Incidence of restenosis after successful coronary angioplasty: a time-related phenomenon

A quantitative angiographic study in 342 consecutive patients at 1, 2, 3, and 4 months

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ABSTRACT Data from experimental, clinical, and pathologic studies have suggested that the process of restenosis begins very early after coronary angioplasty. The present study was performed to determine prospectively the incidence of restenosis with use of the four National Heart, Lung, and Blood Institute and the 50% or greater diameter stenosis criteria, as well as a criterion based on a decrease of 0.72 mm or more in minimal luminal diameter. Patients were recatheterized at 30, 60, 90, or 120 days after successful percutaneous transluminal coronary angioplasty (PTCA). After PTCA all patients received 10 mg nifedipine three to six times a day and aspirin once a day until repeat angiography. Of 400 consecutive patients in whom PTCA was successful (<50% diameter stenosis), 342 underwent quantitative angiographic follow-up (86%) by use of an automated edge-detection technique. A wide variation in the incidence of restenosis was found dependent on the criterion applied. The incidence of restenosis proved to be progressive to at least the third month for all except NHLBI criterion II. At 4 months a further increase in the incidence of restenosis was observed when defined as a decrease of 0.72 mm or more in minimal luminal diameter, whereas the criteria based on percentage diameter stenosis showed a variable response. The lack of overlap between the different restenosis criteria applied affirms the arbitrary nature of angiographic definitions currently in use. Restenosis should be assessed by repeat angiography, and preferably ascertained according to the change in absolute quantitative measurements of the luminal diameter.
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PREVIOUS STUDIES with exercise thallium-201 scintigraphy and exercise-gated radionuclide ventriculography performed in asymptomatic patients after successful percutaneous transluminal coronary angioplasty (PTCA) have suggested that the process of restenosis begins early after the procedure.[1–3] Data from experimental, clinical, and pathologic studies have indicated that restenosis may occur within 60 days via two mechanisms: first, platelet deposition at the site of endothelial denudation early after angioplasty (minutes to days) can induce spasm and the formation of a mural thrombus, which may subsequently undergo organization and cause restenosis[4–7]; second, release of platelet-derived growth factor may induce an excessive intimal fibroproliferative response consisting mostly of proliferating smooth muscle cells which may contribute to late (7 to 150 days) restenosis.[5, 8–15]

It is generally considered that evidence of restenosis usually presents itself within 6 months after angioplasty, and is extremely infrequent after 12 months. However, several angiographic studies have demonstrated that most patients with symptomatic restenosis manifest anginal symptoms by the third month after angioplasty.[16–21] The timing and incidence of "silent" restenosis (e.g., recurrent stenosis without symptoms) in the first 3 months after PTCA remains unknown.

The present study was performed to determine the incidence and time to restenosis with the use of six different angiographic criteria in a consecutive series of patients. For this purpose the study population was subdivided into four groups of patients allocated to be recatheterized at 30, 60, 90, and 120 days after suc-

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cessful PTCA, respectively. This approach permits a critical assessment of the values and limitations of the currently used restenosis criteria and raises several methodologic issues, including those related to how we define and quantify restenosis: should we express our quantitative measurements in absolute values or in relative percentages?

Materials and methods

Study population. The initial cohort of patients consisted of 400 patients who had undergone successful coronary angioplasty, defined as: (1) less than 50% diameter stenosis on visual inspection of the postangioplasty coronary angiogram obtained in multiple views, (2) no in-hospital complications, namely recurrence of angina, coronary bypass grafting, repeat PTCA, acute myocardial infarction, or death.

Patients with stable and unstable angina pectoris, as defined previously,[22, 23] were included. Patients with acute myocardial infarction were excluded.

The recruitment period for the study was subdivided into four equal time intervals of 5 months each. Patients with a successful PTCA enrolled during the first time interval were allocated to undergo follow-up angiography at 30 days, the second at 60 days, the third at 90 days, and the fourth at 120 days.

Of the 400 patients who met the inclusion criteria, 342 patients had repeat angiograms suitable for quantitative analysis. The reasons for failure to complete the study are detailed in figure 1.

Recatheterization was considered to be contraindicated for the following reasons: disabling concomitant disease (e.g., renal failure, lung cancer), severe peripheral vascular disease, or more than four prior angiographic investigations.

Of the total study population of 342 patients (398 lesions), 93 patients were scheduled for recatheterization at 30 days (110 lesions), 79 patients at 60 days (89 lesions), 82 patients at 90 days (93 lesions), and 88 patients at 120 days (106 lesions) after PTCA.

The baseline clinical characteristics of patients in the four groups were comparable for the variables listed in tables 1 and 2. The mean time from PTCA to follow-up angiography in the four study groups were 40 days, 61 days, 102 days, and 120 days, respectively. Patients who were reinvestigated before their preset time because of evidence of recurrent ischemia were retained in their initially assigned follow-up group for the purpose of analysis.

Prior myocardial infarction was defined according to the Minnesota code,[24] and in the case of conduction abnormality the presence of regional akinesia or dyskinesia on the left ventriculogram was used as the criterion. In table 2 the vessels dilated, the number of patients with tandem lesions, and the number of patients with more than one lesion dilated is listed for each follow-up group.

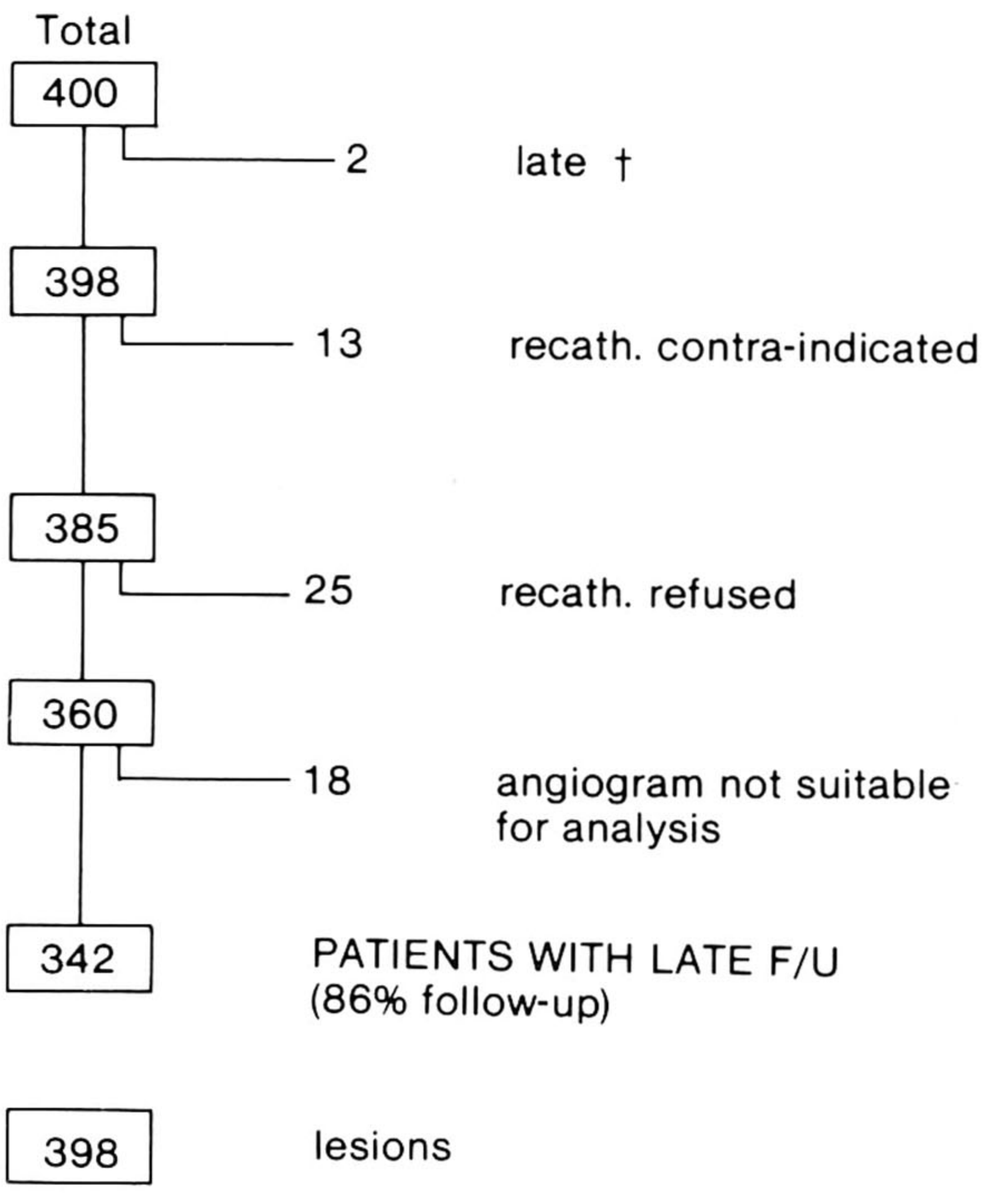

FIGURE 1. Total number of patients who met the inclusion criteria, and the reasons for failure to complete the study. Dsten = diameter stenosis; F/U = follow-up; Recath. = recatheterization.

Methods

Coronary angioplasty was performed with a steerable, movable guidewire system via the femoral route. Details regarding the procedure used in our laboratory have previously been reported.[22, 23] At the beginning of the angioplasty procedure all patients received 10,000 IU of intravenous heparin, 500 mg of intravenous aspirin, and a continuous infusion of Rheomacrodex (low molecular weight dextran) was started. After dilatation 10 mg nifedipine was given orally every 2 hr for the first 12 hr after PTCA, and thereafter three to six times a day together with 500 mg aspirin orally once a day for at least 6 months. β-blockers were withdrawn unless hypertension was present.

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 elsewhere.[25, 26] To analyze a coronary arterial segment in a selected frame of 35 mm cinefilm, an optically magnified portion of the image encompassing that segment was converted into video format by means of a cine-video converter. The contours of the vessel were detected automatically on the basis of the weighted sum of first and second derivative functions applied to the digitized brightness information. Calibration of the diameter data of the vessels in absolute values (mm) was achieved by use of the contrast catheter as a scaling device. To this end, the contours of a user-defined portion of the optimally magnified catheter (optimal magnification factor $2\sqrt{2}$) were detected automatically and corrected for pincushion distortion caused by the image intensifiers. From the contours, the vessel diameter functions, in absolute millimeters, were determined by computing the shortest distances between the two contour positions.

A representative analysis, with the detected contours and the diameter functions superimposed on the original video image, is shown in figure 2. Multiple matched views, orthogonal if possible, were analyzed for each dilated lesion and the results were averaged.

To standardize the method of acquisition and analysis of the PTCA and follow-up angiograms, the following four measures were undertaken.[26] First, the x-ray system was repositioned to correspond as much as possible to the projections and settings used during the previous angiographies. For this purpose, the angular settings of the x-ray gantry and the various height levels were readjusted according to the values previously documented with the on-line registration system.

TABLE 1
Clinical characteristics of the 342 patients with successful PTCA entered into the study

	Follow-up period				
	30 days	60 days	90 days	120 days	Overall
No. of patients	93	79	82	88	342
No. of lesions	110	89	93	106	398
Mean No. of lesions dilated/patient	1.18	1.13	1.13	1.20	1.16
Age (yr; mean ± SD)	57 ± 9 (range, 35–75)	57 ± 9 (range, 31–75)	56 ± 9 (range, 32–74)	57 ± 9 (range, 31–74)	57 ± 9 (range, 31–75)
Sex ratio (M/F)	5.6 (79/14)	5.1 (66/13)	3.3 (63/19)	3.9 (70/18)	4.3 (278/64)
Time from PTCA to F/U (days)	40 ± 7 (range, 18–62)	61 ± 12 (range, 11–80)	102 ± 18 (range, 33–164)	120 ± 32 (range, 4–226)	80 ± 38 (range, 4–226)
Extent of CAD					
1 vessel	62 (67%)	56 (71%)	52 (63%)	62 (70%)	232 (68%)
2 vessels	24 (26%)	13 (16%)	21 (26%)	16 (18%)	74 (22%)
3 vessels	7 (8%)	10 (13%)	9 (11%)	10 (11%)	36 (11%)
Previous coronary bypass grafting (n)	9 (10%)	7 (9%)	6 (7%)	8 (9%)	30 (9%)
Previous myocardial infarction (n)	40 (43%)	39 (49%)	32 (39%)	30 (34%)	138 (40%)
Previous coronary angioplasty (n)	10 (11%)	2 (3%)	11 (13%)	12 (14%)	35 (10%)

CAD = coronary artery disease; F/U = follow-up angiography.

Second, for all studies cineframes to be analyzed were selected at end-diastole to minimize any possible foreshortening and blurring effect.

Third, the user-determined beginning and end points of the major coronary segments were identified according to the definitions of the American Heart Association.[27]

Finally, Polaroid photographs were taken of the video image with the detected contours superimposed to ensure that the analyses were performed on the same coronary segment in the consecutive angiograms. "Interpolated" percent diameter stenosis measurements were used. This is a method that expresses the severity of a coronary obstruction without dependency on a user-defined reference region. The principle of this technique is the computer estimation of the original vessel diameter at the site of the obstruction, assuming there is no coronary artery disease present.[25] The interpolated percent diameter stenosis measurement was obtained by comparison of the minimal luminal diameter value at the obstruction site with the corresponding value of the reference diameter in this position.

The accuracy of this quantification method has previously been validated with Plexiglas phantoms filled with contrast medium (Perspex models).[28]

Definitions of restenosis. To allow comparison of our results with those of other published studies and to evaluate the differences between various criteria, the following six previously proposed definitions of restenosis were applied: (1) an increase in diameter stenosis of at least 30% by the time of follow-up angiography (National Heart, Lung, and Blood Institute [NHLBI] I), (2) an immediate post-PTCA diameter stenosis of less than 50% increasing to greater than or equal to 70% at follow-up (NHLBI II), (3) an increase in stenosis severity to within 10% or less of the predilatation diameter stenosis at the

TABLE 2
Vessel dilated, number of patients with tandem lesions, and number of patients with more than one lesion dilated in each of the four study groups

	Follow-up period									
	30 days		60 days		90 days		120 days		Overall	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Vessel dilated										
LAD	61	(56)	61	(69)	55	(59)	62	(58)	239	(60)
LCX	18	(16)	16	(18)	19	(20)	16	(15)	69	(17)
RCA	26	(24)	11	(12)	16	(17)	23	(22)	76	(19)
Bypass	4	(4)	0	(0)	2	(2)	4	(4)	10	(3)
LMCA	1	(1)	1	(1)	1	(1)	1	(1)	4	(1)
No. of patients with tandem lesion	6	(6)	2	(3)	2	(2)	5	(6)	15	(4)
No. of patients with more than one lesion dilated	15	(16)	10	(13)	10	(12)	18	(20)	53	(15)

Bypass = aortocoronary bypass graft; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LMCA = left main coronary artery; RCA = right coronary artery.

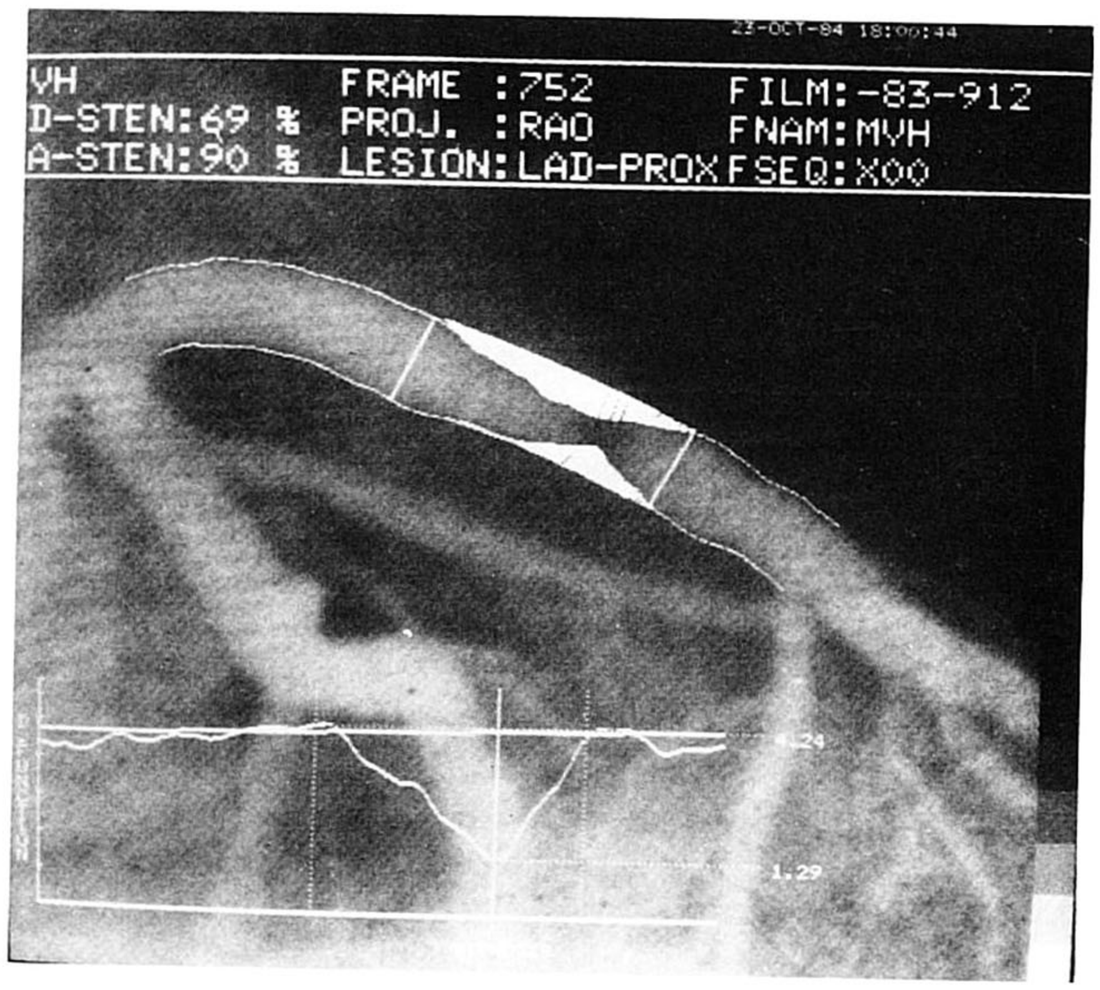

FIGURE 2. A single-frame angiogram of a left coronary artery with superimposition of the automated contours at the coronary artery segment of interest. Beneath this is shown the diameter function of the detected contours of the left anterior descending coronary artery. The minimal luminal diameter (vertical line) is 1.29 mm, corresponding to a diameter stenosis of 69% and an area stenosis of 90%.

time of follow-up angiography (NHLBI III), (4) a loss of at least 50% of the gain in luminal diameter achieved at PTCA (NHLBI IV), (5) an increase of the diameter stenosis from less than 50% after angioplasty to greater than or equal to 50% at follow-up, and (6) a decrease in minimal luminal diameter of greater than or equal to 0.72 mm with respect to the post-PTCA situation. This last definition is based on the variability of minimal luminal diameter measurements in millimeters (0.36 mm). This variability is 1 SD of the difference of the means of two observations on the same lesion, which if used would result in a 17.5% false-positive restenosis rate, while the use of 2 SDs as a criterion ($2 \times 0.36 = 0.72$ mm) results in a false-positive rate of 2.5%.[25]

Statistical analysis. To test for differences in mean values and proportions between the four follow-up groups with respect to the baseline characteristics (tables 1 and 2), univariate analysis of variance was performed for the continuous variables, and multiway chi-square analysis was used for the discrete variables. For the quantitative variables listed in tables 3A and 3B, univariate analysis of variance was performed (BMDP statistical software, University of California Press, Berkeley 1985). Analysis of variance for a linear trend was done on the change in minimal luminal diameter from after PTCA to follow-up (Glim statistical package). All statistical tests were two tailed. A probability value below .05 was regarded as indicating statistical significance.

Results

The results of quantitative angiography in the 342 patients who completed angiographic follow-up are detailed in tables 3A and 3B, together with the p value computed by analysis of variance for the individual variables used to compare the follow-up groups. Before and after PTCA all the quantitative angiographic variables for the four groups were comparable, except for a smaller reference diameter in the 4 month group before angioplasty, and a slightly lower percentage diameter stenosis immediately after PTCA in the 4 month group. After PTCA there was, as expected, a significant improvement in minimal luminal diameter and diameter stenosis for each of the four follow-up groups ($p<.0001$). However, analysis of variance performed on the obstruction-related variables at follow-up showed a significant difference in the four groups: there was no significant change at 1 and 2 months, but a significant increase in the severity of the stenosis in the 3 month group ($p<.001$ for each obstruction-related variable), and a further but smaller increase that did not reach statistical significance in the 4 month group.

Table 4 and figure 3 illustrate the incidence of restenosis according to the NHLBI criteria and the two cri-

TABLE 3A

Results of quantitative coronary angiography, expressed as mean ± 1 SD, for the 93 patients (110 lesions) recatheterized at 30 days, the 79 patients (89 lesions) recatheterized at 60 days, the 82 patients (93 lesions) recatheterized at 90 days, and the 88 patients (106 lesions) recatheterized at 120 days after PTCA

Variable	30 day group	60 day group	90 day group	120 day group	p value[A]
Minimal luminal diam. (mm)					
Pre	1.16 ± 0.41	1.16 ± 0.37	1.20 ± 0.40	1.13 ± 0.41	.70
Post	2.06 ± 0.46	2.00 ± 0.42	2.14 ± 0.42	2.10 ± 0.40	.25
FU	2.11 ± 0.56	1.93 ± 0.64	1.77 ± 0.58	1.69 ± 0.55	<.00001
Diameter stenosis (%)					
Pre	58.2 ± 12.5	59.5 ± 11.8	59.3 ± 11.8	57.7 ± 15.2	.73
Post	28.5 ± 12.0	31.0 ± 12.0	28.1 ± 11.0	26.3 ± 9.9	.04
FU	26.9 ± 14.7	33.5 ± 19.8	37.1 ± 18.4	35.4 ± 16.7	<.0001
Reference diameter (mm)					
Pre	2.81 ± 0.66	2.86 ± 0.62	2.96 ± 0.58	2.69 ± 0.68	.03
Post	2.92 ± 0.63	2.92 ± 0.50	3.02 ± 0.56	2.86 ± 0.49	.31
FU	2.90 ± 0.60	2.92 ± 0.54	2.86 ± 0.55	2.62 ± 0.51	.003

Pre = before PTCA; Post = immediately after PTCA; FU = follow-up.
[A]By analysis of variance.

TABLE 3B

Absolute change in listed variables from pre- to post-PTCA, and from post-PTCA to the respective time of the follow-up angiography

Variable	30 day group	60 day group	90 day group	120 day group	p value[A]
Minimal luminal diam. (mm)					
Pre to post	+0.89	+0.86	+0.94	+0.97	.33
Post to FU	+0.04	−0.06	−0.37	−0.42	<.00001
Diameter stenosis (%)					
Pre to post	−29.8	−28.5	−31.2	−31.5	.53
Post to FU	−1.6	+2.5	+9.0	+9.1	<.00001
Reference diameter (mm)					
Pre to post	+0.12	+0.06	+0.07	+0.19	.03
Post to FU	−0.02	−0.01	−0.17	−0.26	<.00001

Abbreviations are as in table 3A.

[A]By analysis of variance.

teria used at our institution. Table 4 also lists the percentage of patients experiencing recurrent angina at the time of repeat angiography. From these data two conclusions can be drawn: first, there is a wide variation in the incidence of restenosis according to the criterion applied, and second, the incidence of restenosis is progressive to at least the third month for all the criteria except NHLBI II. At 4 months a further increase is observed in the percent restenosis defined as a decrease of 0.72 mm or more in minimal luminal diameter, whereas use of the criteria based on diameter stenosis shows a variable response.

The relationship between the different criteria for restenosis was also analyzed and the results are illustrated in figure 4, which shows the total number of lesions meeting each criteria and also the overlap among individual criteria. Comparison of the four NHLBI criteria showed that all lesions that fulfilled criteria I and II met criteria III and IV. Few patients met all four criteria (n = 9), but when NHLBI criteria III and IV were compared with the two criteria used at our institution, additional lesions were defined as having undergone restenosis. Finally, a large number of lesions

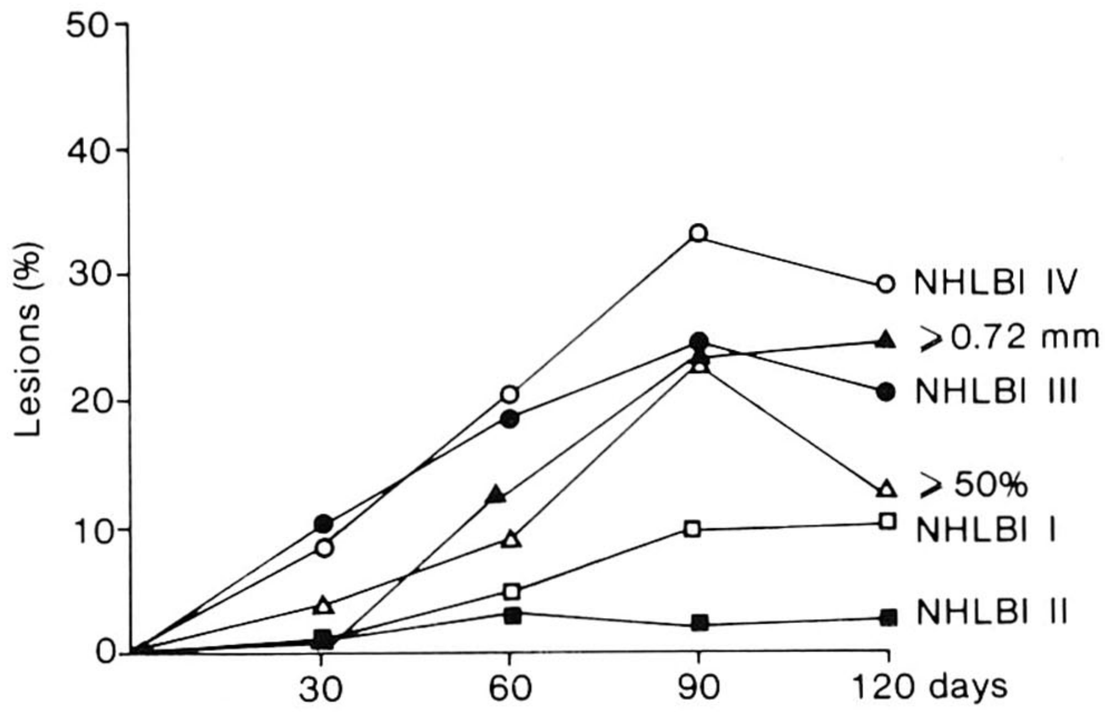

FIGURE 3. Percentages of lesions that fulfilled the various restenosis criteria at 30, 60, 90, and 120 days.

(119 of 398) fulfilled at least one of the six criteria with 29 lesions fulfilling all six of them. Although the percentages of lesions fulfilling the four criteria for restenosis were similar, it must be emphasized that each of the four criteria identified unique lesions that were not identified by the other three.

Figure 5 shows the individual minimal luminal diameters (mm) of all lesions immediately after PTCA compared with the follow-up value at 1, 2, 3, and 4 months. Lesions that had at least a 0.36 mm change are represented by closed circles. Lesions in which there was regression, defined as an increase, and progression, defined as a decrease in minimal luminal diameter of at least 0.72 mm (2 × 0.36 mm), are represented by the closed circles that fall outside of the dashed lines in figure 5. There was a wide scatter in the change in minimal luminal diameter of the individual lesions within each group, and also a clear trend with time. Lesion regression was observed mainly in the first 2 months (6.4% and 5.6%, respectively), while an increasing trend in the number of lesions undergoing progression was demonstrated up to 120 days. These trends could be fitted with the following linear model based on linear trend analysis (p<.0001):

$$\Delta\text{MLD post-fu (mm)} = 0.21 - 0.17 \times \text{time (months)}$$

TABLE 4

Lesion-related incidence of restenosis for each of the four follow-up groups according to six previously proposed angiographic definitions of restenosis

	Recurrent angina	Criterion					
		NHLBI I	NHLBI II	NHLBI III	NHLBI IV	≥50% DS	≥0.72 mm
1 month (%)	15	0.9	0.9	10.0	9.1	3.6	0.9
2 month (%)	19	4.5	3.4	19.1	20.2	9.0	12.4
3 month (%)	28	9.7	2.2	24.7	33.3	23.7	22.6
4 month (%)	32	10.4	2.8	21.7	30.2	13.2	25.5
Cumulative (%)	23	6.3	2.3	18.6	22.9	12.1	17.7

DS = diameter stenosis.

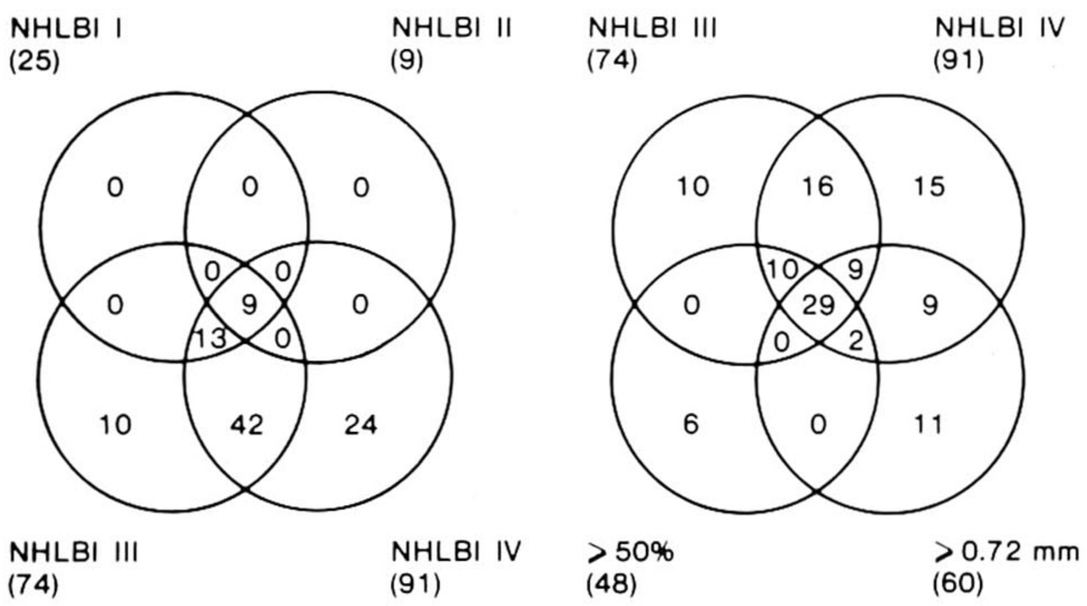

FIGURE 4. The relationships between the different restenosis criteria. On the *left* relationships between all four NHLBI criteria, and on the *right* that between NHLBI criteria III and IV and the two alternative criteria are given. The total number of lesions fulfilling the various restenosis criteria are shown in brackets, and the breakdown of these numbers according to overlap are shown within the circles. The center (overlapped by all four circles) represents the number of lesions fulfilling all four criteria. Three additional lesions were identified as having restenosis according to NHLBI criteria I and IV (left-sided Venn diagram). Similarly, one additional lesion complied with the NHLBI IV and the 50% or greater criteria in the right Venn diagram.

where ΔMLD post-fu = change in minimal luminal diameter from after angioplasty to follow-up.

Discussion

With the high success and low complication rate, restenosis remains the "Achilles' heel" of PTCA.[29] The rate of restenosis reported in a profusion of studies varies from 12% to 48% (table 5): however, critical evaluation and valid comparison of the available data in the literature is extremely difficult for a number of reasons.

First of all, the diagnosis of recurrent stenosis should be based on reproducible quantitative angiographic measurements. Visual estimation of stenosis severity alone yields unacceptable variation in the assessment of changes of coronary artery lesions.[39–43] To obtain objective and reproducible values a computer-assisted technique using either automated edge detection or videodensitometry should be applied.[44–56]

Second, the rate of restenosis varies considerably according to the definition used.[17] Essentially, angiographic definitions of restenosis are either based on the increase in narrowing with respect to the immediate post-PTCA angiographic appearance, or are defined as a loss of the gain achieved by successful PTCA. Since many angiographic definitions of restenosis are now used (table 5), comparative evaluation of these definitions is crucial for interpretation of the data in the literature, and for the assessment of the values and limitations of the currently used criteria for restenosis.

Third, to prevent over- or underestimation, the detection of restenosis requires strict adherence to a protocol that involves routine follow-up angiography at a predetermined time in all patients.

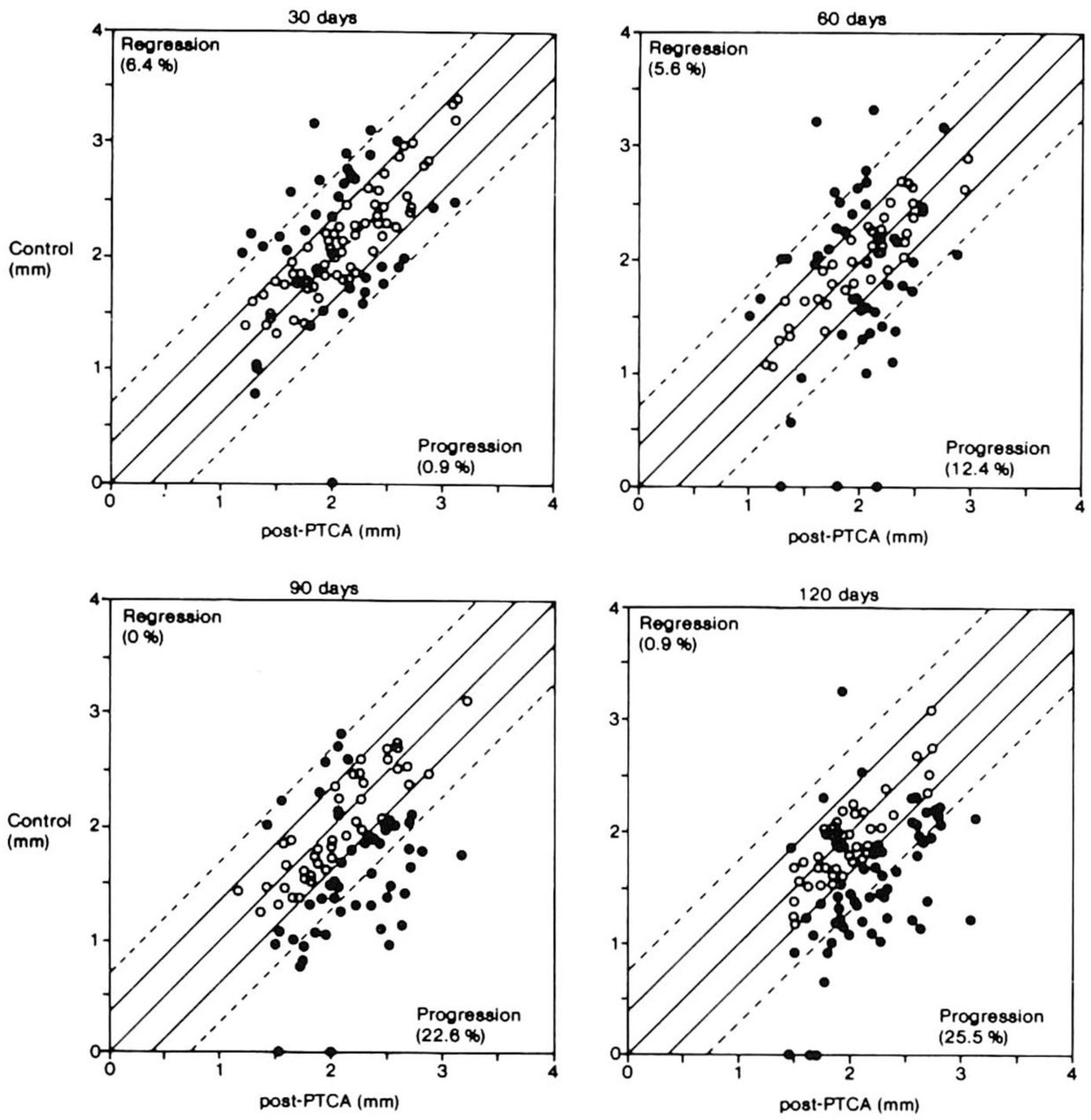

FIGURE 5. Individual minimal luminal diameter (mm) after PTCA compared with that at control angiography for the four groups. The two solid lines on either side of the identity line correspond to the long-term variability (0.36 mm) of repeated measurements for this variable.[25] This variability is 1 SD of the difference in the means of duplicate angiographic measurements. Here 2 SDs were used (2 × 0.36 = 0.72 mm; dashed lines) as a criterion for lesion progression or regression. Based on this criterion the percentages of lesions showing progression or regression (● outside dashed lines) are shown within the relevant brackets.

TABLE 5
Reported restenosis rates, together with the angiographic definition(s) applied, the number of patients studied, and the time interval between PTCA and follow-up angiography

Study	Year	Patients	FU angiography (%)	Interval PTCA–FU (months)	Restenosis criterion	% restenosis
M. Nobuyoshi[30]	1987	137	100	Next day	≥50% loss of gain	5.1
				1	≥50% loss of gain	12.0
				3	≥50% loss of gain	36.4
M. Kaltenbach[18]	1985	356	94	5.6	Ds <20% below pre-PTCA Ds	12
T. Corcos[31]	1985	92	100	8.2	≥70% Ds at FU	18.5
J. Meyer[32]	1983	70	90	6	>85% area stenosis[A]	20
R. Uebis[33]	1986	100	89	5.9	≥50% loss of gain	24.8
P. de Feyter[22]	1985	56[B]	82	2.3	<50% to >50% Ds at FU	28
P.P. Leimgruber[20]	1986	1758	57	7	>50% Ds at FU	30.3
M.A. Thornton[34]	1984	248	72	6–9	≥50% loss of gain	31
M.E. Bertrand[35]	1986	3198	Not reported	7	≥50% loss of gain	32
D.R. Holmes[17]	1984	665	84	6.2	≥30% Ds increase or ≥50% loss of gain	33.6
S. Levine[36]	1985	100	92	6	≥50% loss of gain	40
E. Fleck[37]	1984	51	100	6	>1 mm^2 stenosis area	42
A.R. Zaidi[38]	1985	184	100	Not reported	Not reported	48

The percent restenosis varies considerably. Likewise, the definition(s) used, rate and timing of repeat catheterization, and method of assessment of the arteriograms are far from uniform, making a critical comparison extremely difficult. The authors cited were selected primarily for the purpose of pointing out the variability in rates and definitions, rather than in an attempt to cover all literature on restenosis to date.

Ds = diameter stenosis; FU = follow-up.

[A]Percent stenosis of cross-sectional area.

[B]Patients with unstable angina.

The current literature suggests that evidence of restenosis usually becomes apparent within 5 months of the angioplasty procedure,[17, 20, 21] and the vast majority of restenosis in the series of Kaltenbach et al.,[18] occurred within 3 months. However, some of these studies exhibit a methodologic bias in that the time to and indication for repeat angiography was dictated predominantly by the recurrence of symptoms. In two of the larger studies,[17, 20] the prevalence of ischemic symptoms in patients angiographically reevaluated within 5 months exceeded 80%, whereas the observed restenosis rates were "as low as" 32.8% and 31.6%, respectively (≥50% loss of gain criterion). The selection of symptomatic patients might be expected to either artificially increase the angiographic restenosis rate, or to decrease the rate by not identifying asymptomatic patients with angiographic recurrence.

In the present study only 23% of the total study population of 342 was symptomatic at the time of reinvestigation, while the overall incidence of restenosis within the first 4 months was 22.9% (NHLBI criterion IV; table 4). It therefore appears that the difference in the restenosis rate of 9% to 10% (22.9% vs 32.8% or 31.6%)[17, 20] might be related to the substantial dissimilarity in the percentage of patients with recurrent angina at the time of repeat angiography. This point emphasizes the importance of routine angiographic reevaluation, irrespective of ischemic symptoms, in establishing the "true" incidence of restenosis and consequently in identifying the determinants of this process.

As previously alluded to, direct comparison of our observed rates of restenosis with those of Holmes and Leimgruber and their colleagues[17, 20] is hampered by major differences in study design and follow-up strategy. For instance, Leimgruber et al.[20] reported the follow-up of 998 patients originating from an initial cohort of 1758 patients with single-vessel disease in whom PTCA was successful (57% angiographic follow-up). The observed restenosis rate of 31.6% (≥50% loss of gain criterion) at a mean follow-up time of 7 ± 5 months pertains to a time window ranging from less than 2 to 42 months. This is in contrast to the 22.9% overall restenosis rate at a mean follow-up time of 80 ± 38 days (range 4 to 226 days) in this study (86% angiographic follow-up).

The PTCA Registry of the NHLBI reported on 557 patients who underwent angiographic reinvestigation

from a group of 665 with successful PTCA (84% angiographic follow-up). Their definition of success, a greater than 20% reduction in luminal diameter narrowing, is in contrast to our definition of less than 50% diameter stenosis immediately after PTCA. In this particular report time to follow-up ranged from less than 1 month to approximately 12 months, with only 42% of the patients being reinvestigated within the first 6 months.[17] Moreover, although the number of patients in our study may appear to be relatively small (n = 342) in comparison with the total study population in the reports of Holmes et al.[17] (n = 557) and Leimgruber et al.[20] (n = 998), it should be pointed out that the number of patients reinvestigated within the first 4 months in these two studies did not exceed 125 and 200, respectively.

In view of the above, the question of whether the incidence of restenosis peaks within the first 3 to 5 months can be answered more precisely by an approach that minimizes multiple biases as much as possible. Based on the criteria of the NHLBI, our data show that the incidence of restenosis appears to reach a plateau at 4 months, while restenosis according to the absolute criterion (≥0.72 mm) is still increasing at 4 months.

An interesting observation of this study was that the percent restenosis fell rather unexpectedly from 23.7% to 13.2% between 90 and 120 days, when defined as a 50% or greater diameter narrowing at follow-up. However, this apparent reduction was paralleled by a disproportionate decrease in the reference diameter compared with the change in minimal luminal diameter (figure 6 and table 3B). Consequently, use of the individual diameter stenosis values, derived from the ratio of the reference diameter over the minimal luminal diameter, results in an erroneous lowering of the restenosis rate by the 50% or greater criterion. Additionally, this reduction is discordant with the observation that the mean minimal luminal diameter is still diminishing between 90 and 120 days after angioplasty. Although no definite explanation can be given for the fact that the mean reference diameter progressively decreases with time, it could be hypothesized that this is in some way related to the local remodeling process within the arterial vessel wall after the uncontrolled barotrauma at the site of the obstruction.

The absence of standardization with respect to definition of restenosis, method of angiogram assessment, and timing and indication for angiographic control may lead investigators to prematurely draw important — and possibly erroneous — conclusions about factors responsible for a low or high rate of restenosis, such as technique of angioplasty, drug regimen after angioplasty, or modification of risk factors.[56] In addition to this, it is becoming clear that the

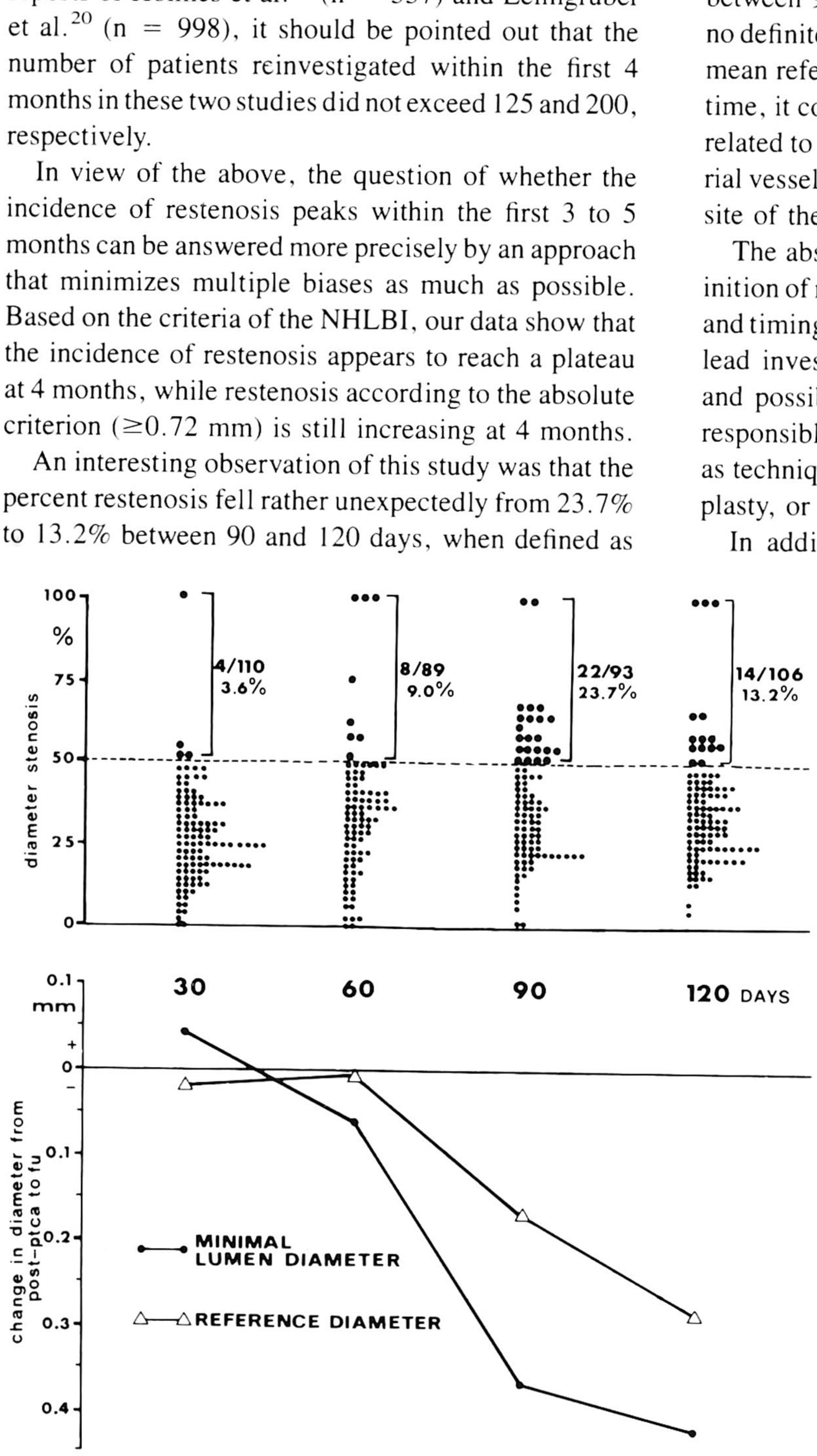

FIGURE 6. The mean changes in minimal luminal and reference diameters from after PTCA to follow-up at 30, 60, 90, or 120 days are graphically displayed by the solid lines in the *bottom* panel. The decrease in reference diameter is most apparent at 120 days after PTCA, and is disproportionate to the decrease in minimal luminal diameter. The effect of this phenomenon on the individual percentage diameter stenosis values, derived from the ratio of the reference over to the minimal luminal diameter, is shown in the *top* panel. The number of lesions with a 50% or greater diameter stenosis diminished from 90 to 120 days. As a result, the incidence of restenosis according to this criterion falls from 23.7% at 90 days to 13.2% at 120 days.

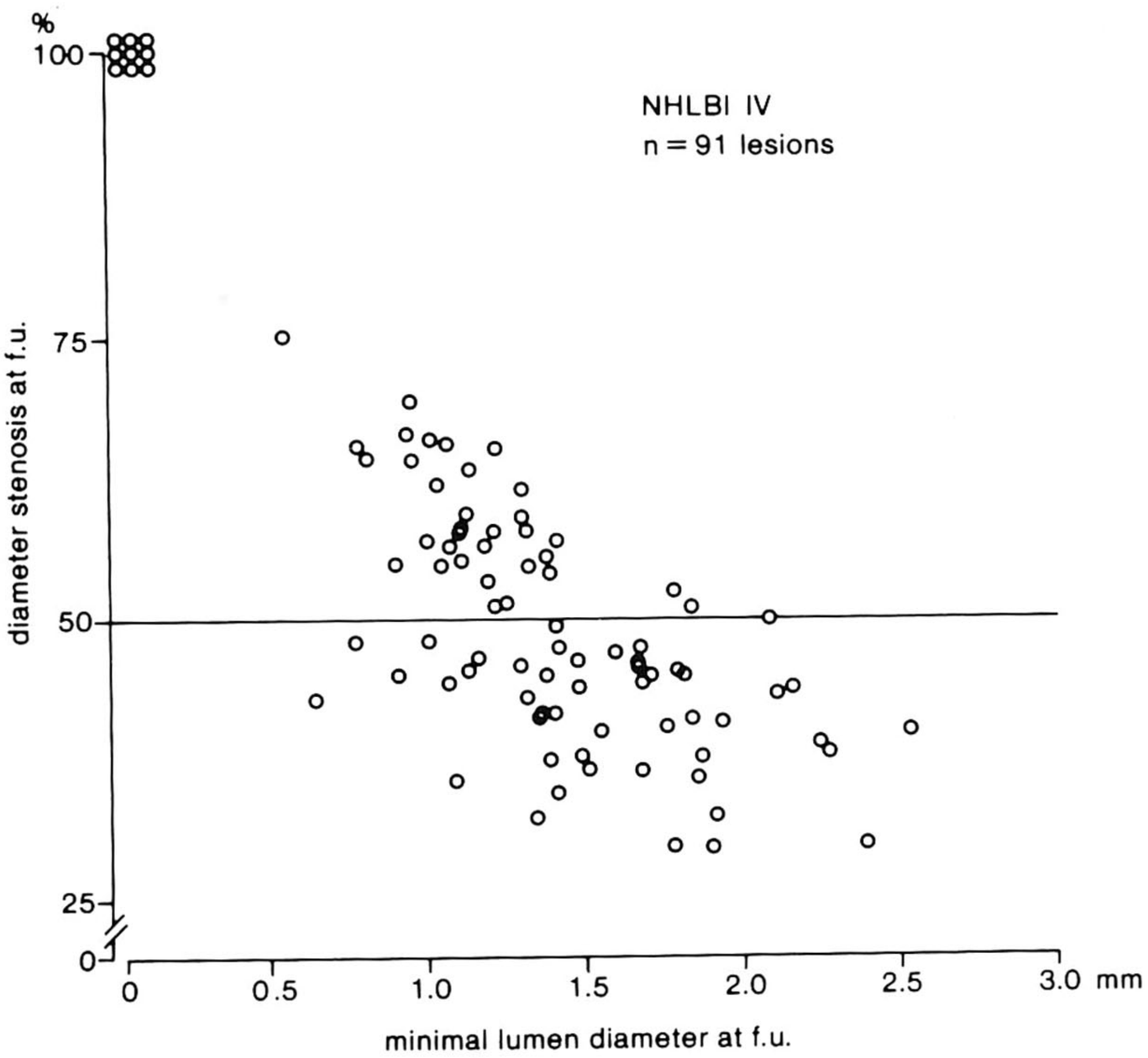

FIGURE 7. Relationship between percent diameter stenosis and the minimal luminal diameter at follow-up for lesions that fulfill NHLBI criterion IV. A total of 48 of the 91 lesions have a diameter stenosis of less than 50%. f.u. = follow-up.

definitions of restenosis in current use, which are based on relative percentages with more or less arbitrary cutoff points, do not adequately describe the progression to a physiologically significant obstruction. For instance, as can be seen from the individual lesion data plotted in figure 7, lesions that fulfill a criterion for restenosis based on changes in the relative percent diameter stenosis (NHLBI criterion IV) may represent relatively mild obstructions (percent diameter stenosis between 30 and 40 with absolute minimal luminal diameters ranging from 2 to 3 mm), amounting to what is a very satisfactory long-term result. Therefore, to avoid the arbitrariness of these floating-scale criteria the use of measurements in absolute terms (mm, mm^2) is advocated.

The most often reported visually assessed percent diameter stenosis overestimates lesion severity by 15% to 25%, as demonstrated by Bove et al.[57] Our quantitative measurements, showing a mean diameter stenosis before PTCA of 58% to 60% (table 3A) corresponding to an area stenosis of 80 to 81%, support this finding. Thus, since values obtained before PTCA or at follow-up are generally below 70% diameter stenosis, we suggest that the more than 70% criterion (NHLBI criterion II) for restenosis not be used when quantitative measurements are employed.

To circumvent the previously mentioned multiple biases and to define the true incidence of restenosis in the first 4 months, we tried to standardize as much as possible our methods and protocol of investigation.

The problem of defining restenosis is not trivial. Applying the stringent criteria of the NHLBI PTCA Registry to visual estimates of severity of stenosis has major limitations, due to the large intra- and interobserver variabilities in interpretation, especially for stenoses of between 20% and 80%.[41] Therefore, in this study stenoses were analyzed by computerized edge detection.[25] Although this method may not be optimal for those lesions with an irregular angiographic vessel wall outline[54, 56] immediately after angioplasty, it provides an objective and reproducible quantitative measurement that avoids unintentional bias in reading the angiogram. The overall accuracy (average difference) and precision (pooled standard deviation of the differences) of this contour detection technique for the percentage diameter stenosis measurements are 2.00% and 2.68%, respectively, and for the minimal luminal diameter, -30 and +90 μm, respectively. The mean differences and standard deviations of the differences in the minimal luminal diameter and interpolated reference diameter, as well as in the interpolated percentage diameter stenosis, have previously been published for the short (5 min), medium (60 min) and long term (90 days). The variability in minimal luminal diameter for these three types of studies ranged from 0.22 mm for the medium-term study to 0.36 mm for the least well controlled long-term study. In the long-term study group, the lack of significant variation in the mean difference in the minimal luminal diameters suggests that no detectable progression or regression of athero-

sclerotic lesions occurred over the period of 90 days. Therefore, a change greater than the long-term measurement variability of repeated coronary cineangiography and quantitative analysis (0.72 mm for the minimal luminal diameter; i.e., 2 SDs of difference of duplicate measurements) was considered significant and indicative of restenosis. This change in absolute values corresponds to a change of $2 \times 6.5\% = 13.0\%$ in percentage diameter stenosis.[25]

It is important to realize that the process of restenosis may be viewed either as a purely angiographic progression in focal narrowing without implication of any functional or clinical consequence, or as a functional deterioration assessed by means of a criterion able to identify a physiologically significant obstruction to blood flow. It is unclear what percent diameter narrowing — which is the traditional method for grading a coronary stenosis — will consistently lead to myocardial ischemia during exercise. However, a number of patients who meet the criteria for restenosis will have no symptoms and an adequate luminal diameter. It is therefore not surprising to see that the arbitrary nature of angiographic definitions of restenosis have further obscured the relationship between angiographic and functional result.

In conclusion, we believe that restenosis, when envisaged as a progressive encroachment on the lumen by the disease process in the vessel wall, should be assessed by repeat angiography and preferably ascertained according to the change in absolute quantitative measurements of the luminal diameter. By doing so, the comparison of various studies and different treatment groups will be more scientifically valid, and more importantly will provide a sound basis for the identification of the determinants of lesion recurrence.

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