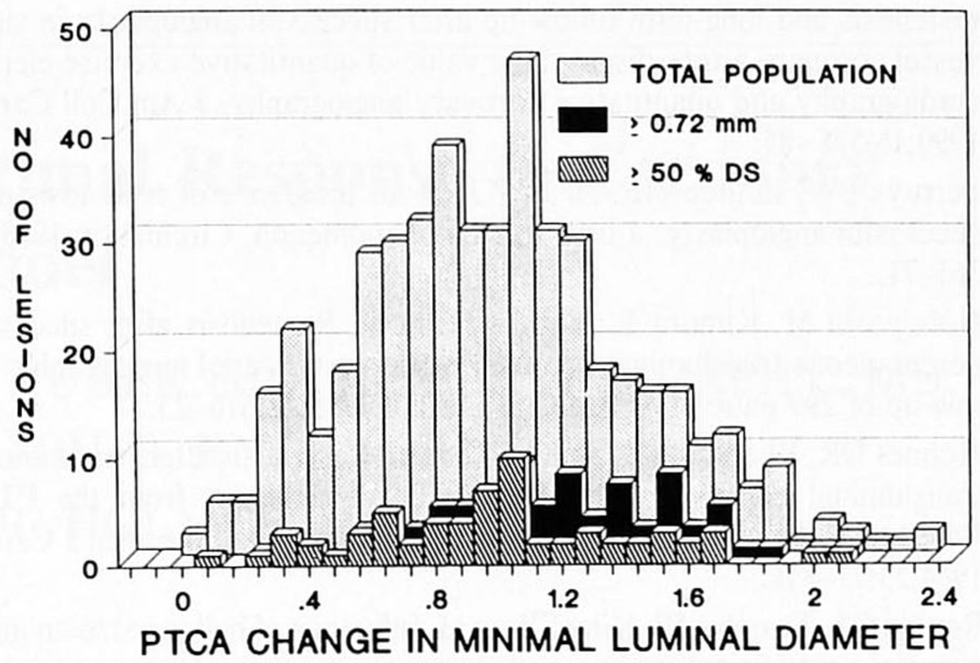

Figure 6. Frequency histogram similar to that in Figure 5 grouped according to change in minimal lumen diameter at angioplasty (PTCA). Again, the distribution is "normal," but with a skew to the right. According to the ≥0.72-mm criterion, the lesions in the third of the group with the largest improvement in the minimal lumen diameter at angioplasty (n = 44) have the highest risk of restenosis. DS = diameter stenosis.

criterion of a ≥50% diameter stenosis is used as the sole definition of restenosis, the preselection of poor postangioplasty results by this criterion may be of such influence that any effect produced by pharmacologic intervention may not be realized by statistical hypothesis testing. More subtly, as the lesions that fulfill the ≥50% diameter stenosis criterion undergo less change between angioplasty and follow-up, it will become statistically difficult to show the effect of a truly beneficial agent because of inadequate statistical power—a verdict of "no benefit" being returned when in fact a benefit exists. It is interesting to note that almost universally the conclusions from these studies have been that no agent has a beneficial effect on restenosis.

The use of restenosis criteria alone for assessing the long-term results of coronary angioplasty has the potential for producing misleading results. A distinction should be made between the postangioplasty result and the restenosis process as measured by the change in minimal lumen diameter or minimal lumen area after the procedure.

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