Restenosis revisited: Insights provided by quantitative coronary angiography

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Since its inception as a specialist discipline, interventional cardiology has been and still is preoccupied with the achievement of a greater understanding and ultimately control of the biologic healing process after percutaneous transluminal coronary angioplasty (PTCA),[1, 2] the apparent enigma of "restenosis." Introduction and application of a wide variety of alternative and adjunctive treatment modalities (endoluminal coronary stent implantation,[3] directional, extractional, or rotational[4-6] atherectomy, laser balloon angioplasty,[7] and laser angioplasty[8, 9] and a wide variety of pharmacologic agents have, thus far, failed to suppress this ubiquitous process.[10-16]

Proceeding with trepidation through the veritable jungle of already available and rapidly proliferating literature on this subject, it is noteworthy that there are perhaps only three observations that are universally held: (1) the attribution of initiation of percutaneous coronary intervention to Dr. Andreas Gruentzig; (2) that this approach to therapy of coronary artery obstructions has become "widely accepted" despite that its inaugural use was only in September 1977[17]; and notwithstanding (3) the apparently inescapable biologic phenomenon of restenosis (the third universal tenet). The unbiased reader will consider it surprising that a treatment modality that was tentatively incorporated into clinical practice marginally more than a decade past and is attended by a "recurrence rate" of 12% to 55% within 6 months (Fig. 1) is already widely accepted, especially because there is no hard evidence that longevity can be improved. (Only since 1987 have formal, randomized prospective studies been initiated to compare PTCA and coronary artery bypass grafting [CABG] in terms of effect on long-term morbidity and mortality; thus objective results will not be available for some time.)

Innovators and exponents of new treatment modalities may allow their enthusiasm to compromise their objectivity, which probably explains why many interventionalists armed with the latest device acquire the expertise to use it largely through self-training techniques and assess its impact by clinical observations in the short term, allowing their judgment to be influenced more by anecdotal experience than by the results of carefully controlled prospective clinical studies. The value of all new treatment modalities must be submitted to objective and critical assessment through such studies by using the best available methodological analytical techniques. The advent of computer-assisted quantitative coronary angiography[18-20] has demonstrated the fallibility of traditional visual and user-dependent techniques for assessment of the coronary cineangiogram,[21] on which most of, if not all, the early reports on restenosis after angioplasty are based. Tenets founded on the results of early clinical studies must, therefore, be reexamined in the light of new revascularization and imaging technology, and we must be prepared to consider potential changes in basic philosophic and methodological approaches to both the treatment of coronary disease and evaluation of outcome after treatment as a consequence of fresh insights provided.

In the following paragraphs we review restenosis from the angiographic point of view because it is

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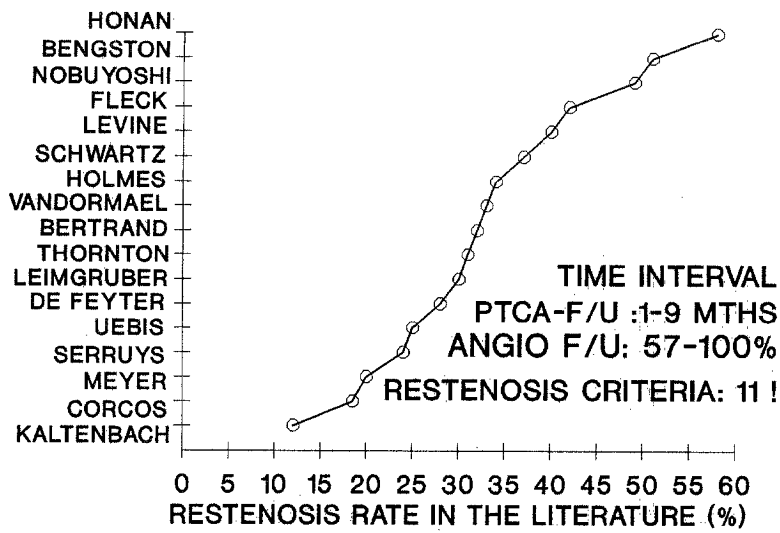

Fig. 1. Nonscientific figure depicting restenosis rates from selection of published studies with different angiographic follow-up rates (57%-100%), follow-up intervals (1-9 months), 11 different restenosis criteria, and various angiographic analysis techniques.

Table I. Angiographic definitions of restenosis that have been used in various clinical studies. NHLBI 1, 2, 3, and 4 are criteria for angiographic restenosis, as laid out by the National Heart, Lung, and Blood Institute of the United States

1. A diameter stenosis ≥50% at follow-up.[22]
2. An immediate post-PTCA diameter stenosis <50% that increases to ≥50% at follow-up.[23, 26]
3. As for 2, but a diameter stenosis ≥70% at follow-up (NHLBI 2).[24]
4. Loss during follow-up of at least 50% of the initial gain at PTCA (NHLBI 4).[25]
5. A return to within 10% of the pre-PTCA diameter stenosis (NHLBI 3).[26]
6. Loss ≥20% diameter stenosis from post-PTCA to follow-up.[27]
7. Loss ≥30% diameter stenosis from post-PTCA to follow-up (NHLBI 1).[23]
8. A diameter stenosis ≥70% at follow-up.[28]
9. Area stenosis ≥85% at follow-up.[29]
10. Loss ≥1 mm^2 in stenosis area from post PTCA to follow-up.[30]
11. Loss ≥0.72 mm in minimal luminal diameter from post-PTCA to follow-up.[31]
12. Loss ≥0.5 mm in minimal luminal diameter from post-PTCA to follow-up.[32]
13. Diameter stenosis >50% at follow-up with >10% deterioration in diameter stenosis since PTCA of a previously successfully dilated lesion (defined as diameter stenosis <50% with a gain of >10% at PTCA).[33]

through this medium that most research has been performed and angiography is still the only universally used objective clinical tool for evaluation of immediate and long-term results of intervention. In this vein we briefly outline the main discrepancies in the restenosis literature and discuss the impact of quantitative coronary angiographic studies on understanding of the restenosis process. We describe some new conceptual approaches to the study of restenosis that we have developed through our own experience in clinical studies, with serial computer-assisted quantitative coronary angiographic analysis (in patients treated by balloon angioplasty, directional atherectomy, and stent implantation) and compare these approaches with findings of other groups. Through these new approaches we have attempted to bridge the gap from angiography to pathology and have explored the theoretic relationship between vessel wall injury at intervention and subsequent restenosis. The ultimate aim of this article is to propose the use of the approach described here as a kind of unifying strategy to studying the restenosis phenomenon through coronary angiography to resolve the currently differing methods.

RESTENOSIS: UNCERTAINTIES AND DISCREPANCIES IN DEFINITION CRITERIA

The first step to improved understanding of the restenosis phenomenon is an accurate, meaningful, and universally accepted definition. Unfortunately, at this time no such agreement exists, and there have been at least 13 different definitions based on coronary angiographic findings and applied by various clinical investigators attempting to address the problem of restenosis through clinical studies in recent years (Table I).[22-33] Most of these are arbitrary categoric cut-off points and, although some are based on

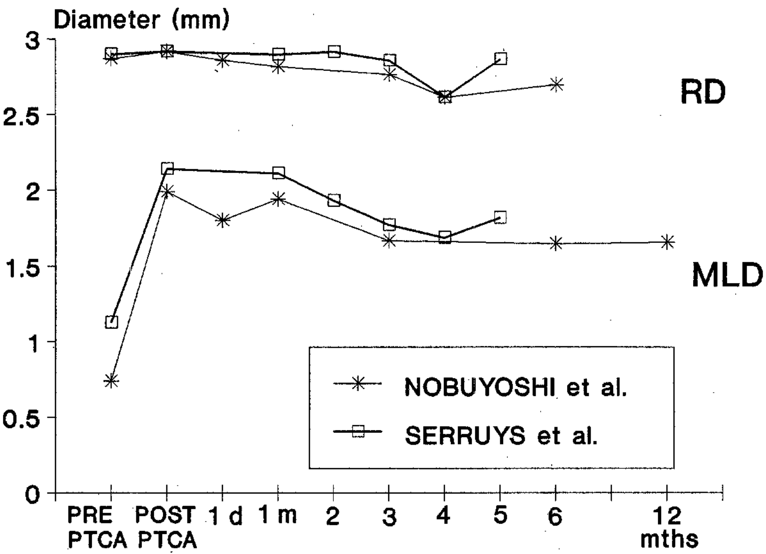

Fig. 2. Graphic representation of MLD and reference diameter *(RD)* values as reported in studies of Nobuyoshi et al.[32] and Serruys et al.[31] showing virtually identical time trends during 6-month follow-up. (From Serruys et al. J Intervent Cardiol 1991;4:265-76.)

historical physiologic concepts,[34] the measurement used is percent diameter stenosis, which is inherently flawed by the method of its computation, as we describe later. Furthermore, a single cut-off point cannot accurately describe what is essentially a "moving target" (Fig. 2), as has been independently demonstrated almost simultaneously by our group[31] and Nobuyoshi et al.[32] By using predetermined serial angiographic follow-up at 1, 2, 3, and 4 months (Nobuyoshi et al. carried out additional angiography at 6 and 12 months), both groups showed that some degree of renarrowing occurs in most dilated lesions and is a time-related phenomenon developing in the first 4 months after therapy and rarely progressing after 6 months.

Percent diameter stenosis is traditionally calculated by assuming a normal diameter value for a segment of coronary vessel immediately proximal or distal to area of interest as a reference point. This assumption has been shown to be erroneous, particularly in the context of multivessel disease, when there is virtually always diffuse intimal and/or subintimal thickening[35, 36] and variable age-related or compensatory ectasia,[37] and after interventions when the reference diameter becomes involved in the restenosis process.[38-40] In recent years quantitative angiographic studies have clearly and definitively revealed that absolute luminal measurements such as minimal luminal diameter (MLD) or minimal cross-sectional area of coronary narrowings provide more reliable and meaningful information than percent diameter stenosis with regard to hemodynamic significance of an obstructive coronary lesion.[41-45]

To circumvent the potential for inaccuracy with respect to percent diameter stenosis measurements calculated by using an arbitrarily selected reference segment by the observer, the computer-based Cardiovascular Angiographic Analysis System (CAAS) (described further later) generates the interpolated reference diameter.[20, 44, 45] The contour detection algorithm reconstructs how the arterial borders of the segment of interest should appear in the disease-free state by the technique of interpolation. According to this process, the actual lesion itself (obstructed region/segment) is excluded by using the curvature analysis, which detects the proximal and distal ends of the lesion (this process may be less accurate in diffusely diseased vessels than where there is a discrete stenosis). Then, in a continuous fashion, on the basis of the detected contours of the proximal and distal segments and allowing for anatomic vessel tapering, by using a second-degree polynomial function, the arterial contours over that segment are interpolated. The measurement taken as the reference diameter, then, is the interpolated reference diameter (from the so-called diameter function curve) at the site of the minimal luminal diameter (Fig. 3). The theoretic basis of and actual mathematic steps involved in this process have been described in detail in technical publications in the past, and their intricacies are beyond the scope of this article.

Fig. 4 illustrates the potential pitfalls of the arbitrary selection of proximal and/or distal coronary segments as a reference point and how a more objective measurement of percent diameter stenosis can be derived by using the interpolated reference diameter.

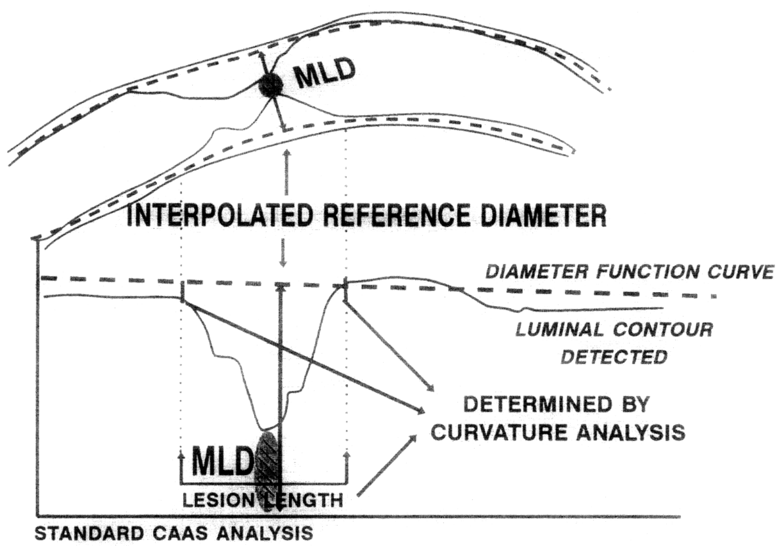

Fig. 3. Graphic representation of CAAS measurement of interpolated reference diameter. Actual luminal contour is detected by edge detection technique. Proximal and distal extremities of obstructive lesion are determined from curvature analysis of detected contour; thus identified lesion is then excluded from determination of interpolated reference diameter. Second-degree polynomial function is applied to diametric measurements made from each scan line (every 0.1 mm) of segment proximal and distal to lesion; anatomic vessel tapering is taken into consideration and vessel contours in area of lesion are reconstructed and interpolated into diameter function curve (shown as *dashed line* in analysis and corresponding upper and lower vessel contours). Actual interpolated reference diameter used then is diametric measurement, from diameter function curve, at point of minimal luminal diameter, as shown.

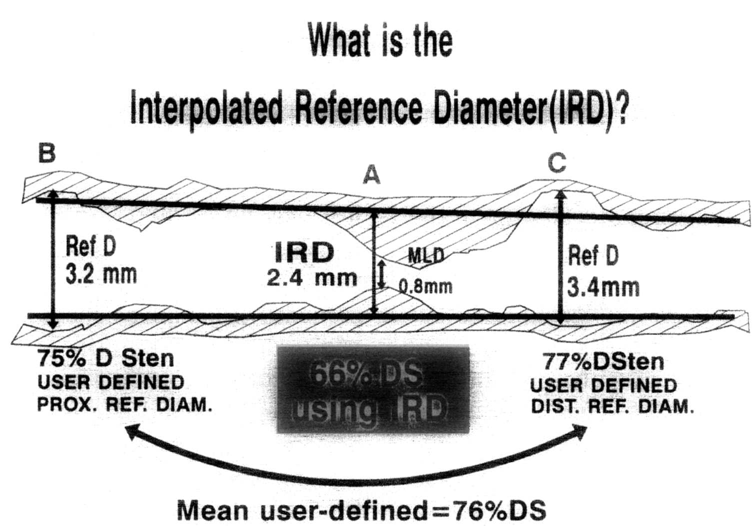

Fig. 4. Variability in percent diameter stenosis measurements of same lesion as a result of arbitrary selection of reference diameter by "user," and more objective derivation of percent diameter stenosis by user-independent method of interpolated reference diameter *(IRD)*. For stenosis where minimal luminal diameter is measured at 0.8 mm, if user-defined proximal or distal reference segment or mean of both is selected then resultant measure of percent diameter stenosis for obstructing lesion is 75%, 77%, or 76%, respectively. If computer-determined interpolated reference diameter (shown as upper and lower thick dark lines) is used, diameter stenosis measurement of 66% is obtained. *Prox ref diam*, Proximal reference diameter; *dist*, distal; *%DSten*, percent diameter stenosis. (From Serruys P, et al. J Intervent Cardiol 1991;4:265-76.)

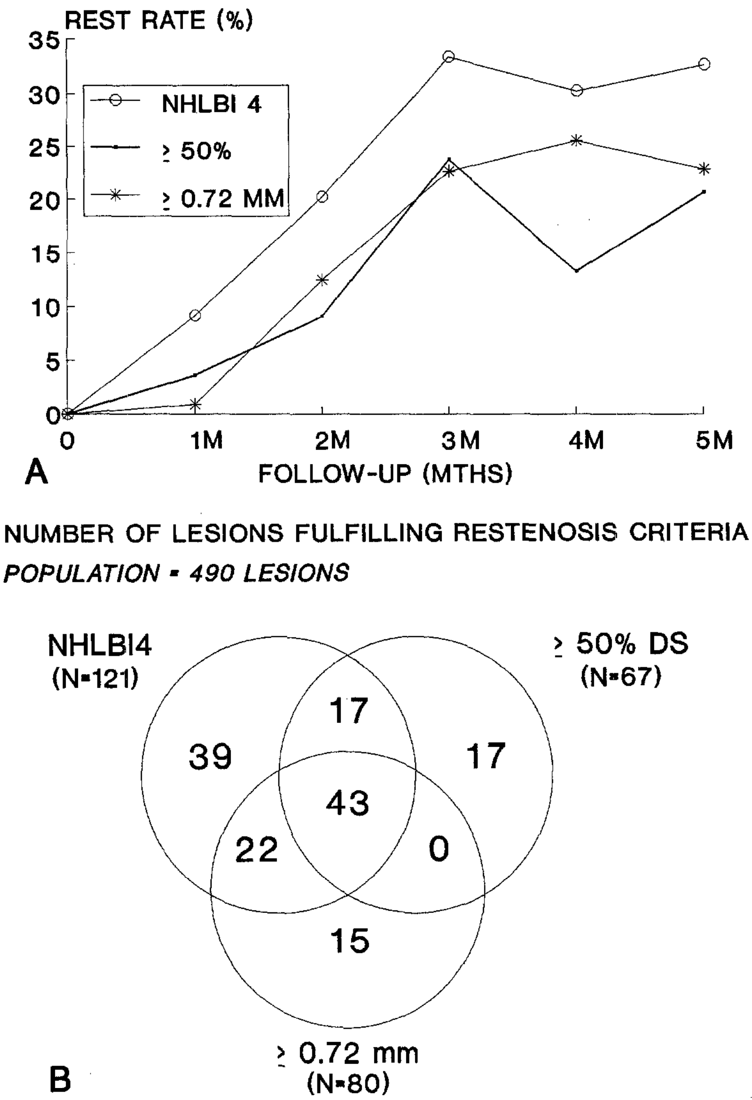

Fig. 5. A, Cumulative incidence of restenosis during 5-month *(MTHS)* follow-up period as defined by three different criteria among 490 successfully dilated lesions. *NHLBI 4,* Criterion 4 of National Heart, Lung and Blood Institute of America: loss of >50% of initial gain at angioplasty; ≥50%, ≥50% diameter stenosis *(DS)* at follow-up; ≥0.72 mm = ≥0.72 mm loss in minimal luminal diameter from after angioplasty to follow-up. (From Beatt et al. J Am Coll Cardiol 1990;15:491-8.) **B,** Venn diagram showing distribution of lesions fulfilling the different criteria applied in Fig. 3. Note that, of 153 lesions undergoing restenosis according to at least 1 of 3 criteria applied, only 43 fulfill all 3. It is appreciated how different definitions of restenosis define separate populations. (From Beatt et al. J Am Coll Cardiol 1990;15:491-8.)

Nevertheless, even with use of interpolated reference diameter, inaccuracy introduced by the presence of diffuse arterial disease (and by the effect of intervention) is not surmounted, and the use of minimal luminal diameter appears more reliable for the purpose of important clinical research, as will be elaborated further in later sections of this article.

As a consequence of definition inaccuracy, in addition to variable angiographic follow-up rates (57% to 100%) and the continued use of visual assessment of the coronary angiogram by most investigators, the reported incidence of restenosis varies widely (Fig. 1). Applying three different and widely used definitions to a series of 398 lesions serially measured during 6-month follow-up, our group[31] demonstrated that: (1) the greatest single determinant of the restenosis rate is the choice of definition (Fig. 5, *A*), and (2) even if the eventual incidence of restenosis is similar, different definitions identify different patient populations (Fig. 5, *B*), making risk factor determination (and indeed meaningful study of the natural history of the restenosis process) impossible.[46] These diversities are almost certainly responsible for much of the confusion surrounding the concept of restenosis after PTCA.

WHAT IS RESTENOSIS?

Restenosis refers to the combined biologic (thrombo-rheo-fibro-proliferative) healing processes taking place after the mechanical or physical injury imparted by balloon inflation or other percutaneous device, which ultimately lead to a progressive renarrowing of the patent lumen to a greater or lesser degree during the immediate weeks and months after the therapeutic procedure. This process of response to injury has been most extensively studied in the context of balloon dilatation and, as such, appears to loosely consist of four elements: (1) Elastic recoil, a natural property of intact blood vessels to respond to stretch. This phenomenon has been characterized by quantitative angiography[47-50] and by intravascular ultrasound (IVUS)[51]; although available data are somewhat conflicting, on balance elastic recoil is depicted as occurring immediately after balloon deflation,[47, 49] with no significant further recoil during the succeeding 24 hours[52, 53] and thus has a doubtful real contribution to the process of late luminal renarrowing[49, 54, 52]; (2) subintimal platelet deposition, mural thrombus formation, and consequent organization may result in rapid luminal obstruction or early restenosis[55] after the apparently unavoidable intimal disruption induced by balloon dilation[56]; furthermore, these early "hemorrheological responses" to vessel wall injury[57] are likely to be an initial pathway to (3) fibrocellular neointimal hyperplasia, which is widely regarded as the final pathologic process by which progressive luminal renarrowing develops in the months after PTCA[1, 58-62]; and (4) reaccumulation or acceleration-progression of classic atherosclerotic plaque.[62]

Alternative pathologic paradigms. The conventional assumption of an outgrowth of proliferating cells (presumably smooth-muscle cells) from the damaged vessel media to form the neointima[1] has lately been challenged by Schwartz et al.[63] On the basis of extensive experience with a domestic swine model,[64, 65] they assign a central role to mural thrombus formation at the site of injury, which has already previously been well recognized as a key event.[1, 55, 57-59, 61, 66, 67] From this point in the paradigm a new aspect is introduced whereby the fresh mural thrombus becomes rapidly endothelialized (3 to 4 days after injury) and is then infiltrated by mononuclear cells from the luminal surface inward. The degenerating thrombus is subsequently colonized by proliferating α-actin staining cells (becoming visible from day 6 onwards) whose origin and exact nature remains elusive (although they are possibly smooth muscle cells or myofibroblasts), again from the luminal surface inward (in the opposite direction to that which is hypothesized in the current conventional model), with concomitant production of extracellular matrix, eventual complete resorption of the thrombus, and the ultimate formation of mature neointima.

Karas et al.[68] have also presented a model of restenosis by using balloon dilatation or implantation of a balloon-expandable stent in normolipemic domestic swine. They observed marked intimal smooth-muscle cell proliferation and an increase in extracellular matrix, destruction of the internal elastica, and thinning of the arterial medial layer, both in stented and balloon-dilated segments. Intimal proliferation was more prominent and significantly greater in stented segments by morphometric analysis; in addition, residual luminal area was significantly less in these segments. These histopathologic changes were described as being comparable with those observed in human restenosis. Furthermore, reactive inflammatory infiltrates were frequently observed in proximity to the stent filaments, suggesting a foreign body type of reaction. The authors hypothesize that, despite provoking more intimal proliferation, stenting maintains a greater morphometric luminal area than balloon dilatation through the achievement of a larger lumen by continued mechanical opposition of elastic recoil. These findings present circumstantial evidence that agrees with the description of a proportional relationship between the extent of neointimal hyperplasia and the severity of vessel wall injury by Schwartz et al.[65] However, the authors disagree with the hypothesis of Schwartz et al.[63] regarding the central role of thrombus in the process of restenosis, on the basis of the rarity of angiographic evidence of large space-occupying clots in clinical practice, and suggest that excessive arterial injury was induced in their model, thus limiting its use as a screening tool.

Further observations of coronary artery dilatation in the porcine overstretch model without stenting provided no evidence for a space-occupying thrombus[69] as suggested by Schwartz et al.[65] Serial examination of the dilated arteries at 1, 3, 7, 14, and 28 days showed little or no thrombus but active migration and proliferation of cells from the area of the disrupted media. Examination of these healed lesions and similar lesions from patients[70] failed to reveal the footprints of preexisting thrombus, that is, hemosiderin deposits, etc. These divergent findings may primarily relate to the extensive use of stents in the Mayo Clinic model (which uniformly produces thrombus) and the overstretch without stenting used in the Emory model (which was found not to produce significant thrombus).

Intracoronary fiberoptic angioscopy allows safe and rapid assessment of the site of percutaneous intervention.[56] One recent clinical study small and preliminary, reports the presence of luminal thrombus in two thirds of patients immediately after angiographically successful balloon dilatation, with progression in thrombus volume, within 1 hour, in half of these, while contrast angiography failed to provide clear evidence of intraluminal thrombus.[71] Further recent technologic advances in angioscopic hardware will undoubtedly facilitate even more detailed and "microscopic" evaluation of the coronary lumen in clinical studies.[72] Thus the technology now appears to be available to prospectively study the role of intraluminal thrombus in the restenosis process and in the clinical setting, and such studies may already be underway in some institutions.

Whatever the exact nature of the histopathologic process, it is evident that the corresponding angiographic appearance of progressive luminal renarrowing is not well encapsulated by traditional conventional definitions or criteria such as "loss of greater than 50% of the gain" or "greater than 50% diameter stenosis at follow-up," two of the most widely used definitions in daily clinical practice, and in restenosis prevention studies (Table I) and trials of new devices. Schwartz et al.[65] and Beatt et al.[73] have each highlighted this inherent limitation of conventional restenosis criteria and the consequent potential for misinterpretation of results of clinical trials relying on such criteria. Similarly, Karas et al.[68] also draw attention to the possibility of considerable intimal proliferation without angiographic restenosis.

Because current understanding of the restenosis process is at best fragmented, until our knowledge becomes more complete, it is crucial to make sensible use of the most objective descriptive methodological approaches available, especially in the minefield of clinical research. The question is, what are the most objective, reliable, and reproducible methods of assessing restenosis?

ASSESSMENT OF RESTENOSIS: SYMPTOMS, FUNCTION, FLOW, OR LUMEN?

Coronary obstructions, whether of primary atheromatous origin or arising as a response to the controlled mechanical or thermal injury inherent in the various currently available nonsurgical therapeutic coronary interventions, can be described from a number of different viewpoints: (1) by the symptomatic sequelae. Although improvement in quality of life (and life expectancy) is the goal of any therapeutic modality, it is also the least objective yardstick by which to evaluate the impact of treatment.[74, 75]

(2) By the physiologic disturbance in myocardial perfusion caused. The physiologic effect of a coronary stenosis may be most certainly the ultimate determinant of management for the individual patient. The increasing battery of noninvasive investigations available for this purpose contribute vital information necessary for clinical decision making, but they cannot provide the reproducibility and objectivity[77-79] required to assess the process of luminal renarrowing after percutaneous revascularization in *large patient groups* in the context of clinical trials. In daily clinical practice it may be considered most prudent to regard restenosis according to the need for a repeat revascularization procedure; thus it is important for the reader to recognize that this treatise is primarily focused on the evaluation of outcome after interventions in the context of large clinical trials of new devices or therapeutic approaches rather than as a direct guide to general clinical practice. Nevertheless, it must not be forgotten that conclusions drawn from the outcome of such trials provide us with the type of information that is ultimately instrumental in our daily clinical decision making, hence the paramount importance of design, method, and approach in these trials and studies.

(3) By its hemodynamic consequences, that is, reduction in coronary blood flow caused by the obstruction. Regional coronary flow reserve (CFR) (defined as the ratio of maximal to resting coronary blood flow) may be directly measured at cardiac catheterization by a number of different techniques, or alternatively may be derived from values obtained by quantitative angiography.[42] Absolute coronary blood flow itself can be measured by Doppler wire, and transstenotic pressure gradients may be obtained by using ultra-thin fiberoptic or fluid-filled catheters. Further sophisticated and precise hemodynamic measurements can be obtained during cardiac catheterization. However, these are mainly research tools that are not at this time generally available to the general nonacademic interventionist and

are unapplicable for multicenter clinical studies in large patient populations.

(4) By its anatomic configuration, namely degree of luminal narrowing. For the present, this aspect is best assessed by conventional contrast angiographic techniques, although intravascular ultrasound (IVUS) is emerging as an exciting and promising imaging modality[36, 51, 85] and will undoubtedly have a useful application in the future in this area. As yet, IVUS is in the developmental stage and many technical obstacles need to be surmounted, particularly transducer size (models used in the most recently published studies are 1.83 mm in diameter, although a 1.15 mm prototype is being tested,[36] cost, ethical considerations, and objective delineation of the relationship between IVUS images and actual morphology of the blood vessel wall,[85] before it can be considered as a realistic or practical alternative to carefully controlled angiography.

At this time the coronary cineangiogram is still the only universally available imaging modality for examination of coronary anatomy; quantitative angiographic techniques as described later have emerged as the gold standard for the accurate and objective analysis and description of the basic cineangiogram, particularly in the context of large, multicenter restenosis prevention clinical studies and trials of percutaneous coronary revascularization devices.

Coronary luminal measurement by quantitative coronary angiography: The CAAS approach. Quantitative coronary angiography (QCA) has been used at our institution for a decade* and is becoming increasing available with the development of on-line quantitative angiographic computer software for digital cineangiographic imaging (DCI) equipment in the catheterization laboratory. The CAAS system has been rigorously and extensively validated, and the methodology is described in detail elsewhere.[18-20, 87, 88, 95-97] To explain the method briefly: After a selected cineangiographic image has been converted to an optically magnified digital image (digitization; this step may soon be rendered unnecessary by the rapid development of on-line digital systems), the contours of the selected coronary segment are detected automatically (so called contour or edge detection) by the computer algorithm applied to the brightness profile of the segment along scan lines that are perpendicular to the segment centerline (scan lines are made every 0.1 mm the approximate size of 1 pixel). The centerline is determined by the computer, which uses as starting points a series of arbitrary centerpoints selected by the analyst, but for which the algorithm can retroactively correct and regenerate the true centerline of the segment image. Absolute diameter measurements are determined in millimeters by using the *outer border* of the contrast-free angiographic catheter[95] (the distal 20 cm of each individual catheter used for contrast injection is retained and measured by micrometer) as a scaling or calibration device. A correction factor is then introduced for the so-called pincushion distortion introduced by the image intensifier (there are 557 different pincushion correction factors in the CAAS database relating to all the catheterization laboratories from which we receive cinefilms for analysis). Pincushion distortion is minimal with modern angiographic systems, and this step may not be necessary in the coming years. The interpolated reference diameter is obtained as previously outlined. From the absolute measurements (minimal luminal diameter, maximal luminal diameter, mean luminal diameter, and lesion length) and the interpolated measurements obtained by the computer (symmetry, curvature, inflow-outflow angle, plaque area, roughness), many others may be derived, such as percent diameter stenosis, percent area stenosis, theoretic transstenotic pressure gradient, calculated Poiseuille resistance, and calculated turbulence resistance.

Videodensitometry assesses the area of a stenosis by comparing the density of contrast in the diseased and normal segment, which has the advantage that only a single angiographic projection is required. However, this must be perfectly perpendicular to the long axis of the vessel, and there must be no overlapping or closely parallel sidebranches or other disturbing radiopacque structures. Only relative values are provided so data obtained by contour detection are also necessary to provide absolute measurements. A further drawback of this otherwise promising technique is its high sensitivity (it is even more sensitive than contour detection) to x-ray scatter, veiling glare, beam hardening, and suboptimal contrast filling of the vessels. These basic limitations have deterred the application of the technique to important clinical angiographic studies. In the latest updated CAAS system, however, steps have been taken to overcome these drawbacks; results of validation studies are eagerly awaited.

Minimal luminal diameter. Of all the measurements acquired by quantitative angiography, the absolute value of the minimal luminal diameter (MLD) has been shown to be the greatest single determinant of the hemodynamic consequences of a stenosis because

*18-20, 31, 38, 42-48, 86-108, 111, 112, 115-120, 127, 135, 136.

this parameter affects blood flow by a fourth power term.[42, 80, 84, 109] It is therefore the most unambiguous, objective, and reproducible parameter to use for primary measurement of coronary arterial (or bypass graft) luminal caliber and changes therein resulting from interventions, that is, the angiographic gain in minimal luminal diameter after intervention and subsequent loss during follow-up and, as described later, the proportional angiographic gain and loss (so called relative gain and relative loss which normalize the gain and loss for the actual vessel size.

Criteria for definition of restenosis on the basis of change in minimal luminal diameter during follow-up. Important multicenter trials examining the impact of various treatment strategies on restenosis have in recent years been availing of central, standardized, blinded, computer-assisted, quantitative angiographic analysis in angiographic core laboratories[98, 99, 110-114] and have begun to use the minimal luminal diameter (MLD) as the most objective and useful measurement.[115] In the past, our group used the long-term minimal luminal diameter measurement variability of the CAAS system as a means of identifying lesions undergoing significant or detectable luminal change during follow-up after balloon angioplasty.[88] The SD of the mean difference between MLD measurements of the same lesions at different points in time where no intervention was carried out was measured under a worst-case scenario and found to be 0.36 mm. Two SDs would identify with 95% confidence lesions undergoing a real, detectable, or significant change. By using the long-term lesion measurement variability it was believed might present an objective approach to dividing patients monitored after PTCA into restenosis and nonrestenosis.

That study may now be considered somewhat obsolete because, as highlighted by Ellis and Muller,[116] and as we ourselves had already recognized, a large number of limitations to this definition of restenosis are now evident. First, the developmental study used vessels with an average reference diameter of 3.7 mm,[88] whereas in two recent large multicenter restenosis prevention studies the mean reference diameter of treated vessels was 2.6 mm.[111, 112] Furthermore, the initial study used a worst case scenario whereas extensive standardization measures (use of intracoronary nitrates to control vasomotor tone, performance of angiography in exactly matched multiple projections, careful identification and selection of an end-diastolic cine frame for QCA analysis, etc.) are now carried out in modern multicenter studies and furthermore *post-PTCA* measurement variability cannot be inferred from the original study because no intervention was carried out.

We have completed a pilot study[53] that provides clear angiographic data in this regard, whereby among 110 lesions (mean vessel size of 2.67 mm) studied after balloon angioplasty and at 24 hours (under optimally standardized conditions, i.e., matched angiographic projections, intracoronary nitrate before angiography, full therapeutic anticoagulation) there was no difference in MLD (0.007 mm, $p = 0.79$), and the SD of the mean difference was 0.2 mm. By extrapolation from these data, it can be concluded that the post-PTCA lesion measurement variability of the CAAS system is 0.2 mm; thus a change of 0.4 mm in MLD can be considered with 95% confidence to represent a real change and thus can be considered a *potential* criterion for detection of significant luminal loss or renarrowing. In the light of the well-recognized difficulties of angiographic interpretation of the postballoon angioplasty result, we believe this measurement variability to be eminently acceptable.

It must be noted that the criterion we propose for detecting significant change in MLD over a period of time is the measurement variability of the analytic system being used and not 0.4 mm per se, because this is the variability of the CAAS system and may not be relevant to other systems. Ultimately, as alluded to already and as discussed further later in this article, the application of dichotomous criteria to the description of long-term outcome after intervention is fraught with imprecision, conflict, controversy, and dissension.

NEW INSIGHT TO THE RESTENOSIS PROCESS FACILITATED BY QCA

Gaussian distribution. Although most biologic phenomena are distributed in nature in normal or gaussian fashion, the outcome of percutaneous coronary interventions and of pharmacologic restenosis prevention trials have been traditionally assessed up to now by using categoric cut-off criteria for the occurrence (or not) of restenosis because, as previously mentioned, clinical decision making is ultimately a binary process. However, for the purposes of large multicenter controlled clinical trials, estimation of sample size required to demonstrate the statistical significance of a treatment effect has been based on the assumption of a gaussian distribution for the loss in MLD during follow-up after balloon angioplasty.[118] That this discussion is not merely a matter of semantics is illustrated in the example shown in Fig. 6.[118] A significant beneficial treatment effect is de-

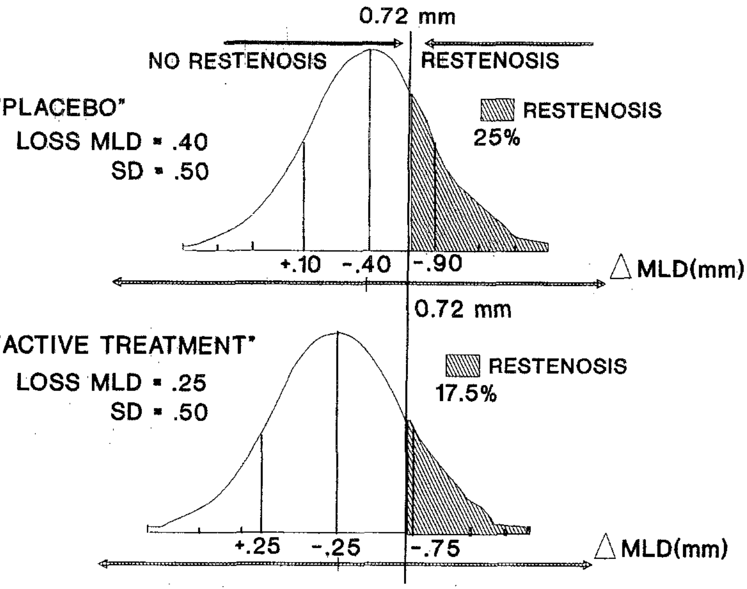

Fig. 6. Gaussian model of restenosis in reference and treatment groups. Lower curve represents 30% reduction in minimal luminal diameter change at follow-up (−0.25 mm vs −0.40 mm) in treated group, upper curve denotes distribution of change in minimal luminal diameter *(ΔMLD)* found at follow-up in prospective study at our institution.[31] If change of 0.72 mm is taken as cut-off point for restenosis, this categoric model would require 620 patients per group to have power of 90%. (From Serruys PW et al. Interventional cardiology. Stuttgart: Hogrefe and Huber, 1990.)

fined as a reduction in the mean loss in minimal luminal diameter during follow-up after balloon angioplasty by 30%, that is, from 0.40 mm to 0.25 mm. It can be calculated that, assuming normal distributions for the loss in MLD, 233 patients are required in each treatment group to demonstrate the significance of this difference at the 95% confidence level with a power of 90%. If a categoric approach (restenosis yes/no) is used (applying loss in MLD of $\geq$0.72 mm as the criterion of detectable significant loss), then the 0.15 mm difference in MLD is equivalent to a reduction in the restenosis rate from 25% to 17.5%; to demonstrate that this difference is significant, 620 patients will be required in each group, almost three times as many as required if a continuous approach is applied.

Historically, in a number of clinical studies focusing on various aspects of the restenosis problem Beatt et al.[38, 119-121] demonstrated that quantitatively measured changes in MLD and in reference diameter during the months after PTCA are normally distributed. This view of a continuous unimodal distribution for luminal change after balloon angioplasty, although strongly challenged at that time, became the nidus of our philosophy regarding methodological approach to addressing the problem of restenosis.* The Beth Israel group subsequently strongly corroborated these early reports, demonstrating similar distribution patterns of luminal change after intervention in patients undergoing directional atherectomy and stent implantation.[122, 124]

At a later date, however, the Emory group examined, by clinical estimation of percent diameter stenosis, a large cohort of patients undergoing balloon angioplasty and follow-up angiography. They found a bimodal distribution and concluded that there was either a physiologic bimodal distribution or a systematic measurement error around the 50% diameter stenosis mark when clinically evaluating cineangiograms.[125] This finding, if confirmed, would therefore justify a categoric approach to the assessment of angiographic outcome in clinical trials, thereby challenging the emerging assumptions of a continuous distribution arising from the separate findings of our group and the Beth Israel group. This prompted our group to reinvestigate this phenomenon in a much larger patient population than had been studied in the original studies,[38, 119-121] and under more standardized and consistent quantitative angiographic conditions. In this study of 1234 patients it was demonstrated unequivocally that luminal renarrowing after PTCA, whether assessed by using minimal luminal diameter or percent diameter stenosis at follow-up or the change in these measurements during follow-up, clearly follows a gaussian or

*47, 48, 54, 73, 94, 100-108, 111, 112, 118.

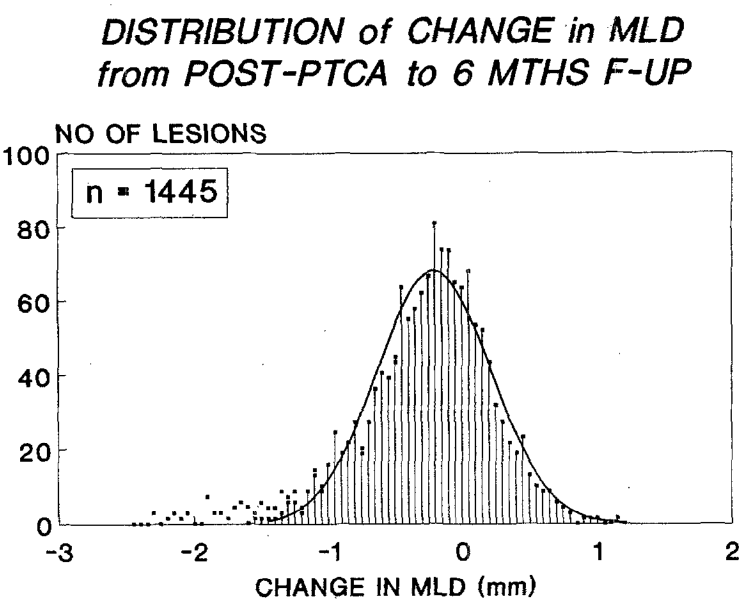

Fig. 7. Histogram of change in minimal luminal diameter during 6-month *(MTHS)* follow-up *(F-UP)* of 1445 primary lesions treated by coronary balloon angioplasty during two large restenosis prevention trials. Theoretic gaussian curve, given mean and SD, is superimposed, clearly illustrating that luminal renarrowing is normally distributed phenomenon. (From Rensing et al. J Am Coll Cardiol 1992;19:939-45.)

normal distribution (Fig. 7[94]) in agreement with our own earlier findings,[38, 73] and the reports by Kuntz et al.[124] in patients treated by other devices. These corroboratory findings appear to identify a basic flaw in the clinical impression of a bimodal phenomenon. On this basis, it is our contention that a dichotomous view of restenosis is inappropriate and that categorically generated restenosis rates should no longer be the *main* focus of important scientific studies or discourse in this vital area.

There may be sound clinical reasons for selecting particular angiographic definitions of restenosis, but in the context of scientific studies or restenosis prevention trials, the use of a blanket, categoric cut-off point (e.g., >50% diameter stenosis) conveys no measure of the extent of luminal renarrowing and therefore cannot provide a comprehensive assessment of the effect of a particular therapeutic approach for the control of the biologic *process of restenosis*. Furthermore, because the threshold level for absolute (or relative) luminal renarrowing that is physiologically or clinically significant is unknown, it is much more realistic and meaningful (and requires much fewer patients[118]) to study the overall effects of an intervention in terms of the mean change in minimal luminal diameter for the entire group.[111, 112] We believe, furthermore, that results of intervention trials may be simply presented in graphic form by using cumulative distribution curves displaying change in MLD during follow-up for treated versus placebo populations (Fig. 8)[111, 112, 124] or indeed for PTCA versus stent or atherectomy[13, 104, 106] as discussed later.

Potential pitfalls of angiographic studies. Having laid out this scheme of the angiographic representation of the phenomenon of restenosis, it must be taken into consideration that the entire hypothesis of a Gaussian phenomenon hinges more or less on the accuracy and reproducibility of quantitative angiographic measurements. Although it seems clear from the foregoing evidence that luminal renarrowing or restenosis after interventions is a continuous or normally distributed phenomenon, it must be recognized that our observations do not always give a clear view of reality. The measurement approaches used to quantify coronary luminal dimensions from cineangiograms have inherent associated measurement variability that may be attributed to a large number of causes. The importance of knowing this measurement variability for the purposes of comparing the results of studies carried out by using different measurement systems is self-evident. It could be hypothesized that this measurement variability may be clouding our view of reality.

To demonstrate this point, let us construct a hypothetical scenario whereby restenosis is in reality

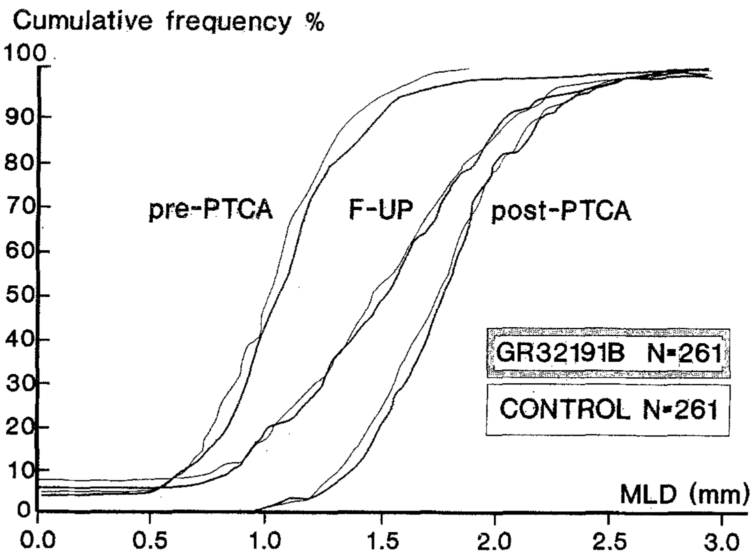

Fig. 8. Cumulative frequency (distribution) curves of change in minimal luminal diameter from after angioplasty to follow-up *(F-UP)* in control and treatment groups for CARPORT restenosis prevention trial showing no treatment benefit. *CUM%*, Cumulative percentage of patients. (From Serruys et al. Circulation 1991;84:1568-81.)

a discrete disease process, so that by using a perfectly accurate and precise quantitative angiographic measurement system and plotting the change in minimal luminal diameter in a frequency distribution plot two groups of patients could be delineated, one in which restenosis occurred and the other in which no restenosis developed (Fig. 9). In panel *A*, the no restenosis group is denoted by the curve *n*, a relatively narrow gaussian function showing no overall loss in MLD (mean = 0, SD = 0.2 mm). The restenosis subgroup response curve *r* was also taken to be Gaussian but broader (more variable) than the normal response, and it displayed a significant loss in MLD (mean = 0.5 mm, SD = 0.4 mm). The difference in the assumed variability of these groups merits an explanation. In the no restenosis group the variability in the measured loss in MLD was assumed to stem from uncontrollable changes in lesion tone between the post-PTCA and follow-up angiograms. Such variance was also assumed for the lesions undergoing restenosis but, in addition, the process of restenosis was also assumed to be variable, thereby exaggerating the variability in loss of MLD in this group. When the subgroup responses are added, the combined study population is seen to be unimodal but skewed toward the right as demonstrated by the heavy solid curve (panel *A*). This population response (the actual response) must now be measured by a QCA system to form our observations. This system, however, is not perfect because frame selection and computer-assisted image interpretation may not be exactly accurate and reproducible. To account for such measurement problems, panel *B* shows two solid gaussian curves which were used to represent the statistical characteristics of two QCA measurement systems. Curve *h* denotes a highly precise and accurate system (mean difference between repeated measurements of MLD = 0 mm, SD of the mean difference = 0.1 mm); curve *m* is a medium-precision but highly accurate system (mean difference = 0 mm, SD = 0.3 mm).

Measuring MLD loss by these systems is akin to mathematically convolving the study population in *A* with a measurement characteristic from *B*, the results of which are shown in panels *C* and *D*. In panel *C* the combined population response (solid curve in *A*) has been measured with the high-precision QCA system, resulting in observations that closely mirror the true population response. Panel *D* shows the observations (solid heavy curve) resulting from less precise measurement of the study population by means of the medium-precision QCA measurement system. The measurement process has blurred our observations to the point that the measured loss in MLD now approaches a gaussian distribution (the light-dashed line in *D*), which has the same mean, SD, and number of observations.

The above scenario proposes an alternative explanation for the observed gaussian distribution of coronary luminal measurements at follow-up after coronary interventions and the change in dimensions

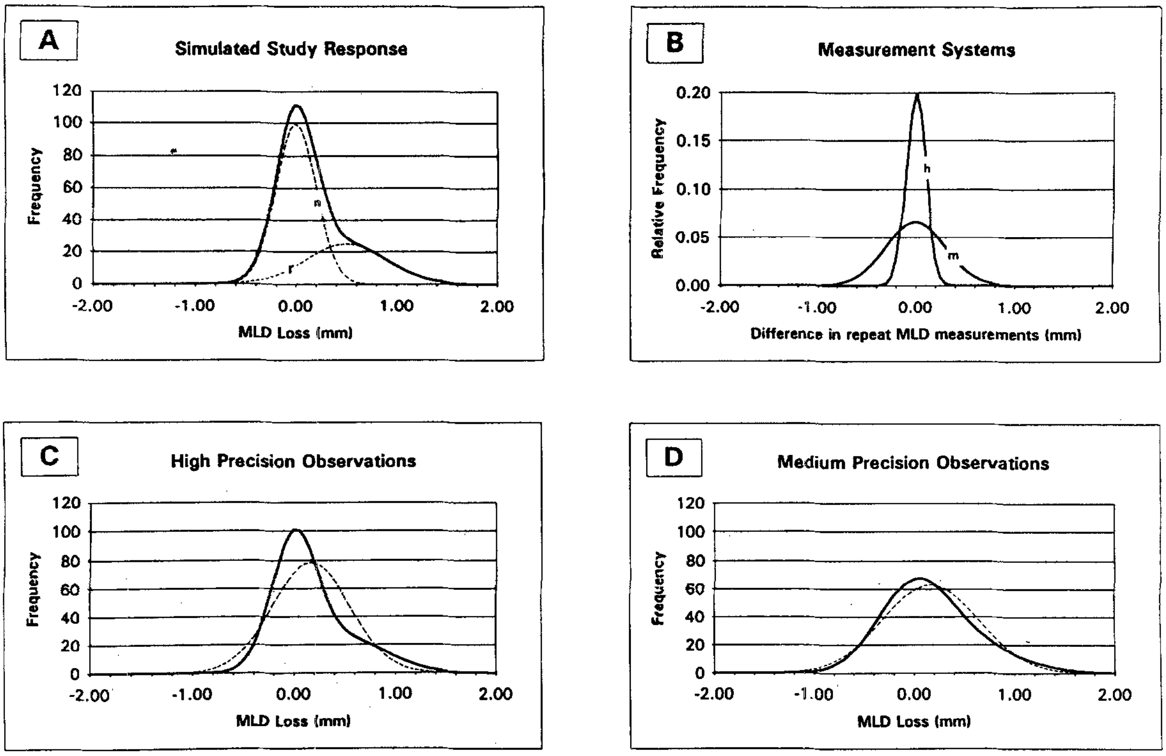

Fig. 9. Simulated PTCA restenosis study. **A,** *solid curve* represents entire study population composed of two separate but overlapping subgroups, both of which can be described by gaussian function. *Curve n* describes loss in MLD for 1000 lesions that did not restenose (mean loss = 0 mm, SD = 0.2 mm). *Curve r*, loss among 500 lesions that did undergo restenosis (mean loss = 0.5 mm, SD = 0.4 mm). **B,** Measurement characteristics of two separate QCA systems, high accuracy and precision system (*curve h*, with accuracy of 0 mm and precision of 0.1 mm) and high accuracy but medium precision system (*curve m*, with accuracy = 0 mm, precision = 0.3 mm). *Heavy curves* in **C** and **D** display distributions of observations that would be produced by measuring actual loss in MLD in populations of lesions in **A** by high-precision system **(C)** and medium precision system **(D)** by using simulation process called curve convolving. *Dashed curves* in panels **C** and **D** show corresponding gaussian distributions.

during follow-up (as reported by our group[38, 73, 94, 121] and by the Beth Israel group,[122, 124]) namely imprecise measurements of a mixed population of lesion responses to intervention. However, without further objective investigation this proposal has no more validity than any other reasonable hypothesis that fits the observations.

The point is that it is important be careful in what is concluded or excluded based on observations. Accepting that there may be multiple explanations for a given set of observations, is there anything that can be done to sharpen our view of reality? We should make all reasonable efforts to minimize measurement inaccuracy and imprecision. As shown in our example, even an imprecision of ± 0.3 mm in measuring MLD loss may significantly contort the observations and thus confound the conclusions drawn. Although this simulation featured QCA measurements as study endpoints, the principles are applicable to all chosen endpoints. If, for example, clinical endpoints were used to evaluate restenosis, we can only wonder how blurred the observations might be as a result of inaccurate or imprecise assignments of clinical events to lesion restenosis. Additionally, sensitive and flexible analyses of the observed data need to be explored. In this regard it might be worthwhile to use our knowledge of the measurement process to try to unblur our observations. Deconvolution, curve-fitting, and curve-stripping procedures are often used in signal and image processing to remove known artifacts, reduce noise, and separate overlapping phenomena. It may prove interesting to see whether such methods could be applied usefully in analysis of restenosis trials.

Clinical correlations of measured MLD. Danchin et al.[126] demonstrated a correlation between the threshold to exercise-induced myocardial ischemia (as demonstrated by thallium-201 tomoscintigraphy) and an

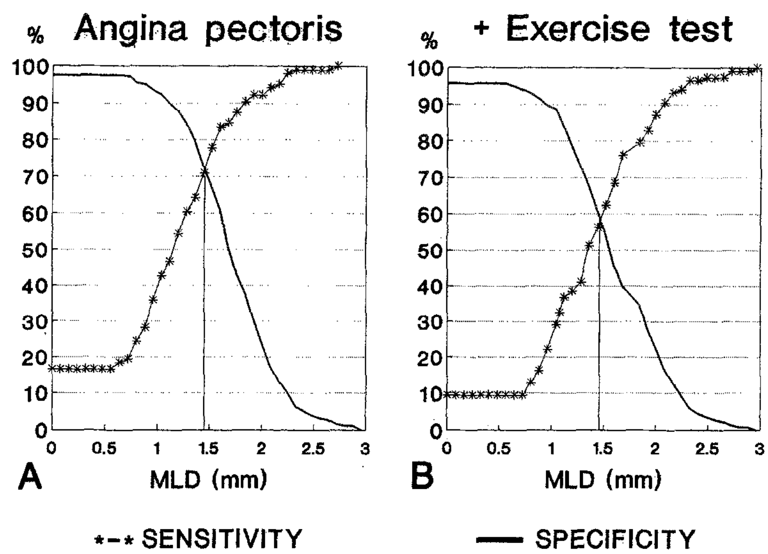

Fig. 10. A, Percentage correct classification of recurrence of angina (sensitivity) and absence of angina (specificity) as function of absolute value obtained for MLD by QCA at follow-up after PTCA in 350 patients taking part in restenosis prevention trial.[111] Intersection of two curves represents cut-off point with greatest diagnostic accuracy. (From Rensing BJ et al. J Am Coll Cardiol 1993;21:317-24.) **B,** Percentage correct classification of a positive exercise test result (horizontal or down-sloping ST-segment depression of >1 mm measured by callipers 80 msec after the J-point) and negative exercise test result (specificity) as function of absolute value obtained for MLD by QCA at follow-up in same patient population as for Fig. 10, **A.** Intersection of two curves represents cut-off point with greatest diagnostic accuracy.

absolute value for minimal luminal diameter from which they conclude that an MLD ≥2 mm is sufficient to provide freedom from myocardial ischemia in 95% patients. Furthermore, Rensing et al.[111] have reported that in 350 patients who underwent successful PTCA for single-vessel disease (as part of a large prospective multicenter restenosis prevention trial) and had exercise testing and repeat coronary angiography at follow-up an MLD of 1.45 mm correlates with the threshold for recurrence of angina pectoris (sensitivity and specificity: 72%).[127] Exercise-induced ST-segment change was found to be a less reliable predictor of luminal renarrowing, although the point of greatest diagnostic accuracy for a positive exercise test corresponded with a measured MLD of 1.46 mm (Fig. 10). This information is somewhat surprising because it would be expected that a large number of additional variables should influence the relationship between minimal luminal diameter and exercise-induced angina or ST-segment depression such as vessel size, extent of myocardium supplied, viability of myocardial tissue, presence of collateral circulation, use of antianginal medication, etc. When vessel size was taken into account by dividing the study group in half according to the median vessel size, the point of intersection of the sensitivity and specificity curves were again virtually identical for recurrence of angina and a positive exercise test, at 1.38 mm in vessels <2.63 mm and 1.58 mm in vessels >2.63 mm in diameter. Thus it is clear that the vessel size does influence the minimal luminal diameter threshold for recurrence of angina or exercise-inducible ischemia. Nevertheless, the observations suggest that the absolute value for MLD at follow-up may ultimately prove to be a simple and clinically useful parameter both for scientific studies and practical clinical patient management, a claim that deserves further and more objective evaluation. This implication supports the approach used in reporting two recent European multicenter restenosis prevention trials[111, 112] and that employed by other groups who have consistently focussed on the MLD at follow up in reporting on angiographic outcome, in patients treated by DCA and stent implantation.[122-124, 128-131]

As a measure of the extent of the hyperplastic healing process itself, the change in MLD during follow-up is clearly the parameter of choice. Rensing et al.[127] also investigated the clinical value of measured change in MLD during follow-up in predicting the physiologic significance of treated lesions 6 months after successful balloon angioplasty and found it to be only slightly less accurate than absolute MLD at follow-up, a deterioration of >0.30 mm yielding sensitivity and specificity of almost 70% for prediction of recurrence of angina and almost 60% for a positive exercise test result. Corresponding values for percentage diameter stenosis measurements are provided in this study for comparative purposes for the benefit of clinicians; however, for the extensive reasons given earlier in this article we discourage the use of percent diameter stenosis in important interventional studies.

COMPARATIVE ASSESSMENT OF NEW DEVICES USING MLD AS THE CENTRAL MEASUREMENT

New dilemmas have arisen as a result of the explosion of new interventional coronary treatments with respect to comparison of results, particularly long-term outcome. The unique mechanisms of action of and subsequent pathophysiologic responses to the various devices renders broad comparison of these treatment modalities basically invalid, especially because it is generally recommended that atherectomy devices should not be used, nor should endoluminal stents be implanted, in coronary vessels <3 mm in diameter. PTCA, however, can be (and is regularly) carried out in arteries <2 mm in size, and rotational atherectomy and excimer laser therapy are best suited to smaller vessels.[132]

We consider that it may be reasonable to compare the effects of interventions in terms of their relative merits or by confining comparisons to matched lesions, i.e., lesions of similar severity, in vessel segments of identical size and location (even though it has lately been demonstrated by our group[100] and others[133] that, contrary to popular belief, restenosis rates are not significantly different throughout the coronary tree). At the Thoraxcenter, facilities are available for the appropriate use of all of these therapeutic techniques. The increasingly widespread application of these devices, despite the lack of any hard evidence of greater long-term clinical benefit than balloon angioplasty, has prompted our search for a unifying descriptive approach to the assessment and comparison of immediate and long-term outcome between devices and has led to the serial development of two methods of comparing the theoretically incomparable.

Matching: A temporary but convenient surrogate for randomization. The first method enables us to actually compare the comparable by matching the lesions in each treatment group for severity, location, and vessel size, thereby defining a population in which any of the treatment modalities to be compared may reasonably be used. There are three basic principles: (1) the angiographic dimensions of the matched lesions are assumed to be identical; (2) the observed difference between the two identical lesions must be within range of reproducibility of the computer analysis system being used (for the CAAS system this is ±0.1 mm, i.e., 1 SD of the difference between repeated measurements of the same angiogram); and (3) the reference diameter of the vessels to be matched are selected within a range of ±3 SD (0.3 mm), giving confidence limits of 99%.[13, 104]

Comparing the immediate angiographic results of PTCA, directional coronary atherectomy (DCA), and intracoronary stenting with this technique illustrates that both DCA and stenting yield a more favorable early result than PTCA and that matching is a useful comparative method.[103] Application of the matching principles to a direct comparison of immediate and long-term angiographic outcome after PTCA and DCA or stent implantation using cumulative distribution curves (Figs. 11 and 12),[103, 135] is similarly rewarding in its clarity and simplicity. Because the lesions are matched for reference diameter, approximate overall improvement in luminal diameter (gain) at intervention and loss in minimal luminal diameter during follow-up can be easily gleaned from the figure and directly compared. It is appreciated that although DCA is associated with a significantly greater initial gain (improvement) in MLD, the loss (restenosis) after DCA is also significantly greater than that after PTCA, so that the ultimate outcome (MLD at follow-up) is similar for both treatment modalities. This technique to compare immediate and long-term angiographic results after PTCA and self-expanding stainless steel stent implantation in 93 matched lesions has revealed that, although associated with a greater loss in luminal diameter during follow-up, stenting yields a significantly larger vessel lumen (reflected by a larger MLD) than PTCA at follow-up.[104]

The matching process, by its principles, may be justifiably used at this time as a surrogate for randomized studies,[104] facilitating otherwise invalid comparisons between interventions in relatively small patient groups. It is noteworthy that observations emerging from the matching of patients undergoing DCA and PTCA[106] have been confirmed by preliminary results of the CAVEAT trial,[113] thus demonstrating a real and undeniable clinical use for this matching approach. Furthermore, superior angiographic results in terms of MLD at follow-up, of DCA, and of stenting over historical PTCA results as reported by Kuntz et al,[122, 124] are put in a slightly

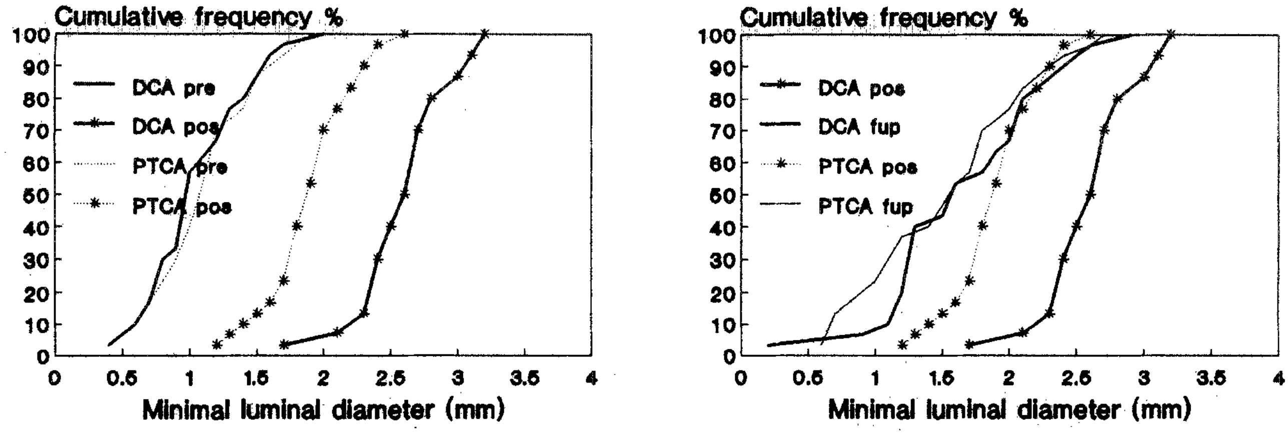

Fig. 11. Cumulative frequency (distribution) curves to illustrate differential immediate (pre to post) and follow-up (post to follow-up) effects of PTCA versus directional coronary atherectomy *(DCA)* on matched coronary lesions with regard to absolute MLD measured by QCA. (From Umans VA et al. J Am Coll Cardiol 1993;21:1382-90.)

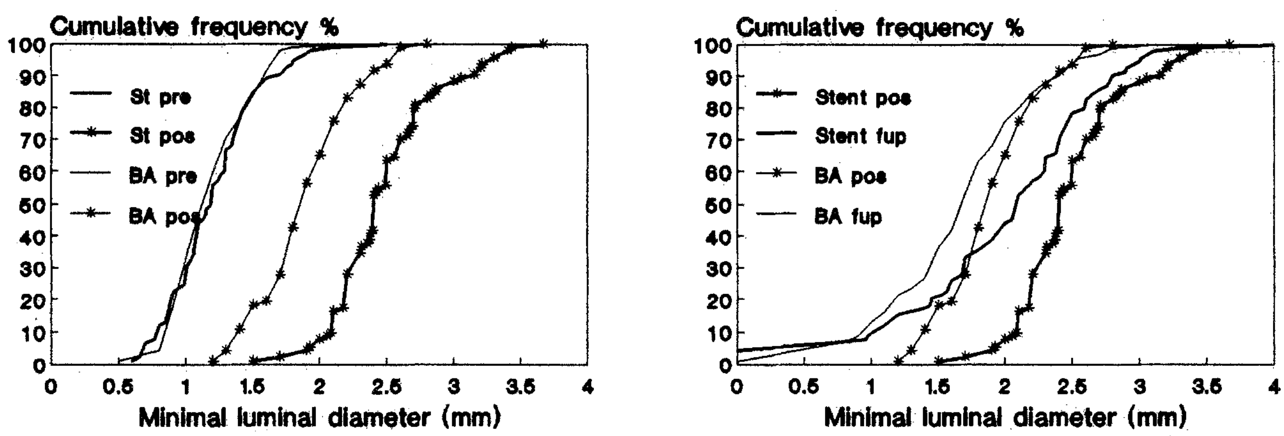

Fig. 12. Immediate (pre to post) and long-term (post to follow-up) angiographic outcome of matched study in 93 patients having balloon angioplasty *(BA)* or self-expanding stainless steel stent *(st)* implantation. Superior initial gain by stenting is somewhat counterbalanced by greater luminal loss during follow-up *(fup)*. Nevertheless, luminal diameter at follow-up remains significantly greater than for balloon angioplasty. (From de Jaegere P. J Am Coll Cardiol 1992;19(suppl):277A.)

different perspective by results obtained from matching. It is clear that the mean vessel size in patients treated by DCA and stent implantation are considerably greater (3.09 mm and 3.35 mm, respectively[124]) than in PTCA studies (2.6 mm)[111, 112]. Therefore direct comparison of absolute angiographic results obtained by these devices with those obtained by balloon angioplasty becomes somewhat irrelevant without either matching or normalizing for the individual vessel size, as described in the next section.

The limitations of the basic matching approach to the comparison of interventional therapies are, of course, that other potentially influential clinical and angiographic parameters are not taken into account in the matching process; therefore the effect of anginal status, medication, diabetes, lesion length, eccentricity, calcification, etc. on the comparative outcome of the treatment modalities is ignored. However, the matching study of stent implantation and balloon angioplasty[104] addressed this issue of potential disparity between patient groups with regard to these other variables and found no significant differences in their distribution between the groups being compared. Furthermore, the matching comparison of balloon angioplasty with directional atherectomy[106] also took account of age, gender, diabetes, and anginal status and found that this additional consideration did not affect the ultimate findings as already

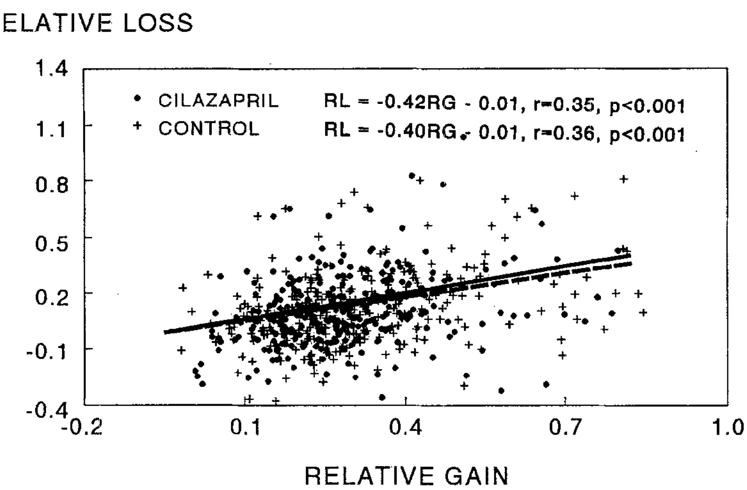

Fig. 13. Scatter-histogram of all values obtained for relative gain after PTCA and relative loss *(RL)* during follow-up in large European multicenter restenosis prevention trial[112] for both placebo and treatment groups. Linear relationship identical for both groups emerges, although coefficient of correlation is low at 0.4. *Full line*, control group; *dashed line*, treatment group.

described,[107] thus perhaps vindicating the application of the simple basic angiographic matching principles used.

Relative gain and relative loss in minimal luminal diameter. The second proposed method of comparison of therapeutic devices arose originally from the need to create some type of sliding-scale criteria to circumvent the previously described limitations of the categoric loss ≥0.72 mm criterion for assessing the outcome of balloon angioplasty in vessels of different sizes. The concepts of relative gain and relative loss in MLD were therefore introduced to adjust luminal changes for individual vessel size by normalizing the *absolute* change in MLD after intervention and during follow-up for the reference diameter of the coronary segment in question[54, 73, 100-108] in a continuous approach. The net difference between relative gain and relative loss is termed the net gain index and is a measure of the ultimate net benefit of intervention. These simple calculations may be presented as follows: *Relative gain* = MLD post intervention − MLD preintervention/vessel size; *Relative loss* = MLD post intervention − MLD at follow-up/vessel size; and *Net gain index* = MLD at follow-up − MLD pre intervention/vessel size.

The vessel size is represented by the interpolated reference diameter of the lesion before intervention because this is the closest possible objective angiographic approximation of the normal, disease-free vessel size. After intervention and at follow-up the interpolated reference diameter is subject to greater potential for measurement variability as a direct consequence of the intervention and of the restenosis process, respectively,[38, 39, 40] although there was no statistically significant difference in interpolated reference diameter between pre- and post-PTCA and at follow-up in the two previously mentioned European multicenter restenosis prevention trials.[111, 112]

Kuntz et al.[123] previously presented a relationship between absolute gain at intervention and late loss during follow-up in their patients treated by directional atherectomy and stent implantation. However, as a result of the wide variability in reference vessel size among lesions treatable by current interventional devices, we believe the application of relative gain and relative loss to be more appropriate and informative for comparative purposes. By using data accumulated prospectively during each of these restenosis prevention trials, we plotted the relative gain and relative loss values for all treated lesions and found a direct linear relationship between relative gain and relative loss (even though the coefficient of correlation was low at 0.4) for each patient population, with virtual superimposition of the regression lines for placebo and treatment groups in each trial (one of these trials is shown in Fig. 13; the other is practically identical). These graphic representations confirmed the outcome of the studies with regard to there being no demonstrable benefit of the agent under evaluation in terms of reduction in the loss in MLD during follow-up, as had been previously established by using cumulative distribution curves. Perhaps more importantly, however, was the relationship between relative gain and relative loss, which is not dissimilar from the relationship demonstrated by Schwartz et al.[6] between depth of vessel

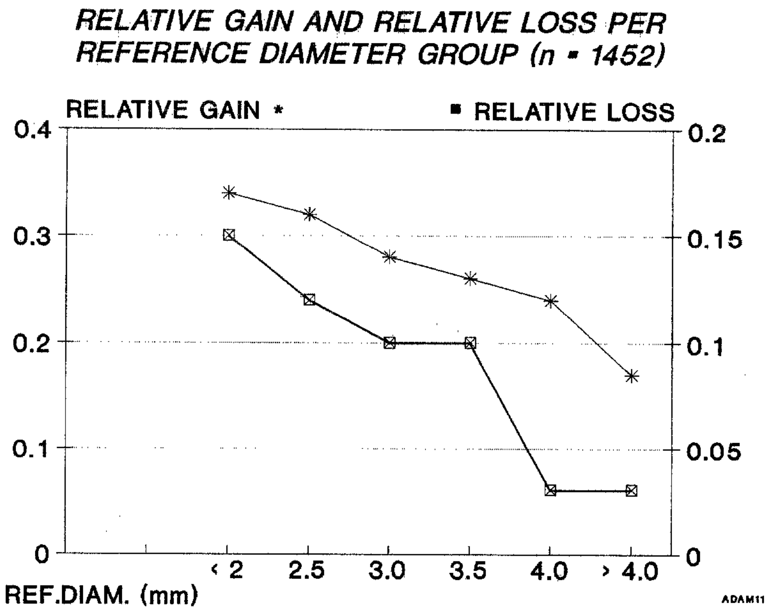

Fig. 14. Relative gain and relative loss (on the *Y* axes) plotted against reference diameter in increments of 0.5 mm on the *X* axis. Parallel trend of decrease in both variables is observed with increasing reference diameter.

wall injury and thickness of the subsequent neointimal hyperplasia in an experimental porcine model and that described by Kuntz et al. in their patients undergoing DCA or stent implantation.

THE INFLUENCE OF VESSEL SIZE ON THE RESTENOSIS PROCESS

Exploration of the relationship of the vessel size itself on the process of luminal renarrowing reveals that the relative loss (proportional loss of lumen during follow-up) decreases significantly as vessel size increases in increments of 0.5 mm, as shown in Fig. 14. However, when it is similarly found that relative gain shows a parallel pattern, it becomes evident that it is the relationship between relative gain and relative loss, as already described, that is of central importance to addressing the injury-hyperplasia phenomenon from an angiographic viewpoint. When the relative gain-relative loss relationship was investigated according to these 0.5 mm increments of vessel diameter, it was apparent that the relationship was exactly similar for all vessels (Fig. 15). Thus what is described here appears to be a real phenomenon that is independent of vessel size. We could speculate that the reason for the greater relative gain in small vessels is the result of the clinical requirement for a good angiographic result in the catheterization room. This demands considerable luminal gain in small vessels given the usual angiographic magnification limitations. In addition, perhaps balloon (or device) oversizing is more likely or frequent in small vessels. With the greater relative gain, more extensive wall injury is imparted, provoking a more intense healing response with formation of thicker neointimal layer that is reflected by greater angiographic relative loss in lumen during follow-up. This may be a simplistic but practical speculation on what is undoubtedly a complex and multifactorial phenomenon, but one message is clear: the inescapable fact that greater proportional luminal gain at intervention induces greater subsequent proportional loss during follow-up.

The restenosis paradox. This apparent paradox of greater luminal renarrowing associated with more substantial luminal improvement at balloon angioplasty has now been demonstrated in several clinical studies from our group by multiple regression analysis applied to large patient populations with respect to many potentially important predictors of restenosis.[54, 105, 117, 136] We have also examined the relationship between relative luminal gain at intervention and relative loss during follow-up for other percutaneous coronary revascularization devices and preliminary results also demonstrate a direct linear relationship.[101] In light of available evidence from previous clinical studies from our own institution[11-13, 16, 93, 105] and others[14, 15, 39, 124], experimental reports,[65, 68] and the commonly held belief that res-

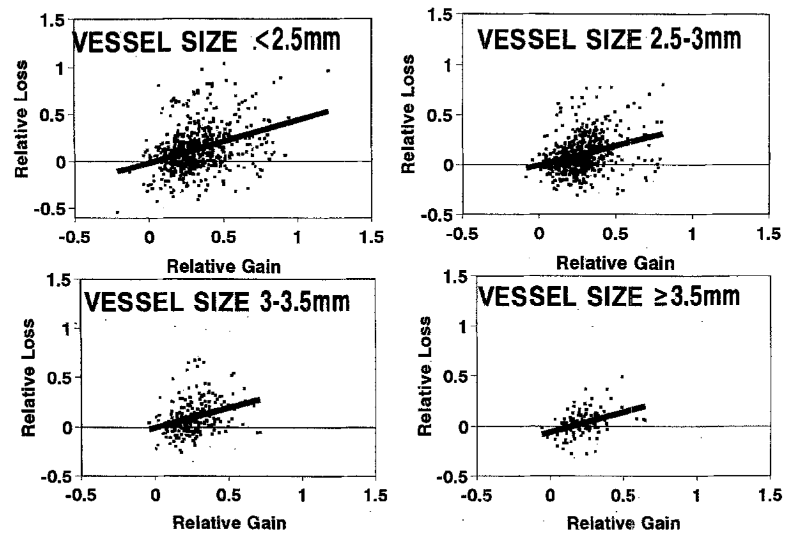

Fig. 15. Linear regression of relative loss on relative gain according to increments of vessel size as shown in Fig. 14. Relationship between variables is similar for each group. It is also possible to glean two other messages from receding scatterplots with increasing vessel size: (1) much greater frequency with which balloon angioplasty procedures are carried out in smaller vessels, and (2) degree of relative gain achieved at balloon angioplasty is less in larger vessels, as shown in Fig. 14.

tenosis is a tissue response to vessel wall injury, the demonstration of such a relationship between relative luminal gain and loss is not all that surprising. The Mayo Clinic report[65] (of a proportional neointimal response to graded vessel wall injury) observing that the extent of coronary artery injury was more closely related to the actual thickness of the neointimal layer than to percent luminal area stenosis highlights the importance in clinical angiographic restenosis studies of attempting to measure the volume of the "doughnut" and the "doughtnut hole." Collectively, all of these studies support previous experimental[137] and autopsy-based[138] claims that the intensity of neointimal proliferation after balloon dilatation is dependent on the depth of vessel wall injury. Furthermore, they sustain the contention that categoric restenosis definitions are inherently limited in their ability to describe the ubiquitous process of luminal renarrowing after interventions.

The deduction from the previously mentioned study by Kuntz et al.[124] that by achieving a greater gain in lumen newer devices may reduce angiographic restenosis, is apparently contradictory to our contention. Although our group focuses mainly on the relationship between the relative gain/relative loss relationship by which to judge the effectiveness of a therapeutic intervention as a reflection of its impact on the injury/hyperplasia relationship, Kuntz et al. focused on the final MLD at follow-up as the ultimate outcome variable. This is the difference, as has been succinctly put by Schwartz et al.,[65] between looking at the "doughnut" or the "doughnut hole." There is little doubt that a larger lumen at follow-up is better for the patient and that this parameter, as discussed previously, is of paramount importance in assessing the long-term clinical success of therapy. However, in large clinical trials directed at prevention of the *process* of restenosis, the effect of therapy must be measured by its ability to restrict or control the thickness of the doughtnut, which we believe is best encapsulated angiographically by the relative gain/relative loss relationship. In Fig. 16 the actual relative gain/relative loss relationships of patients undergoing therapy by four different interventional devices are shown with the line of identity and an imaginary regression line for the ideal interventional device. It is clear that a device whose regression line crosses the identity line can be considered to be associated with a worse angiographic outcome than one with a gentle line slope. The ideal device has a horizontal relationship between relative gain and loss such that despite increasing relative gain there is no increase in relative loss. Such a device may be considered as the magic bullet or golden fleece. This finding is in clear contrast to the published findings of Kuntz et al.,[131, 139] who have reported no difference in loss index (acute gain/late loss) between patients treated by directional atherectomy, stent implantation, or balloon angioplasty and concluded that the most important determinant of favorable long-term angio-

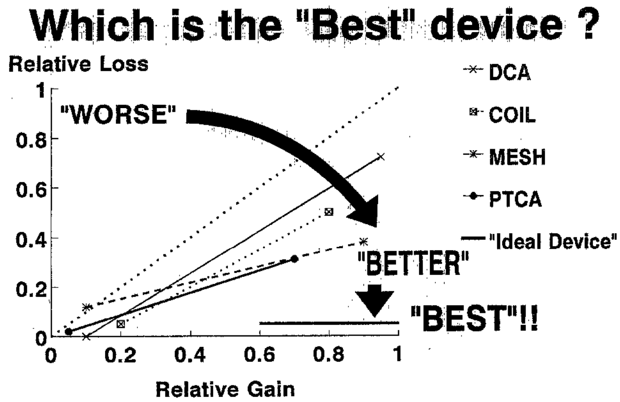

Fig. 16. Linear regression relationship of relative gain/relative loss of patients who underwent therapy by four different interventional devices are shown with line of identity. Imaginary regression line for ideal interventional device is included. It is clear that device whose regression line crosses identity line can be considered to be associated with worse angiographic outcome than one with gentle line slope. Ideal device has horizontal regression line slope so that with increasing relative gain there is no increase in relative loss. *DCA*, Directional atherectomy (n = 123 lesions); *COIL*, balloon-expandable tantalum coil stent (n = 101 lesions); *MESH*, self-expanding stainless steel mesh stent (n = 110 lesions); *PTCA*, percutaneous transluminal coronary (balloon) angioplasty (n = 1435 lesions).

graphic outcome is a large luminal diameter after intervention, regardless of which device is used to achieve this. It is worth noting that despite these apparently conflicting viewpoints, both the Beth Israel[94] and Thoraxcentre[124] groups agree that instead of reducing intimal hyperplasia, newer devices actually provoke increased hyperplasia, and that the process of luminal renarrowing is a ubiquitous and normally distributed phenomenon and should be described as such rather than according to arbitrary binary criteria.[94, 124]

Clinical implications and applications of relative gain and relative loss. This direct relationship between restenosis, as represented by relative loss in luminal diameter during follow-up, and luminal improvement or relative gain at intervention, has important ramifications, not only for clinical trials but also perhaps for clinical decision making in individual patients. With the impending widespread availability of quantitative coronary angiographic facilities for the catheterization room, precise measurements will be readily accessible on-line, allowing a step-by-step objective and accurate assessment of progress during intervention rather than the current practice of eyeballing the video screen with its inherent limitations. This should facilitate appropriate selection of balloon and device sizes to avoid excessive vessel wall injury caused by oversizing. As confirmed by the considerable scatter of data points in the regression analyses shown in Figs. 13 and 15, the phenomenon of wall injury and healing response is clearly multifactorial. In addition, it must be recognized that progressively increasing relative gain will ultimately yield a greater proportional net angiographic benefit (despite provoking concomitantly greater relative luminal loss) because the relationship is always below and diverging from the line of identity. Therefore it would be fallacious to attempt to give individual guidelines as to the ideal relative gain for which to aim. In the final analysis, achievement of the greatest luminal improvement possible by the least traumatic means and avoiding precipitation of acute complications must be the ultimate goal of percutaneous intervention.

The ultimate end-point. The ultimate test of new treatments is, of course, the randomized clinical trial, of which many are now in progress. The issues raised in this article identify a vital aspect of randomized trials, that is, how will the results be presented? As has been mentioned, angiographic endpoints are now evaluated by quantitative analysis in terms of changes in MLD from immediately after intervention to follow-up. The particular characteristic of the randomized population is that baseline demographic and angiographic characteristics in the various treatment groups are assumed to be similar.[135] However, the already emphasized differences between devices with regard to the immediate luminal improvements attainable at intervention and the subsequent luminal loss during follow-up suggest that the within patient change in minimal luminal diameter may not be the measurement of choice to assess the comparative value of the various interventions. The most objective and clinically meaningful parameter to use in *randomized clinical trials* is the minimal luminal diameter *at* follow-up as the ultimate endpoint of treatment, taking all aspects of the trial into account. This simple approach may be equally usefully applied to trials of pharmacologic agents for the control of restenosis. Change in MLD during follow-up is undoubtedly the clearest angiographic measure of the hyperplastic healing process, but it can only be usefully applied if, in addition to baseline clinical and angiographic features, luminal gain at intervention is also likely to be similar in the groups being compared thus where the same mechanical intervention is used. The therapeutic effectiveness of interventional devices in achieving satisfactory luminal increase without provoking excessive hyperplasia among different patient groups may best be assessed through comparison of the relative gain/relative loss relationship (Fig. 16). The application of this approach to randomized trials will provide its ultimate test of usefulness.

Conclusions. We submit, in agreement with others, that angiographic restenosis as a process of luminal renarrowing should be considered as a continuous phenomenon and be so described in clinical trials. In addition, a proportional relationship is described between luminal increase at intervention and subsequent renarrowing during follow-up for a number of interventional devices. It is clear therefore that restenosis is an unavoidable consequence of any therapy that inflicts injury on the arterial wall. In contrast to the findings of other groups, clear differences are observed between the devices in the relative gain/relative loss relationship, which may reflect inherent device-specific characteristics of the injury/hyperplasia phenomenon. We have no erudite solutions to offer to this persistent limitation of all interventional devices except to suggest that the search for a magic bullet now seems more compelling than ever.

SUMMARY

In this editorial, the problem of restenosis after coronary balloon angioplasty and other transluminal interventions is reviewed from the perspective of quantitative coronary angiography. The review is largely based on the experience of the Thoraxcentre in the application of quantitative angiography to the study of restenosis over the past decade, with incorporation and discussion of relevant and significant contributions from other groups. Current discrepancies in the angiographic definition of restenosis are highlighted and the use of percent diameter stenosis or MLD as the measurement parameter of choice is objectively addressed. Perspectives on the pathologic paradigm of restenosis are briefly reviewed as a basis from which to evaluate quantitative angiographic information provided by various studies. Particular attention is then paid, in chronologic fashion, to discussion and elaboration of insights to the restenosis process provided by quantitative angiographic studies, which have led to the introduction of some new methodological approaches to the comparison of short- and long-term angiographic luminal changes after various interventions. A word of caution on the potential pitfalls of quantitative angiographic studies is provided and counterbalanced with a discussion of clinical correlations of quantitative angiographic measurements. Finally, a proposal is made for the application of quantitative angiographic measurements to randomized clinical trials for the purpose of comparing new interventional devices.

REFERENCES

1. Forrester JS, Fishbein M, Helfant R, Fagin J. A paradigm for restenosis based on cell biology: clues for development of new preventive therapies. J Am Coll Cardiol 1991;17:758-69.
2. Myler RK, Shaw RE, Stertzer SH, Ziphin RE, Rosenblum J, Hecht HS, Ryan C, Briskin JG, Dunlap RW, Hanson CL, Zapolanski A, Cumberland DC. There is no such thing as "restenosis." J Inv Cardiol 1992;4:282-290.
3. Sigwart U, Puel J, Mircowitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med 1987;316:701-6.
4. Simpson JB, Hinohara T, Selmon MR, Robertson G, White N, Rorve M, Braden L. Comparison of early and recent experience in percutaneous coronary atherectomy [Abstract]. J Am Coll Cardiol 1989;13:109A.
5. Stack RS, Califf RM, Phillips HR, Pryor DB, Quigley PJ, Boumann RP, Tcheng JE, Greenfield JC Jr. Advances in cardiovascular technologies: interventional cardiac catheterization at Duke Medical Centre. Am J Cardiol 1988;62:1-44F.
6. Ahn SS, Auth D, Marcus DR. Removal of focal atheromatous lesions by angioscopically guided high speed rotary atherectomy. J Vasc Surg 1988;7:292-300.
7. Spears JR, Reyes V, Sinclair N, Hopkins B, Schwartz L, Aldridge H, Plokker HWT. Percutaneous coronary laser balloon angioplasty: preliminary results of a multicenter trial [Abstract]. J Am Coll Cardiol 1989;13(suppl A):61A.
8. Abela GS, Seeger JM, Barbieri E, Franzini D. Laser angioplasty with angioscopic guidance in humans. J Am Coll Cardiol 1986;8:184-92.
9. Karsch KR, Haase KK, Mauser M, Ickrath O, Voelker W, Duda S. Percutaneous coronary excimer laser angioplasty: initial clinical results. Lancet 1989;2:647-50.
10. Hermans WRM, Rensing BJ, Strauss BH, Serruys PW. Prevention of restenosis after percutaneous transluminal coronary angioplasty (PTCA): the search for a "magic bullet." Am Heart J 1991;122:1:171-87.
11. Serruys PW, Strauss BH, Beatt KJ, Bertrand ME, Puel J, Rickards AF, Meier B, Goy JJ, Vogt P, Kappenberger L, Sigwart U. Angiographic follow-up after placement of a self-expanding coronary artery stent. N Engl J Med 1991;324:13-7.
12. Serruys PW, Strauss BH, van Beusekom HM, van der Giessen WJ. Stenting of coronary arteries: has a modern Pandora's box been opened? J Am Coll Cardiol 1991;17:143-54B.
13. Umans VA, Beatt KJ, Rensing BJ, Hermans WR, de Feyter PJ, Serruys PW. Comparative quantitative angiographic analysis of directional coronary atherectomy and balloon angioplasty: a new methodologic approach. Am J Cardiol 1991;68:1556-63.
14. Karsch KR, Haase KH, Voelker W, Baumbach A, Mauser M, Seipel L. Percutaneous coronary excimer laser angioplasty in patients with stable and unstabla angina pectoris: acute results and incidence of restenosis during 6-month follow-up. Circulation 1990;81:1849-59.
15. Bertrand ME, Lablanche JM, Leroy F, Bauters C, de Jaegere P, Serruys PW, Meyer J, Dietz U, Erbel R. Percutaneous transluminal coronary rotational ablation with rotablator (European experience). Am J Cardiol 1992;69:470-4.
16. De Jaegere P, Serruys PW, Bertrand M, Wiegand V, Gisbert K, Marquis JF, Valeix B, Uebis R, Piessens J. Wiktor stent implantation in patients with restenosis following balloon angioplasty of a native coronary artery lesion: immediate and long-term clinical and angiographic results of the first fifty patients. Am J Cardiol 1992;69:598-602.
17. Gruentzig AR, Myler RK, Hanna ES, Turina MI. Transluminal angioplasty of coronary-artery stenosis [Abstract]. Circulation 1977;56(suppl II):III-84.
18. Reiber JHC, Booman S, Tan HS, Slager CJ, Schuurbiers JCH, Gerbrands JJ, Meester GT. A cardiac image analysis system. Objective quantitative processing of angiocardiograms. Proc Comp Cardiol, 1978:239-42.
19. Reiber JHC, Booman S, Tan HS, Gerbrands JJ, Slager CJ, Schuurbiers JCH, Meester GT. Computer processing of coronary occlusions from x-ray arteriograms. Proceedings VI International Conference on Information Processing in Medical Imaging (Paris), 1979:79-92.
20. Serruys PW, Booman F, Troost GJ, Reiber JHC, Gerbrands JJ, van den Brand M, Cherrier F, Hugenholtz PG. Computerized quantitative coronary angiography applied to percutaneous transluminal coronary angioplasty: advantages and

limitations. In: Kaltenbach M, Rentrop P and Gruentzig AR eds. Transluminal coronary angioplasty and intracoronary thrombolysis. Berlin: Springer-Verlag, 1982:110-24.
21. Fleming RM, Kirkeeide RL, Smalling RW, Gould KL. Patterns in visual interpretation of coronary angiograms as detected by quantitative coronary angiography. J Am Coll Cardiol 1991;18:945-51, 72.
22. Hirshfeld JW, Schwartz SS, Jugo R, Macdonald RG, Goldberg S, Savage MP, Bass TA, Vetrovec G, Cowley M, Taussig AS, Withworth HB, Margolis JR, Hill JA, Pepine CJ, and the M-Heart Investigators. Restenosis after coronary angioplasty: a multivariate statistical model to relate lesion and procedural variables to restenosis. J Am Coll Cardiol 1991; 18:647-56.
23. Holmes DR Jr, Vliestra RE, Smith HC, Vetrovec GW, Kent KM, Cowley MJ, Faxon DP, Grüntzig AR, Kelsey SF, Detre KM, van Raden MJ, Mock MB. Restenosis after percutaneous transluminal coronary angioplasty: a report from the PTCA Registry of the National Heart, Lung and Blood Institute. Am J Cardiol 1984;53:77-81C.
24. Corocos T, David PR, Val PG, Renkin J, Dangoisse V, Rapold HG, Bourassa MG. Failure of diltiazem to prevent restenosis after percutaneous transluminal coronary angioplasty. AM HEART J 1985;109:926-31.
25. Thornton MA, Gruentzig AR, Hollman Y, King BS, Douglas JS. Coumadin and aspirin in the prevention of recurrence after transluminal coronary angioplasty: a randomized study. Circulation 1984;69:721-7.
26. Leimgruber PP, Roubin GS, Hollman J, Cotsonis GA, Meier B, Douglas JS, King SB III, Gruentzig AR. Restenosis after successful coronary angioplasty in patients with single-vessel disease. Circulation 1986;73:710-7.
27. Vandormael MG, Deligonul U, Kern MJ, Harper M, Presant S, Gibson P, Galan K, Chaitman BR. Multilesion coronary angioplasty: clinical and angiographic follow-up. J Am Coll Cardiol 1987;10:246-52.
28. Reis GJ, Boucher TM, Sipperly ME, Silverman DJ, McGabe CH, Baim DS, Sachs FM, Grossman W, Pasternak RC. Randomised trial of fish oil for prevention of restenosis after coronary angioplasty. Lancet 1989;2:177-81.
29. Meyer J, Schmitz HJ, Kiesslich T, Erbel R, Krebs W, Shultz W, Bardos P, Minale C, Messmer BJ, Effert S. Percutaneous transluminal coronary angioplasty in patients with stable and unstable angina pectoris: analysis of early and late results. AM HEART J 1983;106:973-80.
30. Fleck E, Dacian S, Dirschinger J, Hall D, Rudolph W. Quantitative changes in stenotic coronary artery lesions during follow-up after PTCA [Abstract]. Circulation 1984;70(suppl II):II-176.
31. Serruys PW, Luijten HE, Beatt KJ, Geuskens R, de Feyter PJ, van den Brand M, Reiber JHC, Ten Katen F, van Es GA, Hugenholtz PG. Incidence of restenosis after successful angioplasty: a time related phenomenon. A quantitative angiographic study in 342 consecutive patients at 1, 2, 3 and 4 months. Circulation 1988;77:361-71.
32. Nobuyoshi M, Kimura T, Nosaka H, Mioka S, Ueno K, Hamasaki N, Horiuchi H, Oshishi H. Restenosis after successful percutaneous transluminal coronary angioplasty: serial angiographic follow-up of 299 patients. J Am Coll Cardiol 1988;12:616-23.
33. Bourassa MG, Lesperance J, Eastwood C, Schwartz L, Gote G, Kazim F, Hudon G. Clinical, physiologic, anatomic, and procedural factors predictive of restenosis after percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1991; 18:368-76.
34. Gould KL, Lipscomb K, Hamilton GW. Physiological basis for assessing critical coronary stenosis: instanteous flow response and regional distribution during coronary hyperaemia as measures of coronary flow reserve. Am J Cardiol 1974;33:87-97.
35. Arnett EN, Isner JM, Redwood DR, Kent KM, Baker WP, Ackerstein H, Roberts WC. Coronary artery narrowing in coronary heart disease: comparison of cineangiographic and necropsy findings. Ann Intern Med 1979;91:350-6.
36. Nissen SE, Gurley JC, Grines CL, Booth DC, McClure R, Berk M, Fischer C, DeMaria AN. Intravascular ultrasound assessment of lumen size and wall morphology in normal subjects and patients with coronary artery disease. Circulation 1991;84:1087-99.
37. Glagov S, Weisenberg E, Zarins CK, Stankunavicius K, Kolettis GJ. Compensatory enlargement of various human atherosclerotic coronary arteries. New Engl J Med 1987;316: 1371-5.
38. Beatt KJ, Luijten HE, de Feyter PJ, van den Brand M, Reiber JH, Serruys PW. Change in diameter of coronary artery segments adjacent to stenosis after percutaneous transluminal coronary angioplasty: failure of the percentage of diameter stenosis measurement to reflect morphologic changes induced by balloon dilation. J Am Coll Cardiol 1988;12:315-23.
39. Smucker ML, Kil D, Howard PF, Sarnat WS. "Whole artery restenosis" after coronary atherectomy: a quantitative angiographic study [Abstract]. AHA 64th scientific sessions; Circulation 1991;84:II-81.
40. Foley DP, Hermans WRM, Rutsch BJ, Emanuelsson H, Danchin N, Wijns W, Chappuis F, Serruys PW, for the Mercator group. Restenosis after PTCA affects the entire vessel segment that is being dilated [Abstract]. J Am Coll Cardiol 1993;21:322A.
41. White CW, Wright CB, Doty DB, Hiratza LF, Eastham CL, Harrison DG, Marcus ML. Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? N Engl J Med 1984;310:819-24.
42. Zijlstra F, van Ommeren J, Reiber JHC, Serruys PW. Does quantitative assessment of coronary artery dimensions predict the physiological significance of a coronary stenosis? Circulation 1987;75:1154-61.
43. Serruys PW, Wijns W, Geuskens R, de Feyter P, van den Brand M, Reiber JHC. Pressure gradient, exercise thallium 201 scintigraphy, quantitative coronary cineangiography: in what sense are these measurements related? In: Reiber JHC, Serruys PW, eds. State of the art in quantitative coronary arteriography. Lancaster: Martinus Nijhoff Publishers, 1986:251-70.
44. Wijns W, Serruys PW, Reiber JHC, van den Brand M, Simoons ML, Kooijman CJ, Balakumaran K, Hugenholtz PG. Quantitative angiography of the left anterior descending coronary artery: correlation with pressure gradient and results of exercise thallium scintigraphy. Circulation 1985; 71:273-9.
45. Reiber JHC, Serruys PW. Quantitative coronary angiography. In: Marcus ML, Schelbert HR, Skorton DJ, Wolf GI, eds. Cardiac imaging, a companion to Braunwalds heart disease. New York: WB Saunders, 1991:211-80.
46. Beatt KJ, Serruys PW, Hugenholtz PG. Restenosis after coronary angioplasty: new standards for clinical studies. J Am Coll Cardiol 1990;15:491-9.
47. Rensing BJ, Hermans WRM, Beatt KJ, Laarman GJ, Suryapranata H, van den Brand M, de Feyter PJ, Serruys PW. Quantitative angiographic assessment of elastic recoil after percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1991;17:34-8B.
48. Rensing BJ, Hermans WR, Strauss BH, Serruys PW. Regional differences in elastic recoil after percutaneous transluminal coronary angioplasty: a quantitative angiographic study. J Am Coll Cardiol 1991;17:34-8B.
49. Hanet C, Wijns W, Michel X, Schroeder E. Influence of balloon size and stenosis morphology on immediate and delayed elastic recoil after percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1991;18:506-11.
50. Hermans WR, Rensing BJ, Strauss BH, Serruys PW. Methodological problems related to the quantitative assessment of stretch, elastic recoil, and balloon-artery ratio. Cathet Cardiovasc Diagn 1992;25:174-85.

51. Isner JM, Rosenfield K, Losordo DW, Rose L, Langevin RE Jr, Razvi S, Kosowsky BD. Combination balloon-ultrasound imaging catheter for percutaneous transluminal angioplasty. Validation of imaging, analysis of recoil, and identification of plaque fracture. Circulation 1991;84:739-54.
52. Hanet C, Michel X, Schroeder E, Wijns W. Lack of detectable delayed elastic recoil during the first 24 hours after coronary balloon angioplasty [Abstract]. Eur Heart J 1992;13 (suppl):2228.
53. Foley DP, Rensing BJ, Vos J, Deckers J, Serruys PW. Is there a need for angiography after 24 hours to assess the result of coronary balloon angioplasty in clinical studies [Abstract]. Circulation 1992;86:I-785.
54. Rensing BJ, Hermans WR, Vos J, Beatt KJ, Bossuyt P, Rutsch W, Serruys PW, on behalf of the Carport study group. Quantitative angiographic risk factors of luminal narrowing after coronary balloon angioplasty using balloon measurements to reflect stretch and elastic recoil at the dilatation site. Am J Cardiol 1992;69:584-91.
55. Steele PM, Chesebro JH, Stanson AW, Holmes DR Jr, Dewanjee MK, Badimon L, Fuster V. Balloon angioplasty: natural history of the pathophysiological response to injury in the pig model. Circ Roman Res 1985;57:105-12.
56. Uchida Y, Hasegawa K, Kawamura K, Shibuya I. Angioscopic observation of the coronary luminal changes induced by coronary angioplasty. AM HEART J 1989;117:769-76.
57. Chesebro JH, Lam JYT, Badimon L, Fuster V. Restenosis after arterial angioplasty: a hemorrheologic response to injury. Am J Cardiol 1987;60:10-6B.
58. Clowes AW, Reidy MA, Clowes MM. Mechanisms of stenosis after arterial injury. Lab Invest 1983;49:208-15.
59. Essed CE, van den Brand M, Becker AE. Transluminal coronary angioplasty and early restenosis: fibrocellular occlusion after wall laceration. Br Heart J 1983;49:393-6.
60. Austin GE, Ratliff NB, Hollman J, Tabei S, Phillips DF. Intimal proliferation of smooth muscle cells as an explanation for recurrent coronary artery stenosis after percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1985;6:369-75.
61. Ip JH, Fuster V, Israel D, Badimon L, Chesebro JH. The role of platelets, thrombin and hyperplasia in restenosis after a coronary angioplasty procedure. J Am Coll Cardiol 1991;17:77-88B.
62. Waller BF, Pinkerton CA, Orr SM, Slack JD, Van Tassel JW, Pinto RP. Restenosis 1 to 24 months after clinically successful coronary balloon angioplasty: a necropsy study of 20 patient. J Am Coll Cardiol 1991;17:58-70B.
63. Schwartz RS, Holmes DR, Topol EJ. The restenosis paradigm revisited: an alternative proposal for cellular mechanisms. J Am Coll Cardiol 1992;20:1284-93.
64. Schwartz RS, Murphy JG, Edwards WD, Camrud AR, Vliestra RE, Holmes DR. Restenosis after balloon angioplasty. A practical proliferative model in porcine coronary arteries. Circulation 1991;82:2190-200.
65. Schwartz RS, Huber KC, Murphy JG, Edwards WD, Camrud AR, Vlietstra RE, Holmes DR. Restenosis and the proportional neointimal response to coronary artery injury: results in a porcine model. J Am Coll Cardiol 1992;19:267-74.
66. Feigl W, Susani M, Ulrich W, Matejka M, Losert U, Sinzinger H. Organisation of experimental thrombosus by blood cells. Evidence of the transformation of mononuclear cells into myofibroblasts and endothelial cells. Virchows Arch A Pathol Anat Histopathol 1985;406:133-48.
67. Leu HJ, Feigl W, Susani M. Angiogenesis from mononuclear cells in thrombi. Virchows Arch A Pathol Anat Histopathol 1987;411:5-14.
68. Karas SP, Gravanis MB, Santoian EC, Robinson KA, Anderberg KA, King SB III. Coronary intimal proliferation after balloon injury and stenting in swine: an animal model of restenosis. J Am Coll Cardiol 1992;20:467-74.
69. Santonian EC, Gravanis MB, Karas SP. Sequence of the reparative phenomena and development of smooth muscle cell proliferation following coronary angioplasty in a swine restenosis model [Abstract]. Clin Res 1992;40:364A.
70. Gravanis MB, Roubin GS. Histopathologic phenomenona at the site of percutaneous transluminal coronary angioplasty: the problem of restenosis. Hum Pathol 1989;20:477-85.
71. den Heijer P, van Dijk RB, Pentinga ML, Lie KI. Serial angioscopy during the first hour after successful PTCA [Abstract]. Circulation 1992;86:I-458.
72. Uchida Y, Tomaru T, Fujimora Y, Miwa A, Nakamura F, Yamada K. Observation of luminal changes in human coronary artery by an intravascular microscope [Abstract]. Circulation 1992;86:I-503.
73. Beatt KJ, Serruys PW, Luijten HE, Rensing BJ, Suryapranata H, de Feyter P, van den Brand M, Laarman GJ, Roelandt J. Restenosis after coronary angioplasty: the paradox of increased lumen diameter and restenosis. J Am Coll Cardiol 1992;19:258-66.
74. Kent KM, Bonow RO, Rosing DR, Ewels CJ, Lipson LC, McIntosh CL, Bacharach S, Green M, Epstein SE. Improved myocardial function during exercise after successful percutaneous transluminal coronary angioplasty. N Engl J Med 1982;306:441-6.
75. Califf RM, Ohman EM, Frid DJ, Fortin DF, Mark DB, Hlatky MA, Herndon JE, Bengtson JR. Restenosis: the clinical issues. In: Topol EJ, ed. Textbook of interventional cardiology. Philadelphia: WB Saunders, 1990:363-94.
76. Popma JJ, van den Berg EK, Dehmer GJ. Long-term outcome of patients with asymptomatic restenosis after percutaneous transluminal angioplasty. Am J Cardiol 1989; 62:1298-9.
77. Jain A, Mahmarian JJ, Borges-Neto S, Johnston DL, Cashion R, Lewis JM, Raizner AE, Verani MS. Clinical significance of perfusion defects by thallium-201 single photon emission tomography following oral dipyridamole early after coronary angioplasty. J Am Coll Cardiol 1988;11:970-6.
78. Vlay SC, Chernilas J, Lawson WE, Dervan JP. Restenosis after angioplasty: don't rely on the exercise test. AM HEART J 1989;4:980-6.
79. Laarman GJ, Luijten HE, van Zeyl LG, Beatt KJ, Tijssen JGP, Serruys PW. Assessment of "silent" restenosis and long-term follow-up after successful angioplasty in single-vessel coronary artery disease: the value of quantitative exercise electrocardiography and quantitative coronary angiography. J Am Coll Cardiol 1990;16:578-85.
80. Klocke FJ. Measurements of coronary blood flow and degree of stenosis: current clinical implications and continuing uncertainties. J Am Coll Cardiol 1983;1:31-41.
81. Serruys PW, Zijlstra F, Laarman GJ, Reiber JHC, Beatt K, Roelandt J. A comparison of two methods to measure coronary flow reserve in the setting of coronary angioplasty: intracoronary bloodflow velocity measurements with a Doppler catheter and digital subtraction cineangiography. Eur Heart J 1989;10:725.
82. Zijlstra F, den Boer A, Reiber JHC, Van Es GA, Lubsen J, Serruys PW. The assessment of immediate and long-term functional results of percutaneous transluminal coronary angioplasty. Circulation 1988;1:15-24.
83. Hodgson JM, Riley RS, Most AS, Williams DO. Assessment of coronary flow reserve using digital angiography before and after successful percutaneous transluminal coronary angioplasty. Am J Cardiol 1987;60:61-5.
84. Kirkeeide RL, Gould KL, Parsel L. Assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilation. Validation of coronary flow reserve as a single integrated functional measure of stenosis severity reflecting all its geometric dimensions. J Am Coll Cardiol 1986;7:103-13.
85. Honye J, Mahon DJ, Jain A, White CJ, Ramsee SR, Wallis JB, Al-Zarka A, Tobis JM. Morphological effects of coronary balloon angioplasty in vivo assessed by intravascular ultrasound imaging. Circulation 1992;85:1012-25.
86. Serruys PW, Wijns W, van den Brand M, ??????. Is translu-

minal coronary angioplasty mandatory after successful thrombolysis? A quantitative angiographic study. Br Heart J 1983;50:257.

87. Serruys PW, Reiber JHC, Wijns W, van den Brand M, Kooijman CJ, ten Katen HJ, Hugenholtz PG. Assessment of percutaneous transluminal coronary angioplasty by quantitative coronary angiography: diameter versus densitometric area measurements. Am J Cardiol 1984;54:482.
88. Reiber JHC, Serruys PW, Kooijman CJ, Wijns W, Slager CJ, Gerbrands JJ, Schuurbiers JCH, den Boer A, Hugenholtz PG. Assessment of short-, medium-, and long-term variations in arterial dimensions from computer-assisted candidate of coronary cineangiograms. Circulation 1985;71:280-8.
89. Serruys PW, Juilliere Y, Bertrand ME, Puel J, Rickards A, Sigwart U. Additional improvement of stenosis geometry in human coronary arteries by stenting after balloon dilation: a quantitative angiographic study. Am J Cardiol 1988;61:71-6G.
90. Strauss BH, Juilliere Y, Rensing BJ, Reiber JHC, Serruys PW. Edge detection versus densitometry for assessing coronary stenting quantitatively. Am J Cardiol 1991;67:484-90.
91. Umans VA, Strauss BH, de Feyter PJ, Serruys PW. Edge detection versus videodensitometry for quantitative angiographic assessment of directional coronary atherectomy. Am J Cardiol 1991;68:534-9.
92. de Feyter PJ, Serruys PW, Davies MJ, Richardson P, Lubsen J, Oliver MF. Quantitative coronary angiography to measure progression and regression of coronary atherosclerosis. Values, limitations and implications for clinical trials. Circulation 1991;84:412-23.
93. Strauss BH, Serruys PW, de Scheerder IK, Tijssen JGP, Bertrand ME, Puel J, Meier B, Kaufmann U, Strauffer JC, Rickards AF, Sigwart U. A relative risk analysis of the angiographic predictors of restenosis within the coronary Wallstent. Circulation 1991;84:1636-43.
94. Rensing BJ, Hermans WR, Deckers JW, de Feyter PJ, Tijssen JGP, Serruys PW. Luminal narrowing after percutaneous transluminal coronary balloon angioplasty follows a near gaussian distribution. A quantitative angiographic study in 1445 successfully dilated lesions. J Am Coll Cardiol 1992; 19:939-45.
95. di Mario C, Hermans WRM, Rensing BJ, Serruys PW. Calibration using angiographic catheters as scaling devices - importance of filming the catheters not filled with contrast medium [Letter]. Am J Cardiol 1992;69:1377.
96. di Mario C, Haase J, den Boer A, Reiber JHC, Serruys PW. Edge detection versus videodensitometry in the quantitative assessment of stenosis phantoms: an in-vivo comparison in porcine coronary arteries. AM HEART J 1992;124:1181-9.
97. Haase J, de Mario C, Slager CJ, van der Giessen WJ, den Boer A, de Feyter PJ, Verdow PD, Reiber JHC, Serruys PW. In-vivo validation of on-line and off-line geometric coronary measurements using insertion of stenosis phantoms in porcine coronary arteries. Cathet Cardiovasc Diagn 1992;27:16-27.
98. Serruys PW, de Jaegere P, Bertrand M, Kober G, Marquis JF, Piessens J, Uebis R, Valeix B, Wiegand V. Morphological change of coronary artery stenosis with the Medtronic Wiktor stent. Initial results from the core laboratory for quantitative angiography. Cathet Cardiovasc Diagn 1991; 24:237-45.
99. Hermans WRM, Rensing BJ, Paameyer J, Serruys PW. Experiences of a quantitative coronary angiographic core laboratory in restenosis prevention trials. In: Reiber JHC, Serruys PW, eds. Advances in quantitative coronary arteriography. Dordrecht: Kluwer Academic Publishers, 1993:117-95.
100. Hermans WR, Rensing BJ, Kelder JC, de Feyter PJ, Serruys PW. Postangioplasty restenosis rate between segments of the major coronary arteries. Am J Cardiol 1992;69:194-200.
101. Foley DP, Hermans WR, de Jaegere PP, Umans VA, Vos J, Escaned J, de Feyter PJ, Serruys PW. Is "bigger" really "better"? A quantitative angiographic study of immediate and long term outcome following balloon angioplasty, directional atherectomy and stent implantation [Abstract]. Circulation 1992;86:I-530.
102. Foley DP, Hermans WR, Umans VA, de Jaegere PP, Serruys PW. The influence of vessel size on restenosis following percutaneous coronary interventions [Abstract]. Circulation 1992;86:I-255.
103. Umans VAWM, Strauss BH, Rensing BJWM, de Jaegere P, de Feyter P, Serruys PW. Comparative angiographic quantitative analysis of the immediate efficacy of coronary atherectomy with balloon angioplasty, stenting and rotational ablation. AM HEART J 1991;122:836-43.
104. de Jaegere P, Strauss BH, de Feyter P, Suryapranata H, van den Brand M, Serruys PW. Stent versus balloon angioplasty: matching based on QCA, a surrogate for randomized studies. AM HEART J 1993;125:310-8.
105. de Jaegere P, Bertrand M, Wiegand V, Kober G, Marquis JF, Valeix B, Uebis R, Piessens J, de Feyter P, Serruys PW. Angiographic predictors of restenosis following Wiktor stent implantation [Abstract]. J Am Coll Cardiol 1992;19(Suppl): 277A.
106. Umans VA, Hermans WR, Foley DP, de Feyter PJ, Serruys PW. Restenosis after directional coronary atherectomy and balloon angioplasty: comparative analysis based on matched lesions. J Am Coll Cardiol 1993;21:1382-90.
107. Umans VA, Hermans WR, Rensing BJ, de Feyter PJ, Serruys PW. Directional coronary atherectomy versus balloon angioplasty: a matched comparative quantitative angiographic analysis [Abstract]. J Am Coll Cardiol 1992;19:276A.
108. Hermans WRM, Rensing BJ, Foley DP, Deckers JW, Rutsch W, Emanuelsson H, Danchin N, Wijns W, Chappuis, Serruys PW. on behalf of the Mercator Study group. Therapeutic dissection after successful coronary angioplasty: no effect on restenosis nor on clinical outcome nor in 693 patients. J Am Coll Cardiol 1992;20:767-80.
109. Gould KL. Identifying and measuring severity of coronary artery stenosis. Quantitative coronary arteriography and positron emission tomography. Circulation 1988;78:237-45.
110. Savage M, Fischman D, Leon M, Ellis S, Goldberg S. Restenosis risk of single Palmaz-Schatz stents in native coronaries: report from the core angiographic laboratory [Abstract]. J Am Coll Cardiol 1992;(suppl);19:277A.
111. Serruys PW, Rutsch W, Heyndrickx GR, Danchin N, Mast EG, Wijns W, Rensing BJ, Vos J, Stibbe J. Prevention of restenosis after percutaneous transluminal coronary angioplasty with thromboxane A_2 receptor blockade. A randomized, double-blind, placebo controlled trial. Circulation 1991; 84:1568-81.
112. The Mercator Study Group. Does the new angiotensin-converting enzyme inhibitor cilazapril prevent restenosis after percutaneous transluminal coronary angioplasty? The results of the Mercator study: a multicenter randomized double-blind placebo-controlled trial. Circulation 1992;86:100-11.
113. Topol EJ, Leya F, Pinkerton CA, Whitlow PL, Hofling B, Simonton CA, Masden RR, Serruys PW, Leon MB, Williams DO, King SB III, Mark DB, Isner JM, Holmes Dr Jr, Ellis SG, Lee KL, Keeler GP, Berdan LG, Hinohara T, Califf RM for the Caveat Study group. A comparison of directional atherectomy with coronary angioplasty in patients with coronary artery disease. N Eng J Med 1993;329:221-7.
114. Cohen EA, Adelman AG Kimball BP, Bonan R, Ricci DR, Webb JG, Laramee L, Barbeau G, Traboulsi M, Corbett BN, Schwartz L, Logan AG. A comparison of directional atherectomy with balloon angioplasty for lesions of the left anterior descending coronary artery. N Engl J Med 1993;329:228-33.

115. Popma JJ, Califf RM, Topol EJ. Clinical trials of restenosis following angioplasty. Circulation 1991;84:1426-37.
116. Ellis SG, Muller DWM. Arterial injury and the enigma of restenosis. J Am Coll Cardiol 1992;19:275-7.
117. Serruys PW, Hermans WRM, Rensing BJ, Thijssen J, Rutsch W, Emanuelsson H, Danchin N, Wijns W, Chappuis F on behalf of the Mercator study group. Are clinical, angiographic or procedural variables predictive of luminal renarrowing after successful coronary balloon angioplasty [Abstract]? Circulation 1992;86:I-849.
118. Serruys PW, Rensing BJ, Luijten HE, Hermans WR, Beatt KJ. Restenosis following coronary angioplasty. In: Meier B, ed. Interventional cardiology. Stuttgart: Hogrefe and Huber, 1990;79-115.
119. Beatt KJ, Luijten HE, Suryapranata H, de Feyter PJ, Serruys PW. Dilatation variables: the paradox of optimal improvement in stenosis by percutaneous transluminal coronary angioplasty and restenosis [Abstract]. Br Heart J 1989;61:439.
120. Beatt KJ, Luijten HE, Suryapranata H, de Feyter PJ, Serruys PW. Dilatation parameters: the paradox of optimal luminal improvement in stenosis by PTCA and restenosis [Abstract]. Eur Heart J 1989;(suppl);10:A28.
121. Beatt KJ, Luijten HE, Suryapranata H, de Feyter PJ, Serruys PW. Suboptimal post-angioplasty result. The principle risk factor for "restenosis" [Abstract]. Circulation 1989(suppl)80;1024.
122. Kuntz RE, Schmidt DA, Levine MJ, Reis GJ, Safian RD, Baim DS. Importance of post-procedure luminal diameter on restenosis following new coronary interventions [Abstract]. Circulation 1990;82:III-314.
123. Kuntz RE, Safian RD, Schmidt DA, Levine MJ, Reis GJ, Baim DS. Restenosis following new coronary devices: the influence of post-procedure luminal diameter [Abstract]. J Am Coll Cardiol 1991;17:2A.
124. Kuntz RE, Safian RD, Levine MJ, Reis GJ, Diver DJ, Baim DS. Novel approaches to the analysis of restenosis after the use of three new coronary devices. J Am Coll Cardiol 1992; 19:1493-9.
125. King SB III, Weintraub WS, Tao X, Hearn J, Douglas JS Jr. Bimodal distribution of diameter stenosis 4 to 12 months after angioplasty: implications for definitions and interpretation of restenosis [Abstract]. J Am Coll Cardiol 1991;17 (suppl):345A.
126. Danchin N, Marie PY, Julliere Y, Karcher G, Bertrand A, Aliot E, Serruys PW, Cherrier F. What is the minimum luminal diameter necessary to avoid exercise-induced myocardial ischemia in post-PTCA patients? Long-term quantitative angiographic study. Eur Heart J 1991;12(suppl):A-889.
127. Rensing BJ, Hermans WRM, Deckers JP, de Feyter PJ, Serruys PW. Which angiographic parameter best describes functional status 6 months after successful single vessel coronary balloon angioplasty. J Am Coll Cardiol 1993;21:317-24.
128. Fischman RF, Kuntz RE, Carroza JP Jr, Miller MJ, Senerchia CC, Schnitt SJ, Diver DJ, Safian RD, Baim DS. Long-term results of directional coronary atherectomy: predictors of restenosis. J Am Coll Cardiol 1992;20:1101-10.
129. Carroza JP Jr., Kuntz RE, Levine MJ, Pomerantz RM, Fishman RF, Mansour M, Gibson CM, Senerchia CC, Diver DJ, Safian RD, Baim DS. Angiographic and clinical outcome of intracoronary stenting: immediate and long-term results from a single-center experience. J Am Coll Cardiol 1992;20: 328-37.
130. Kuntz RE, Hinohara T, Robertson GC, Safian RD, Simpson JB, Baim DS. Influence of vessel selection on the observed restenosis rate after endoluminal stenting or directional atherectomy. Am J Cardiol 1992;70:1101-8.
131. Kuntz RE, Hinohara T, Safian RD, Selmon MR, Simpson JB, Baim DS. Restenosis after directional coronary atherectomy effects of luminal diameter and deep wall excision. Circulation 1992;86:1394-9.
132. Forrester JS, Eigler N, Litvack F. Interventional cardiology: the decade ahead. Circulation 1991;84:942-4.
133. Tcheng JE, Frid DJ, Fortin DF, Nelson CL, Stack RK, Peter RH, Stack RS, Califf RM. Anatomic propensity for restenosis following coronary angioplasty [Abstract]. J Am Coll Cardiol 1991;17(suppl):345A.
134. Reifart N, Preusler W, Storger H, Schwarz F, Hofmann M, Klopper JW, Vandormael M. Comparison of excimer laser, rotablator and balloon angioplasty for the treatment of complex coronary lesions: a randomized trial [Abstract]. Circulation 1992;86:I-374.
135. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Emanuelsson H, Heyndrickx G, de Bruyne B, Rutsch W, Legrand V, Matterne P, Bolland J, Marco J, Fajadet J, van den Heuvel P, van den Brande F, Bonnier H, Bracke F, Colombo A, Morel MA for the Benestent study group. Clinical events and angiographic results of the first 120 patients randomized in the Benestent Study [Abstract]. Circulation 1992;86:I-373.
136. Rensing BJ, Hermans WRM, Vos J, Thijssen JGP, Rutsch W, Danchin N, Heyndrickx GR, Mast EG, Wijns W, Serruys PW, on behalf of the Coronary Artery Restenosis Prevention on Repeated Thromboxane Antagonism (CARPORT) study group. Luminal narrowing after percutaneous transluminal coronary angioplasty. A study of clinical, procedural and lesional factors related to long term angiographic outcome. Circulation 1993 (in press).
137. Barbeau GR, Friedl SE, Santon JM, Federman M, Abela GS. Rupture of internal elastic lamina is essential for restenosis following balloon angioplasty [Abstract]. Circulation 1991; 84:II-603.
138. Nobuyoshi M, Kimura T, Ohishi H, Horiuchi H, Nosaka H, Hamasaki N, Yokoi H, Kim K. Restenosis after percutaneous transluminal coronary angioplasty: pathologic observations in 20 patients. J Am Coll Cardiol 1991;17:433-9.
139. Kuntz RE, Gibson CM, Nobuyoshi M, Baim DS. Generalized model of restenosis after conventional balloon angioplasty, stenting and directional atherectomy. J Am Coll Cardiol 1993;21:15-25.