

EDITORIAL REVIEWS

Restenosis After Coronary Angioplasty: New Standards for Clinical Studies

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With the high initial success rates for coronary angioplasty that are reported regularly, it has become increasingly difficult to demonstrate methods or techniques that are able to provide more beneficial early results than can be achieved by conventional angioplasty. On the other hand, the incidence of late restenosis has remained much the same over the 10 years that angioplasty has been part of clinical practice, and there is still no proved intervention that modifies the restenosis process. Therefore, the problem of restenosis has assumed increasing relevance in determining the clinical value of coronary angioplasty and, accordingly, studies that address the problem of restenosis need to become more exacting.

Although numerous articles have addressed the problem of restenosis in the clinical setting, many defining certain factors associated with restenosis and possible interventions to reduce the incidence of restenosis, there is surprisingly little consensus. Most of the discrepancies can be attributed to three factors: 1) the selection of patients, 2) the method of analysis, and 3) the definition of restenosis employed. This review shows how these three factors influence the outcome and conclusions of restenosis studies.

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Studies aimed at reducing the incidence of restenosis after coronary angioplasty have become an important field of investigation in interventional cardiology. In general, the early results of medical treatments and interventions are relatively simple to assess, but the long-term studies frequently prove more difficult to evaluate and, historically, often have been unreliable. Early or preliminary results often have been misleading and frequently contradict those of well controlled definitive studies. It appears that innovators and exponents of new treatments may allow their enthusiasm to compromise their objectivity. Therefore, it is important that any new technique or pharmacologic treatment is assessed objectively using a methodology with known reproducibility and in which the technical limitations are known and understood.

Over the past 2 to 3 years, there has been a rapid increase in new devices and techniques designed to augment or replace conventional balloon angioplasty. With the progressive improvement in the immediate success rate and complication rate of the conventional procedure, it has become more difficult to demonstrate the additional efficacy of new devices and interventions. Any improvement in the immediate results may be, as it was with coronary artery bypass surgery in the past, misleading and, therefore, the attention of investigators has rightly turned from the immediate results to the long-term outcome. Restenosis after coronary angioplasty, a recognized late complication in 25% to 35% of cases since the introduction of the procedure in 1977 (1), remains its main limitation.

Despite the established importance of this topic, there has been no consensus on how these studies should be performed, with widely differing methodologic approaches giving diverse and conflicting results. Although the long-term clinical outcome will remain important in any assessment, the most objective means of assessing restenosis following angioplasty is by carefully controlled coronary angiography at the time of the procedure and at a defined follow-up time. In the past the visual estimation of the angiographic films has been used, but a consensus is now beginning to emerge that

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Table 1. Studies Addressing the Incidence of Coronary Restenosis

First Author and Ref	Year	Patients		Interval (mo) PTCA to Follow-Up	Restenosis Criterion	% Restenosis		
		Total	% Follow-Up					
Meyer (22)	1983	70	90	6	AS >85%	20		
Thorton (5)	1984	248	72	6-9	NHLBI 4	31		
Holmes (7)	1984	665	84	6.2	NHBLI 4	34		
Kaltenbach (14)	1985	356	94	5.6	DS <20% of pre-PTCA	12		
Levine (13)	1985	100	92	6	NHLBI 4	40		
Corcos (8)	1985	92	100	8.2	>70% DS at follow-up	18.5		
Leimgruber (6)	1986	1758	57	7	NHLBI 4	30		
Bertrand (23)	1986	229	Not reported	7	NHLBI 4	32		
Vandormael (3)	1987	129	62	7	≥20% reduction and ≥50% DS	33		
Studies addressing the timing and incidence of restenosis								
Serruys (9)	1988	400	85	1	≥0.72 mm	0.9		
				2	≥0.72 mm	12.4		
				3	≥0.72 mm	22.6		
				4	≥0.72 mm	25.5		
Nobuyoshi (2)	1988	185	81	24 h	NHLBI 4	14.6		
				229	100	1	NHLBI 4	12.7
				219	96	3	NHLBI 4	43.0
				149	65	6	NHLBI 4	49.4

AS = % area stenosis; DS = % diameter stenosis (mm); NHLBI 4 = criterion 4 of the National Heart, Lung, and Blood Institute (loss of ≥50% of gain); Ref = reference.

recognizes the limitations of this approach. The use of a quantitative angiographic measuring system for assessing both the immediate and the long-term results of therapeutic interventions such as angioplasty appears mandatory.

Methodologic Considerations

Currently there are many studies on coronary restenosis reported that are distinguished by their lack of consistency in their methodologic approach, their definition of restenosis and the reported factors influencing restenosis (Table 1). These studies are demanding in terms of time and financial resources and are also demanding on the patient because, at least for the time being, there is a need for repeat angiography even if the patient is asymptomatic. This is because of the reported incidence of silent restenosis, which may be as high as 33% if a sensitive enough index is used (2). Particularly with studies that look at the impact of a new intervention on restenosis, it is important that their design is capable of showing the effect of the intervention, if indeed one exists. Many of the studies published so far have failed to be sufficiently exacting to form a basis for their conclusions. In order to improve the situation, there are in principle three areas that need to be addressed:

1. *Study population.* If the results are intended to apply to the angioplasty population, then the study population must reflect this. This means a high angiographic follow-up rate with individual patient's time for restudy being predeter-

mined at the time of angioplasty, and not influenced by the recurrence of symptoms or the anatomy of the lesion after angioplasty. This will avoid a selection bias of symptomatic patients or patients with borderline postangioplasty results.

It can be estimated that if a 30% reduction in the restenosis rate is to be realized at the 0.05 significance level, then in a double-blind randomized study 400 patients will be needed in each of the placebo and active treatment groups. For a 50% reduction in restenosis rate, 150 patients will be needed in each group.

2. *A well validated system of analysis with known accuracy and variability should be employed.* The use of a visual percent diameter stenosis measurement with its inherent variability precludes meaningful results, and edge tracing by hand or other techniques that can produce values not physiologically possible are also unacceptable.

3. *The measured variables must be chosen so as to reflect the restenosis process and distinguish between the results of angioplasty and this process.* The conventional assessment of percent diameter stenosis is not sufficiently discriminating to do this, because, when there is a concomitant decrease in the reference or normal diameter of the vessel, a smaller lumen may have a larger measured percent diameter stenosis.

Angiographic Definitions of Restenosis

Limitations of criteria to define restenosis. The definition of restenosis of choice has been the subject of much debate,

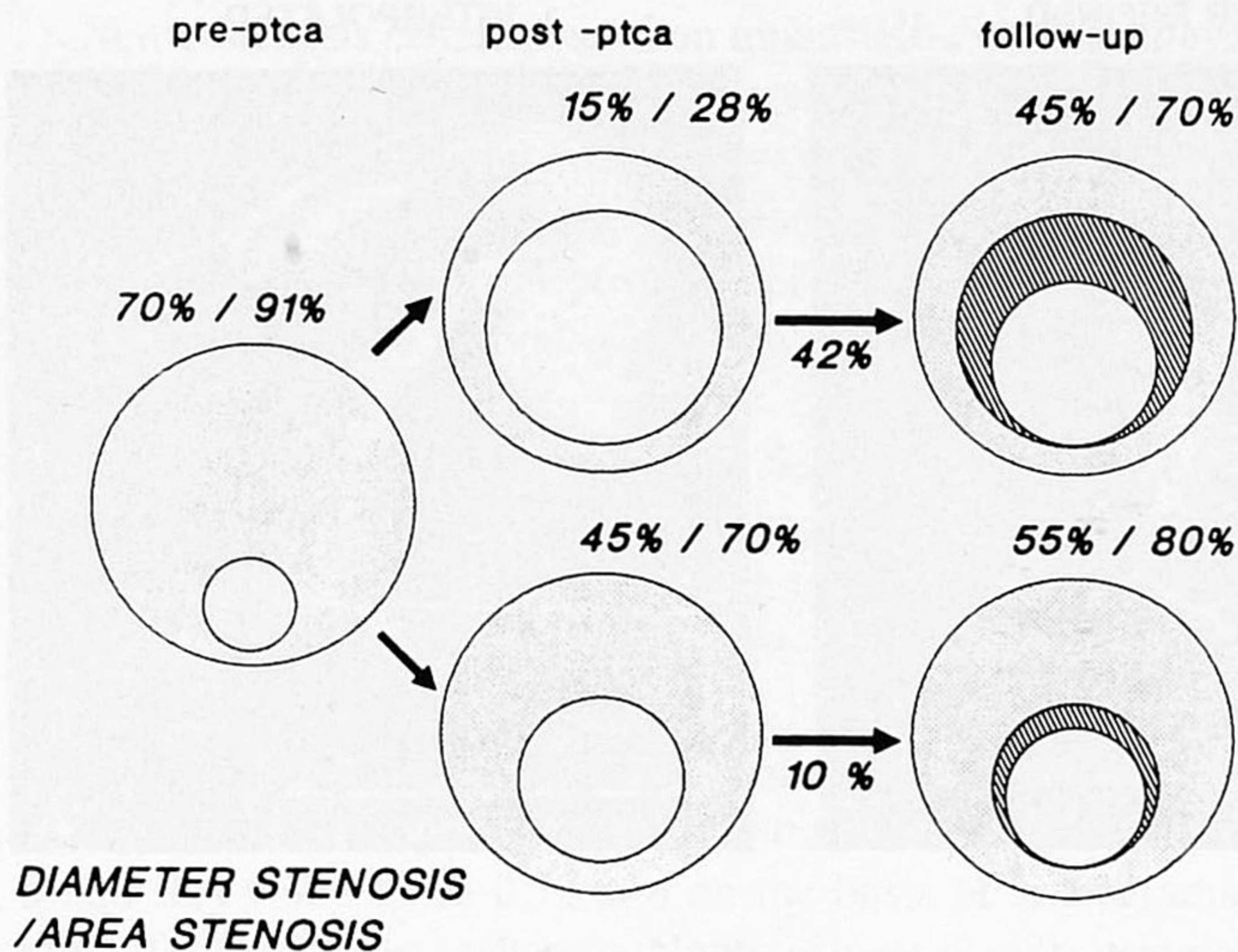


Figure 1. Shown in terms of cross-sectional area are two possible outcomes of an initially severe lesion after coronary angioplasty (PTCA). On the **left**, the lesion before angioplasty with a 70% diameter stenosis (area stenosis = 91%). **Middle**, a good result, represented by the upper profile leads to a 15% diameter stenosis (area stenosis = 28%). At follow-up (**right**), there has been a 42% change in the area of stenosis represented by the shaded area in the **top circle**. Although there is a considerable increase in the plaque cross-sectional area, the follow-up diameter stenosis is only 45% and, therefore, using the criterion of >50% diameter stenosis at follow-up, this is designated as not being a restenosis. In contrast, the lesion represented on the **bottom**, which is successfully dilated, but to a lesser degree (45% diameter stenosis after angioplasty), will be designated as restenosis if there is even a small deterioration in the plaque area (change in diameter stenosis of 10%) resulting in a follow-up diameter stenosis of 55% (percent diameter stenosis/percent area stenosis).

and there is currently no satisfactory definition that takes into account both the functional and the angiographic outcome of the patient after angioplasty. The confusion and controversy that surround the subject of restenosis are essentially due to four factors:

1) Many angiographic definitions try to combine the angiographic outcome with a clinical outcome. The known discrepancy between these two variables means that this objective will not be realized, particularly in multivessel disease (3).

2) A single "stenosis" measurement should not be confused with a measurement of "restenosis," which should represent the change in stenosis severity.

3) Criteria that are defined by a cut-off value at follow-up or that are biased by the improvement in lesion diameter obtained at angioplasty will preselect those lesions with a less satisfactory result postangioplasty. The definition of a $\geq 50\%$ diameter stenosis at follow-up is used to illustrate this point in Figure 1.

4) Definitions based on percent diameter stenosis measurements may fail to identify lesions undergoing significant

deterioration. These criteria are chosen to reflect the change in minimal luminal diameter in relation to the so-called normal diameter of the vessel in the immediate vicinity of the obstruction. It also assumes that this normal diameter (or the reference diameter) of the vessel, proximal or distal to the obstruction, does not change either as a result of angioplasty or during the immediate follow-up period when restenosis of the dilated lesion is a well recognized phenomenon. Quantitative angiographic studies have shown this premise to be false. This seriously questions the use of percent diameter stenosis as the only index of restenosis (2,4).

Figure 2 illustrates how the choice of reference diameter may influence the assessment of restenosis in what is a relatively simple segment to analyze. The choice of reference diameter, whether interpolated, proximal or distal, has little effect on the percent diameter stenosis in the examples before (Fig. 2A) or after (Fig. 2B) angioplasty because the reference diameter is similar in all cases. In contradistinction, the choice of reference diameter is highly relevant to the determination of the percent diameter stenosis at follow-up (Fig. 2C), largely because of the discrepancy between the reference diameter proximal to the stenosis and the one distal to it. The "moving baseline" created by the fact that the reference diameter may decrease means that lesions that should be regarded as restenosis may not be.

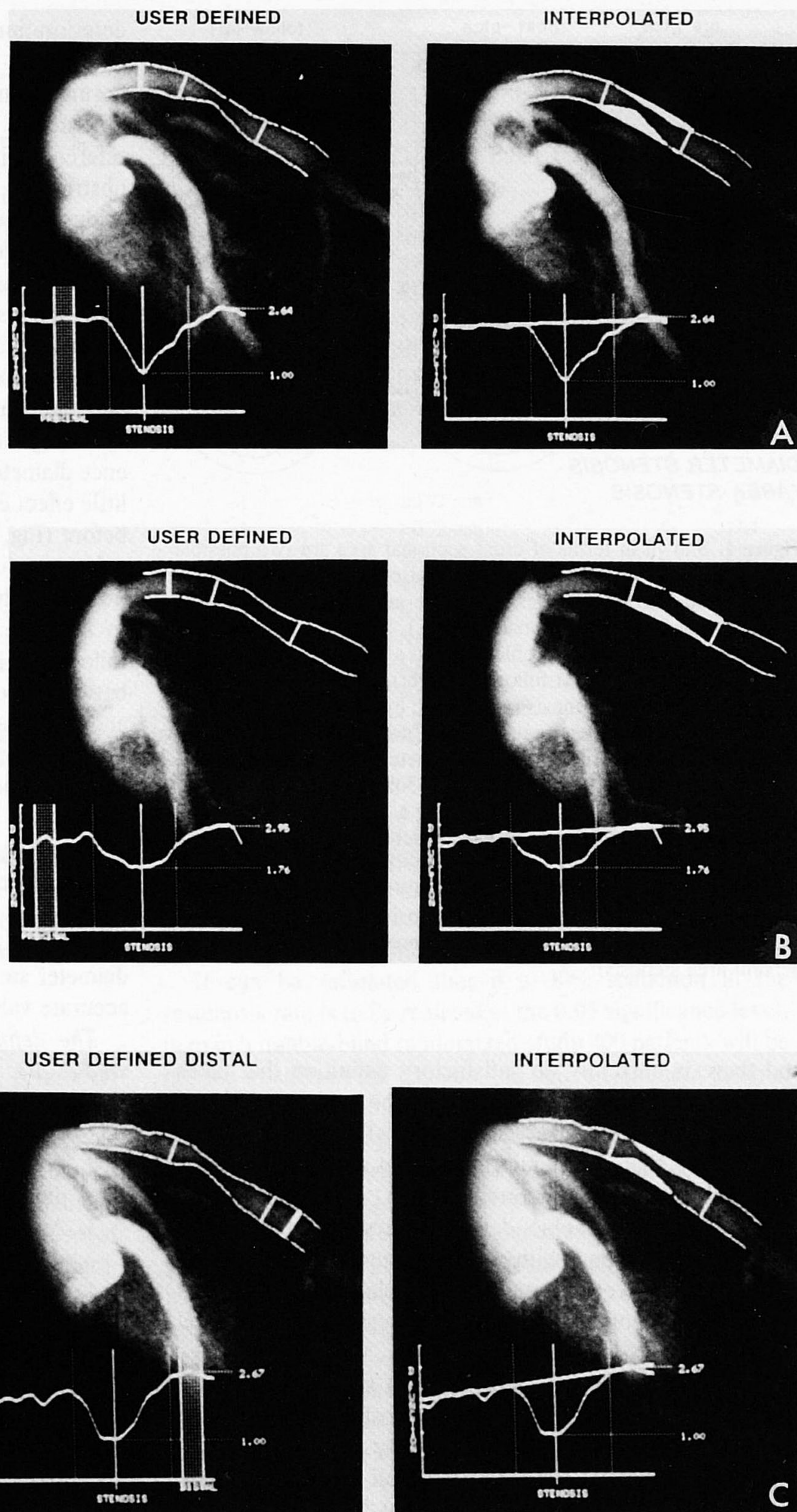
Criteria of restenosis in current use. What is the rationale for the restenosis criteria in current use? Most are entirely arbitrary, some are based on doubtful logic and some, although of some relevance for visual estimation of percent diameter stenosis, are unrealistic when applied to the more accurate values obtained from quantitative angiography.

The definitions of restenosis used in major restenosis studies are:

1. Loss of at least 50% of the initial gain achieved at angioplasty (5).
2. A return to within 10% of the preangioplasty stenosis diameter (6).
3. An immediate postangioplasty stenosis diameter of <50% that increases to $\geq 50\%$ at follow-up (6,7).
4. As for 3, but for a stenosis diameter $\geq 70\%$ at follow-up (8).
5. Deterioration of 0.72 mm in minimal luminal diameter or greater from immediately postangioplasty to follow-up (9).
6. Deterioration of 0.5 mm in minimal luminal diameter or greater from immediately postangioplasty to follow-up (2).

Examining the commonly used definition of $\geq 50\%$ stenosis diameter at follow-up. This is based historically on the physiologic concept of coronary flow reserve and is taken because it represents the approximate value in animals with normal coronary arteries at which a blunting of the hyperemic response occurs (10). Although this value may be of

Figure 2. Single frame angiograms of a proximal left anterior descending artery stenosis. **A**, predilation (PRE-PTCA), **B**, postdilation (POST-PTCA) and **C** at follow-up. Quantitative coronary analysis was performed using a coronary angiography analysis system. The arterial boundaries detected by the system are shown on the angiogram and below the diameter function curve derived from these contours. The example illustrates the importance of the choice of reference diameter, the fact that the dilated but nonstenotic coronary artery may be involved in the restenosis process, and the value of the interpolated reference diameter for calculating the appropriate diameter stenosis. **A**, Before angioplasty, the lesion is relatively easy to analyze. The segments proximal and distal to the stenosis are of similar caliber and the lesion is relatively discrete, so that its length can easily be defined on the diameter function curve. **B**, After angioplasty, there is a satisfactory result, the diameter stenosis decreasing from 59% to 36% (area stenosis from 83% to 59%). **C**, At follow-up, the result is very dependent on the method of analysis. The artery proximal to the stenosis has already been involved in the restenosis process; if this is chosen as a reference diameter (**left**), a 42% diameter stenosis is obtained (no "restenosis"). The distal portion is of a larger caliber than the proximal portion; if it is chosen as a reference diameter (**middle**), the result is a 62% diameter stenosis ("restenosis"). If the interpolated technique is used (**right**), the reference diameter is similar to the postangioplasty value, and a 58% diameter stenosis is obtained that accurately reflects what is happening between the postangioplasty result and the follow-up. Even with this high quality angiogram of a well visualized segment with a discrete stenosis, there are problems in obtaining accurate and realistic results.



some relevance in determining a significant stenosis in human atherosclerotic vessels, it tells us nothing about the way the lesion has behaved since the angioplasty procedure. It is clear from Figure 1 that no criterion defining the

restenosis as such can include the second example and not the first. Similar arguments concerning a bias in selection can be applied to the other commonly used definition of a loss >50% of the gain.

New restenosis criteria based on quantitative angiography.

As a result of quantitative angiographic studies, a new concept for defining restenosis criteria based on the change in minimal luminal diameter has been introduced (9). The change in this value from postangioplasty to follow-up can be expected to give a good quantitative measurement of the degree of restenosis. The restenosis criterion or the cutoff point dividing the restenosis group from the nonrestenosis group is then derived by determining the variability of measurement (1 SD of the difference in means) of the same lesion taken from separate catheter sessions. Twice the variability (95% confidence intervals) defines with reasonable certainty those lesions that have undergone significant deterioration from those that have not. Reiber et al. (11) found this value to be 0.72 mm on the basis of angiograms taken 90 days apart, whereas Nobuyoshi et al. (2), using a different measurement system, have taken 0.5 mm on the basis of angiograms taken 7 to 10 days apart. It is important to realize that the variability will be considerably greater for angiograms taken from repeat catheterization sessions, as opposed to repeat angiograms from the same session (11), something that has not been appreciated by all investigators using this methodology (12).

Criteria based on the absolute change in minimal luminal diameter are nevertheless limited because they make no attempt to relate the extent of the restenosis process to the size of the vessel. What may be a significant increase in plaque area in a 1.5 mm diameter vessel may be of no hemodynamic consequence in a larger vessel of 3.5 mm. Studies need to be undertaken to assess the variability of measurement in different diameter vessels, and a "sliding scale" criterion created that adjusts for vessel size.

Incidence of Restenosis

Role of defined criteria of restenosis. In the same way as the method of analyzing an angiographic frame will influence the measurement of percent diameter stenosis, so it will influence the restenosis rate. However, the factor that most influences the rate is the definition of restenosis used. Figure 3 shows the number of lesions fulfilling three criteria of restenosis: although 43 of the lesions included by at least one criterion are included by all three, 32% of those included in one criterion ("a loss of greater than half the gain") are not included in either of the other two. Despite this discrepancy, the incidence of restenosis is not too dissimilar, ranging from 21% to 34% (Fig. 4). What should be clear is that a similar incidence of restenosis with different criteria may be defining different populations. This point has particular relevance when determining the risk factors for restenosis: if restenosis cannot be reliably determined, then it is unlikely that the associated risk factors will be identified. The most sensitive index of restenosis in common use is that of a loss of $\geq 50\%$ of the gain, with reported incidence rates ranging from 16%

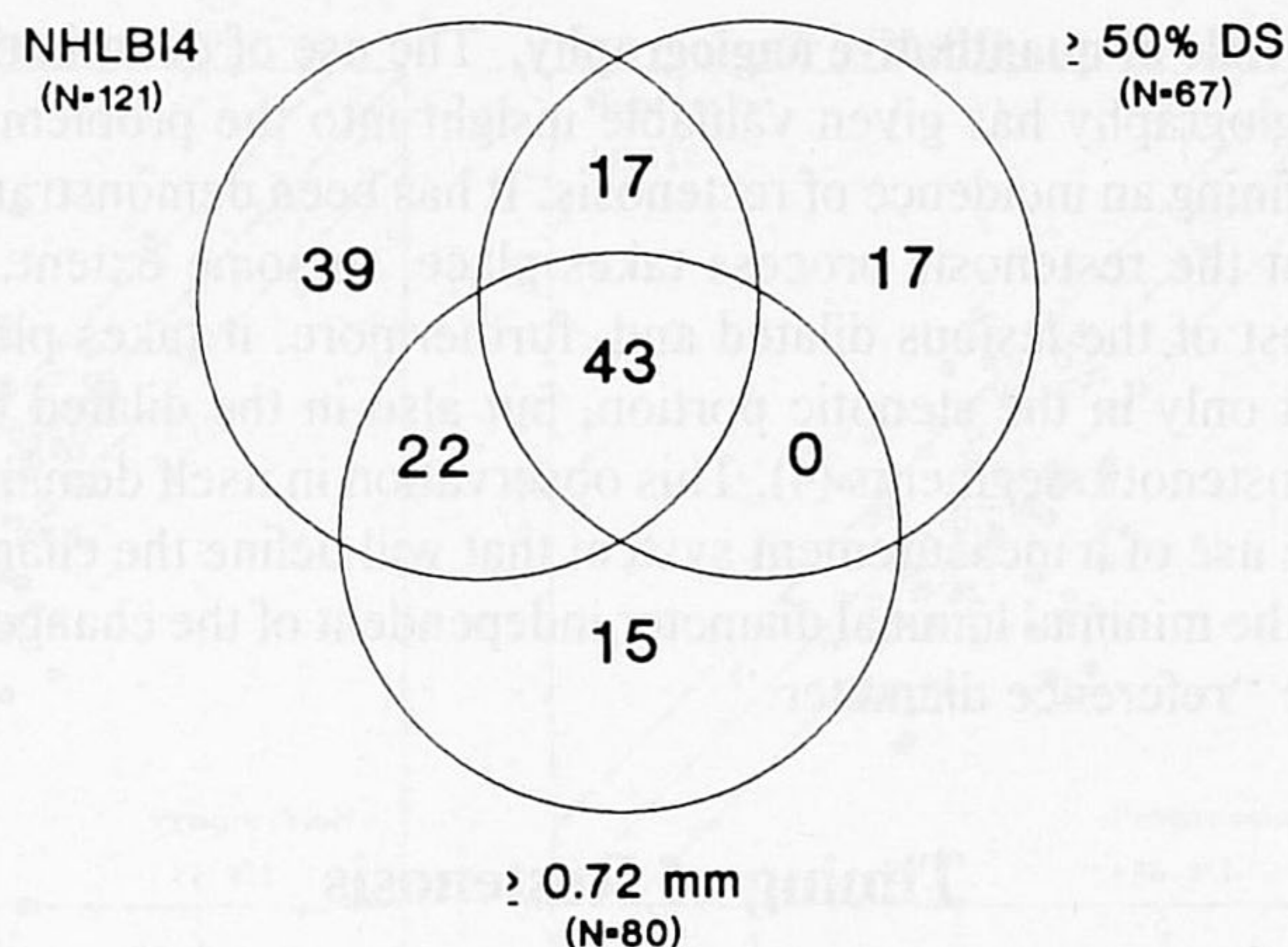
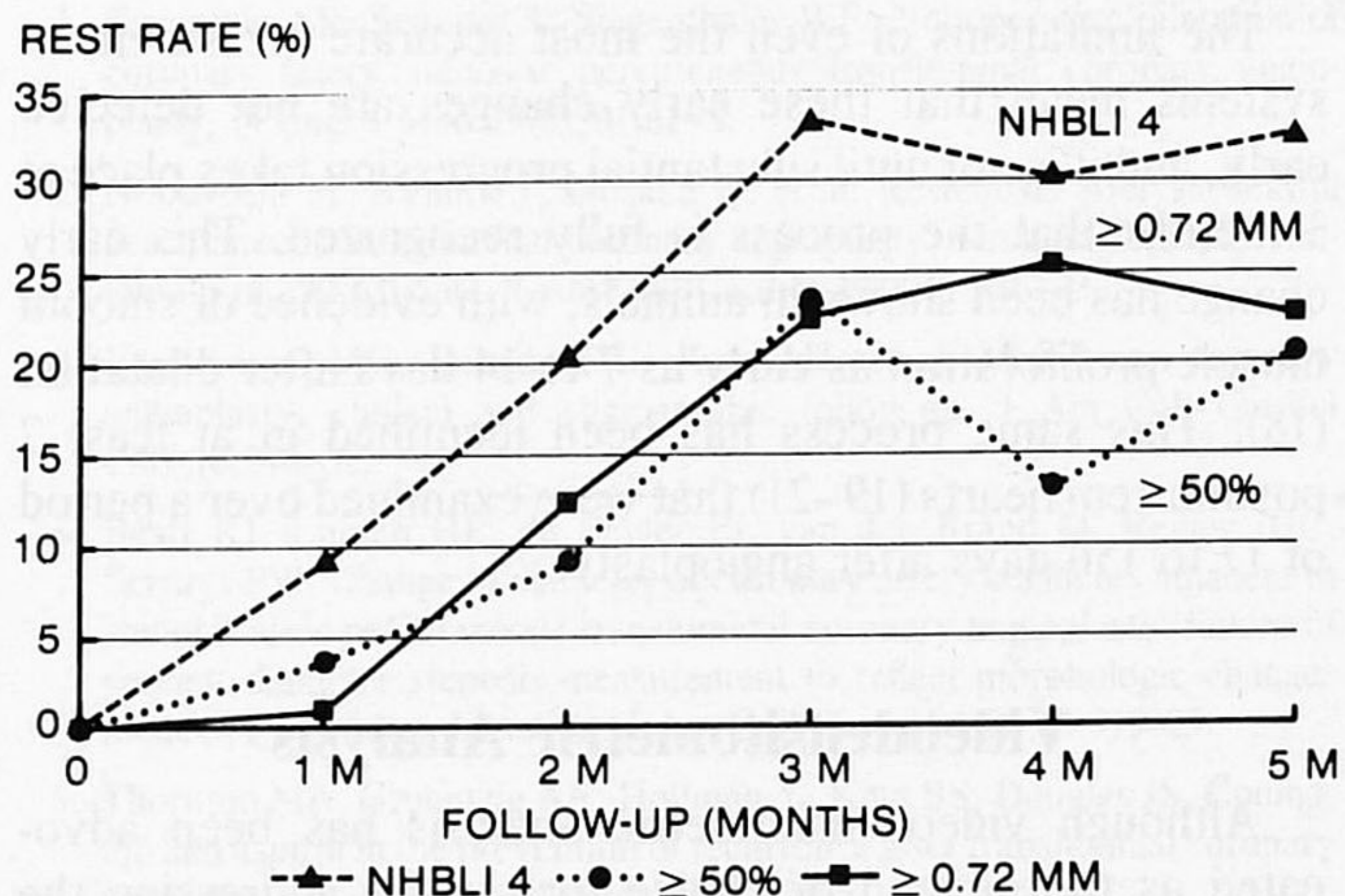


Figure 3. The number of lesions fulfilling three restenosis criteria, taken from a group of 490 lesions measured at follow-up within 6 months. The total number of lesions that fulfill each criterion are shown under the criteria, and those lesions fulfilling that criterion and none other are enclosed by only one circle. Lesions included by any two criteria are enclosed by two circles, and lesions that fulfill all three criteria (n = 43) are enclosed by all three circles. It can be seen that lesions that are designated as restenosis are highly dependent on the criteria for restenosis employed. NHLBI4 = criterion 4 of the National Heart, Lung, and Blood Institute: loss of $>50\%$ of the gain at angioplasty. $\geq 50\%$ DS = $\geq 50\%$ diameter stenosis at follow-up. ≥ 0.72 mm = ≥ 0.72 mm change from postangioplasty to follow-up.

to 52% (2,5,6,9,13). On the other hand, $\geq 50\%$ diameter stenosis at follow-up will tend to give a lower incidence of restenosis because lesions that deteriorate significantly, but remain within the 0 to 49% range, are not designated as restenosis. Of the two studies with larger numbers that document the change in minimal luminal diameter, only one uses this value to derive a restenosis value of 26% at 4 months (9).

Figure 4. Incidence of restenosis (REST) according to three criteria in the first 150 days after angioplasty derived from the patient group with 490 successfully dilated lesions shown in Figure 3. Abbreviations in Figure 3.



Role of quantitative angiography. The use of quantitative angiography has given valuable insight into the problem of defining an incidence of restenosis. It has been demonstrated that the restenosis process takes place, to some extent, in most of the lesions dilated and, furthermore, it takes place not only in the stenotic portion, but also in the dilated but nonstenotic segments (4). This observation in itself demands the use of a measurement system that will define the change in the minimal luminal diameter independent of the change in the "reference diameter."

Timing of Restenosis

It has been clear for some time that restenosis most often takes place within the first 6 months after dilation (7,14). Further progression after this time is unusual, with lesion improvement or deterioration occurring in a small number of instances, a pattern more characteristic of coronary artery disease in general (15-17). Recently two reported studies (2,9) performing follow-up angiography at different preselected follow-up intervals gave remarkably similar results and showed more precisely how the lesion behaves after angioplasty. Early after angioplasty, within 30 min, "recoil" may take place, which in principle should be regarded as a separate problem from that of the restenosis (Fig. 5). This decrease in the luminal diameter may be exaggerated by a vasoconstrictive component if vasodilators are not administered after the angioplasty procedure. The recoil, together with remodeling and possibly thrombus formation, results in "restenosis" in 11% to 16% of the lesions in the first 24 h (using the National Heart, Lung, and Blood Institute definition 4 of restenosis) (2). It then appears that healing and remodeling may lead to improvement in an appreciable number of lesions, so that at 30 days the restenosis rate lies between 6% and 13%. Between 1 and 3 months, most lesions that will develop restenosis do so, with the restenosis rate reaching 25% to 37% (Fig. 6). A small number may show further progression between 4 and 6 months. It seems likely that the restenosis process begins early and is progressive over the first 3 to 4 months.

The limitations of even the most accurate measurement systems mean that these early changes are not detected early, and it is not until substantial progression takes place at 3 months that the process is fully recognized. This early change has been shown in animals, with evidence of smooth muscle proliferation as early as 7 to 14 days after dilatation (18). This same process has been identified in at least 7 postmortem hearts (19-21) that were examined over a period of 17 to 150 days after angioplasty.

Videodensitometric Analysis

Although videodensitometric analysis has been advocated as the method of choice for studies addressing the

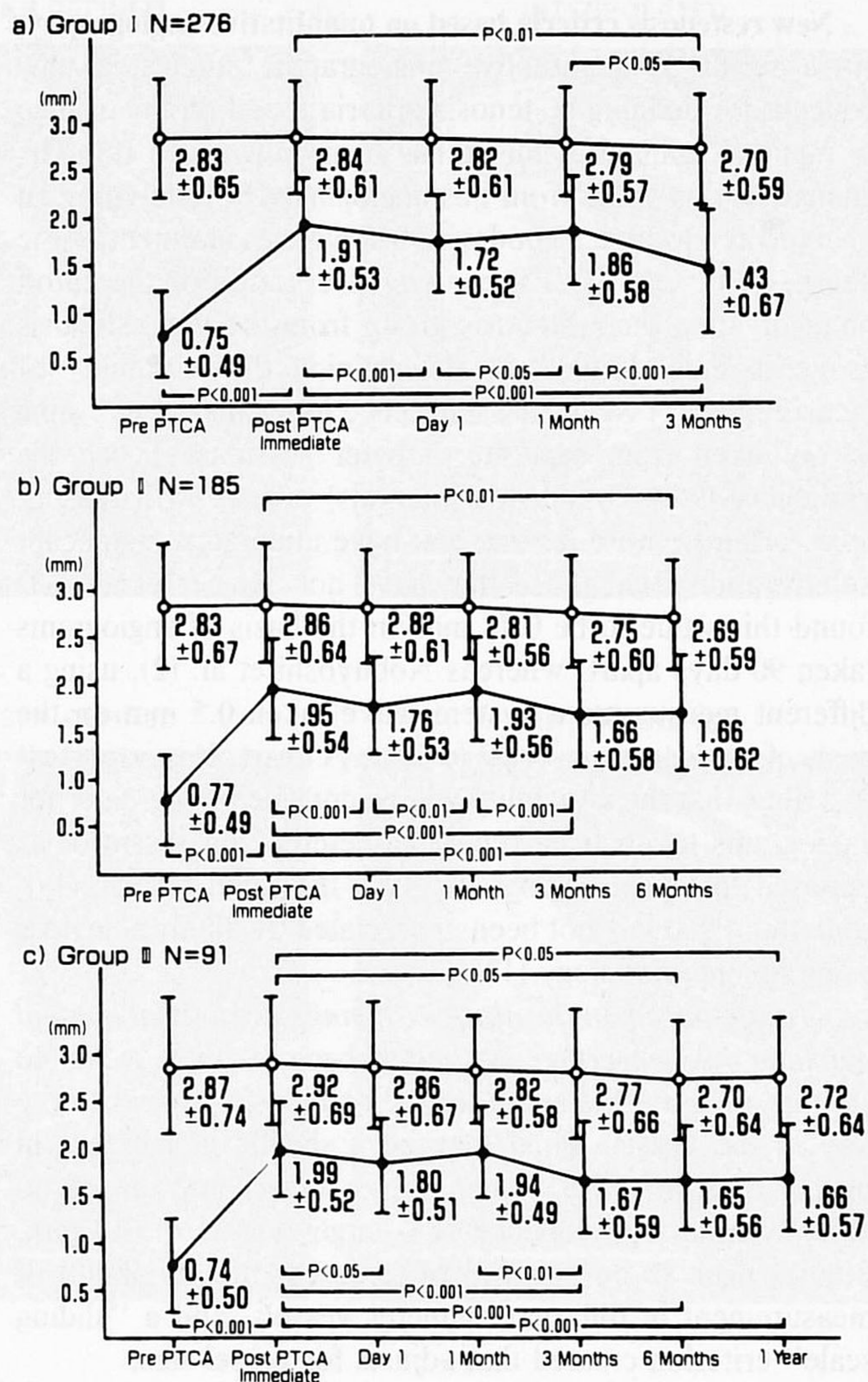
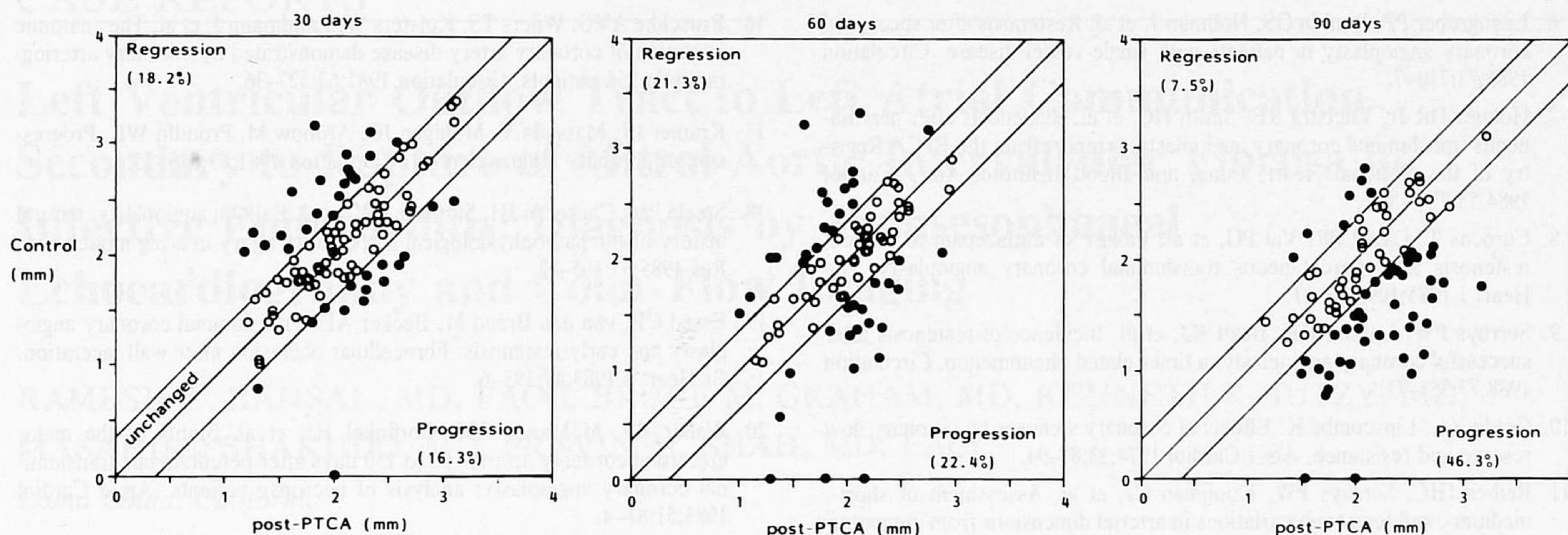


Figure 5. Serial changes in the absolute diameter of normal (open circles) and stenotic (closed circles) segments after coronary angioplasty (PTCA) for three follow-up groups. Group I = 3 month angiographic follow-up, Group II = 6 month angiographic follow-up, Group III = 1 year angiographic follow-up. The change in both the normal (○) and stenotic (●) segments with time are illustrated. Most of the deterioration in the stenotic segments occurs between 1 and 3 months, whereas there is a less pronounced steady deterioration in the nonstenotic segments up to 6 months. (Reprinted with permission from Nobuyoshi et al. [2]).

problem of restenosis, it has not proved practical in large studies. The technique is promising, but the number of lesions that can be analyzed effectively by this technique is limited, and the use of the videodensitometric technique would mean that a significant number of patients undergoing routine angioplasty (>10%) would be excluded from restenosis studies. Future developments may mean that this method, which is potentially easier to perform and requires only one angiographic projection to obtain a three-dimensional representation, will become the method of choice for restenosis studies.



Risk Factors for Restenosis

Identifying the risk factors. There are no studies using quantitative coronary angiography that report on the risk factors in large numbers of patients. There are some factors relating to the restenosis process that have been identified and confirmed in more than one study. These include a proximal left anterior descending coronary artery stenosis, a totally occluded vessel before angioplasty, the presence of collateral vessels supplying the distal part of the dilated coronary artery and associated insulin-dependent diabetes. Factors that relate to the success of the angioplasty, such as a residual stenosis >30% or 40%, with current knowledge should not be considered as risk factors for "restenosis." For most of the other described risk factors, there are as many studies that do not as studies that do identify a particular factor. No procedure-related factor, that would allow the operator to modify the way angioplasty is performed has yet been identified, and no pharmacologic intervention has been able to show a reduced rate of restenosis. Quantitative angiography offers the possibility of objective measurement of lesion morphology, such as length of lesion and eccentricity, and when this more objective information becomes available, then perhaps it will be possible to identify lesion-related factors associated with restenosis.

Role of quantitative angiography in evaluating new procedures and interventions. To date, quantitative coronary angiography has been used in a limited number of studies addressing the problem of restenosis. It has already provided valuable insight into the restenosis problem and has identified some of the sources of confusion surrounding this topic. It seems likely that, with better measurement systems, particularly those that become on-line in the catheterization laboratory, it will be easier to perform these studies, and with more reliable data in smaller numbers of patients, the effect of various interventions to prevent restenosis will be assessed more accurately and more efficiently. Currently there is a wide variety of revascularization devices, procedures and pharmacologic interventions under investigation,

Figure 6. Individual minimal luminal diameter (mm) after coronary angioplasty (PTCA) compared with the control angiographic study for three different groups at 30, 60 and 90 days. The two solid lines on either side of the identity line correspond to the long-term variability (0.36 mm) of repeat measurement for this variable (5). This variability is 1 standard deviation of the difference in means of duplicate angiographic measurements. Therefore, 2 standard deviations ($2 \times 0.36 = 0.72$ mm) define the 95% confidence limits for lesion progression or regression. The lesions showing progression or regression is represented by closed circles, and the numbers are shown in the brackets in the left upper and right lower corners.

and of crucial importance in their evaluation will be the restenosis rate associated with each of these strategies. It is already clear that a meaningful comparison among the various strategies and evaluation of their relative merits is not possible because of a lack of standardization of methodology and lack of objectivity. In the future, we should demand that quantitative analysis be employed in important studies addressing the long-term outcome of new coronary interventions, so that the present confusion is not perpetuated.

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