PERSPECTIVE

# Restenosis after percutaneous interventions: the evolving angiographic perspective

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Percutaneous transluminal coronary angioplasty (PTCA), by balloon or the wide variety of alternative and adjunctive devices, appears to be firmly established as a therapeutic option for patients with obstructive coronary artery disease. Unfortunately (or fortunately), nature has provided a major limitation to the maintained long-term success of such therapies in the guise of the so-called 'Achilles' heel of restenosis'. This perceived spectre is, of course, no more than the biological healing process of the coronary artery wall [1] in response to the obligatory injury inflicted during these innovative but rather crude mechanical attempts at treatment. As a biological phenomenon, therefore, the process is ubiquitous and normally distributed in its intensity throughout the treated population. Bearing this fundamental law of nature in mind, the inherent inappropriateness of arbitrary and subjective categorization of long-term results of intervention into restenosis or non-restenosis, by whatever means, is self-evident.

## Advantages of intervention and limitations of quantitative angiography

Evaluation of the immediate and long-term success of percutaneous revascularization may take many forms. Broadly speaking, four approaches may be identified: symptomatic, functional, physiological, and anatomical [2]. Despite technological advances, the first three have been repeatedly criticized as being too subjective to provide reliable, reproducible, and widely applicable results and information [2]. Thus, the anatomical approach, using the coronary cine-angiogram, has provided the universal substrate for objective evaluation of the outcome of interventions. Of course, the conventional visual estimation of the severity of coronary obstructions from the angiogram was no more objective than the interpretation of the results of functional testing and was repeatedly reported to be associated with wide and unacceptable intra- and inter-observer variability [3]. Quantitative coronary angiography (QCA) was consequently born to provide some sort of objectivity; however, there is no universal agreement on the appropriate quantitative approach. Many studies providing actual luminal dimensional measurements through widely differing methodological approaches have been reported. It is easily accepted that any quantitative approach that requires observer interaction is prone to observer error and thus variability. Only a completely automated system can boast no interobserver variability and 100% reproducibility. No such system exists, although many systems minimize user interaction. For example, the Cardiovascular Angiographic Analysis System (CAAS) developed by our group can automatically detect the coronary contours, in a given cine-frame, of a user-selected segment, whereby the user is not obliged to make any manual corrections [4]. Obviously, the cine-frame must be selected and the coronary segment of interest must be identified by the user. Nevertheless, such an approach clearly allows superior objectivity and reproducibility than an approach with which the user traces the outline or manually identifies the minimal luminal diameter (MLD) or the so-called reference segment.

Given that in reporting the angiographic effect of interventions we are in quest of objectivity and reliability, these considerations are much more than semantic. As evidence for the importance of these attributes, we recently embarked on a multicentre

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collaborative study [5] to establish the comparative qualities of a variety of automated QCA systems in current clinical use in Europe and North America, using cine-angiograms, recorded in a clinical interventional suite, of 'phantom' coronary artery stenoses of known dimensions percutaneously inserted in the coronary arteries of anaesthetized swine. Preliminary results show a considerable variation in the measurement accuracy and precision as well as in correlations between, and linear regression of, measured and true diameters. It could thus be concluded that the same clinical angiograms analyzed using different systems would provide different coronary luminal measurements, although serial changes over a period of time measured by any one system would provide objective and reliable results providing the measurement accuracy and variability of the system are known. Therefore, comparison of the absolute coronary luminal measurements from study to study may be as incomparable as were restenosis rates based on visual estimation of the angiogram, if measured by different quantification methods. This likelihood must now be taken into account when evaluating the outcome of current interventional studies and randomized trials, in the light of our own personal experience or previously published reports. However, it is anticipated that progress is being made in standardizing the approach, and it is not inconceivable that different automated quantitative systems may continue to be justifiably applied and that results are intracomparable provided that we know the standard measurement errors at various vessel sizes (because it is known that lumen size is an important source of systematic error).

## Lessons learned from QCA: continuous versus categorical approaches

Despite its emerging limitations, QCA has provided many clinically useful insights into the process of restenosis. Most important, perhaps, has been the demonstration that the renarrowing process after intervention is clearly ubiquitous [6] and normally distributed [7,8], in accordance with the biological evidence. This finding has formed a platform for the evolving concept of restenosis and for some well-known, if somewhat controversial, interventional philosophies of some prominent investigators in the field [9,10]. The application of categorical definitions or criteria for the development of restenosis is, as already stated, doomed to providing incomplete and inaccurate information. It has been emphatically illustrated in the past that the application of categorical criteria provides an arbitrary and ambiguous stratification without conveying useful information on the extent of renarrowing of the lumen developing during follow-up [11–14]. Both 'cut-off' (diameter stenosis >50% at follow-up angiography) and 'loss' (deterioration during follow-up of more than half the original gain) categorical criteria are equally uninformative, although at least 'loss' criteria imply some degree of lesion deterioration [14]. Given that the measurement variability for the degree of stenosis, by all quantification approaches, is >6% [4], a detected change from post-intervention to follow-up of <12% would lie within 95% confidence limits for measurement variability and thus could not be considered to be a real change. For example, a lesion measured as 45% diameter stenosis immediately after intervention (not untypical for PTCA), without undergoing any real deterioration during 6 months, could be measured as 55% at follow-up, simply because of measurement variability; applying the 50% diameter stenosis cut-off criterion, this lesion would be considered as having undergone restenosis. Furthermore, according to this criterion, a 51% stenosis is considered to be the same as a total occlusion at follow-up, i.e., restenosis, and 0% stenosis is given the same score as a 49% stenosis, i.e., no restenosis. Similarly, a change from 0% after intervention to 49% at follow-up is not considered to be restenosis, whereas a change from 45% after intervention to 55% at follow-up is. The inherent limitation of such an approach to the description of the late outcome of important clinical trials is therefore obvious.

The Coronary Angioplasty Versus Excision Atherectomy Trial (CAVEAT) [15] provides an example of the dubious value of this categorical approach. Initially, a borderline statistically significant difference was reported in restenosis rate (diameter stenosis 50% at follow-up angiography), favouring directional atherectomy over balloon angioplasty (46% versus 57%) in this randomized trial [16]. Examination of the MLD data in a continuous fashion, using cumulative distribution curves, casts doubt on the usefulness of these categorical findings. A trend towards a greater median MLD was found in the atherectomy-treated group, but no clear separation of the cumulative curves of MLD at follow-up — as would be expected in order to provide a confident conclusion — to the satisfaction of clinicians who ask the question 'does atherectomy provide a better long-term result than PTCA?'. Subsequently, in the published report [15] there was no longer a significant difference in restenosis rates (57% for PTCA versus 50% for atherectomy; $P=0.055$), although a trend favouring atherectomy was observed. The finding of a mean MLD at follow-up of 1.42 mm in the atherectomy-treated group and 1.44 mm in the angioplasty group demonstrates the reality that, in this trial, directional atherectomy provided no better long-term angiographic outcome than balloon angioplasty. This finding confirms the dubious value of a categorical approach in defining the outcome of such a major trial. It is worth noting, in retrospect, that this neutral outcome was, in fact, predicted by Umans *et al.* [17] in an observational study of patients treated with directional atherectomy matched for baseline features with patients who had been

treated with balloon angioplasty (Fig. 1). This approach has also been applied to a comparison of stenting with balloon angioplasty. The results suggested that the long-term angiographic outcome after stent implantation is significantly better than after balloon angioplasty in comparable lesions [18] (Fig. 2). In this regard, the results of the Benestent trial [19], as the first randomized trial of stent implantation with balloon angioplasty, are eagerly awaited to confirm or refute these observational findings. This simple matching technique may prove extremely useful in obtaining valid comparative information between devices, and may help in the design of future randomized trials of interventional devices.

The QCA approach in the CAVEAT used the 'single worst view' for analysis before intervention, repeated after intervention and at follow-up. Our group [4] has demonstrated in the past that the use of multiple matched projections provides more comprehensive and reliable data in consideration of the two-dimensional geometric approach to the measurement of a three-dimensional object. Evaluation of the angiographic measurements produced

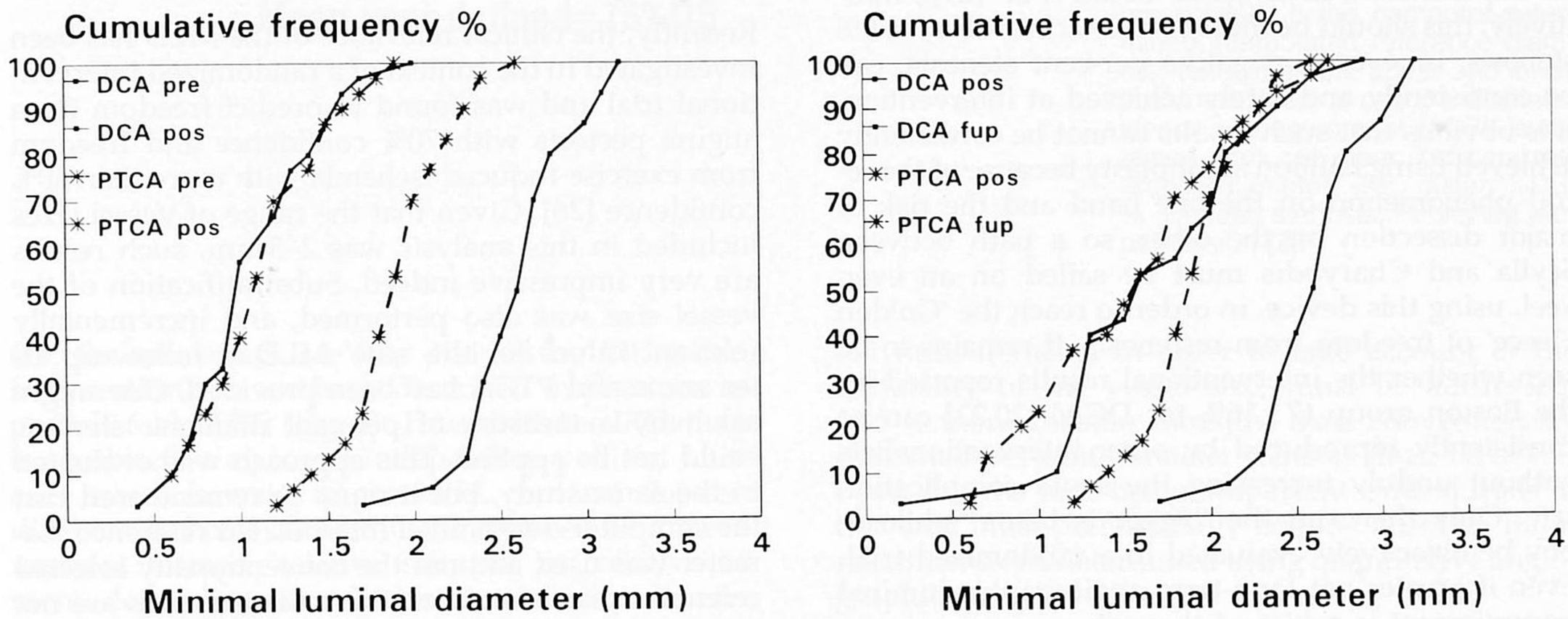


**Fig. 1.** Cumulative frequency (distribution) curves illustrating the differential immediate [pre–post (a)] and follow-up [post-follow-up (b)] effects of percutaneous transluminal coronary angioplasty (PTCA) compared with directional coronary atherectomy (DCA) on 'matched' coronary lesions, with regard to absolute minimal luminal diameter (MLD) measured by quantitative coronary angiography. The superior acute result of atherectomy is attenuated during follow-up, so that the angiographic outcome is similar between the two groups. These results are clearly similar to the subsequent findings of the coronary angioplasty versus excision atherectomy trial (CAVEAT), which included 1012 patients in 35 institutions. Published with permission [17].

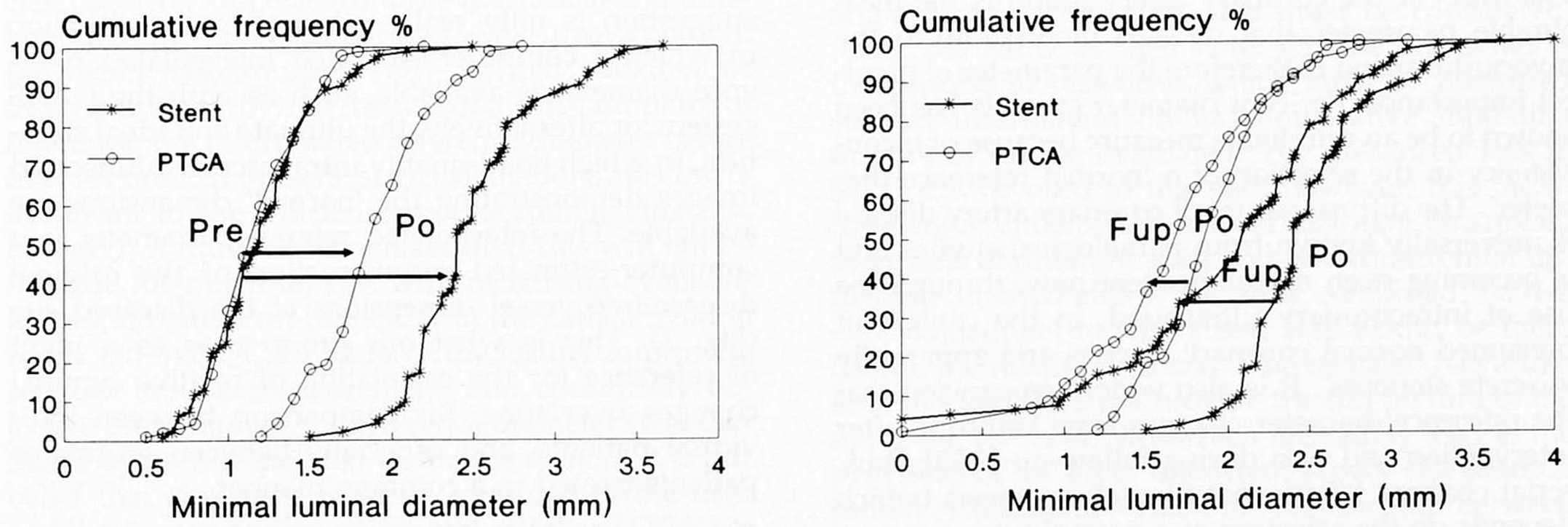


**Fig. 2.** Representation of the immediate [pre–post (a)] and long-term [post-follow-up (b)] angiographic outcome of a matched study in 93 patients undergoing balloon angioplasty or self-expanding stainless steel stent implantation. The superior initial gain from stenting is somewhat counterbalanced by a greater luminal loss during follow-up. Nevertheless, luminal diameter at follow-up remains significantly greater than for balloon angioplasty. Published with permission [18].

in CAVEAT must therefore take this quantitative analytical approach into account.

The practical criticisms of the CAVEAT trial have been mainly that non-aggressive atherectomy was performed, and also that the proportion of patients with unstable angina was, perhaps, undesirably high (more than 60% in each group). Kuntz *et al.* [20] have reported better immediate and long-term angiographic results in their consecutive series of patients treated at the Beth Israel Hospital, where a 'bigger is better' policy is espoused [9]. Undoubtedly, if the ultimate outcome of therapy is a diameter stenosis <50% (a cut-off point based on the historical experimental findings of Gould *et al.* [21]), intuitively, this should be more readily achievable if a 0% stenosis, or even a negative per-cent stenosis, can be consistently and safely achieved at intervention. It is obvious that such results cannot be consistently achieved using balloon angioplasty because of the recoil phenomenon on the one hand and the risk of major dissection on the other, so a path between Scylla and Charybdis must be sailed on an even keel, using this device, in order to reach the 'Golden Fleece' of freedom from restenosis. It remains to be seen whether the interventional results reported by the Boston group (7±16% for DCA) [20,22] can be consistently reproduced by other interventionalists without unduly increasing the acute complication rate. Only then can the 'bigger is better' philosophy be objectively evaluated in a randomized trial. Even if greater net long-term angiographic luminal improvement is achieved through aggressive intervention, the long-term biological consequences of the greater vessel wall injury imparted must not be forgotten.

## Luminal diameter and per-cent stenosis

The MLD of the coronary artery lesion is the measurable parameter that dictates blood flow to the myocardium and is therefore the parameter of greatest importance. Per-cent diameter stenosis has been shown to be an unreliable measure because of inconsistency in the selection of a 'normal reference diameter'. The diffuse nature of coronary artery disease is universally known from pathological studies and is becoming even more apparent now, through the use of intracoronary ultrasound, in the context of presumed normal coronary arteries and apparently 'discrete stenoses'. It is also widely recognized that the reference diameter changes from before to after intervention and also during follow-up [2,23]; thus, serial changes in per cent diameter stenosis (which depends on the selection of a normal reference segment) over time may be even more unreliable than a single measurement. The only reliable measure of stenosis severity is thus the MLD. Our group has emphasized the need for multiple projections in order to provide a three-dimensional measurement of the MLD [4] in the context of interventional trials, especially when measuring serial changes, when the projections should be identically reproduced at each phase of intervention (before, after, and at follow-up [24]), a practice we have termed performance of 'multiple matched projections'. In a recent study [25], we compared quantitative angiographic measurements acquired from multiple matched projections with those using only the single worst view, before and after intervention, and at follow-up after successful balloon angioplasty, and we observed highly significant differences that obviously carry considerable implications for evaluation of the angiographic outcome of interventional trials.

Recently, the clinical relevance of the MLD has been investigated in the context of a randomized interventional trial and was found to predict freedom from angina pectoris with 70% confidence and freedom from exercise-induced ischemia with more than 60% confidence [26]. Given that the range of vessel sizes included in this analysis was 2–5 mm, such results are very impressive indeed. Substratification of the vessel size was also performed, and incrementally relevant values for the 'safe' MLD at follow-up after successful PTCA had been provided. One might ask why a measure of per-cent diameter stenosis could not be applied. This approach was evaluated in the same study, but it must be remembered that the computer-determined interpolated reference diameter was used and not the conventionally selected reference diameter; thus, the measurements are not comparable to clinical measures of per-cent diameter stenosis [3]. The real reason for not recommending per-cent diameter stenosis has been already given; its measurement according to conventional practice is unreliable.

What about a better relative measure then, in order to take account of the vessel size, because there would be universal agreement that this has a large bearing on the clinical relevance of the MLD? Our suggestion is only really relevant to the situation in which a computer-estimated interpolated reference diameter is available, such as with the CAAS system, or alternatively, the ultimate and ideal situation, in which good-quality intravascular ultrasound images demonstrating the 'normal' dimensions are available. The interpolated reference diameter is a computer-estimated reconstruction of the original disease-free vessel dimensions at the diseased site (Fig. 3). This is what our group uses as a point of reference for the calculation of relative luminal changes over time, for comparison between individual patients, and especially between groups of patients treated in a common manner.

Relative gain is the luminal increase at intervention adjusted for the interpolated reference diameter (IRD) before intervention (i.e., the measured acute gain divided by the measured IRD before intervention) and relative loss is the change during follow-up adjusted for the IRD before intervention

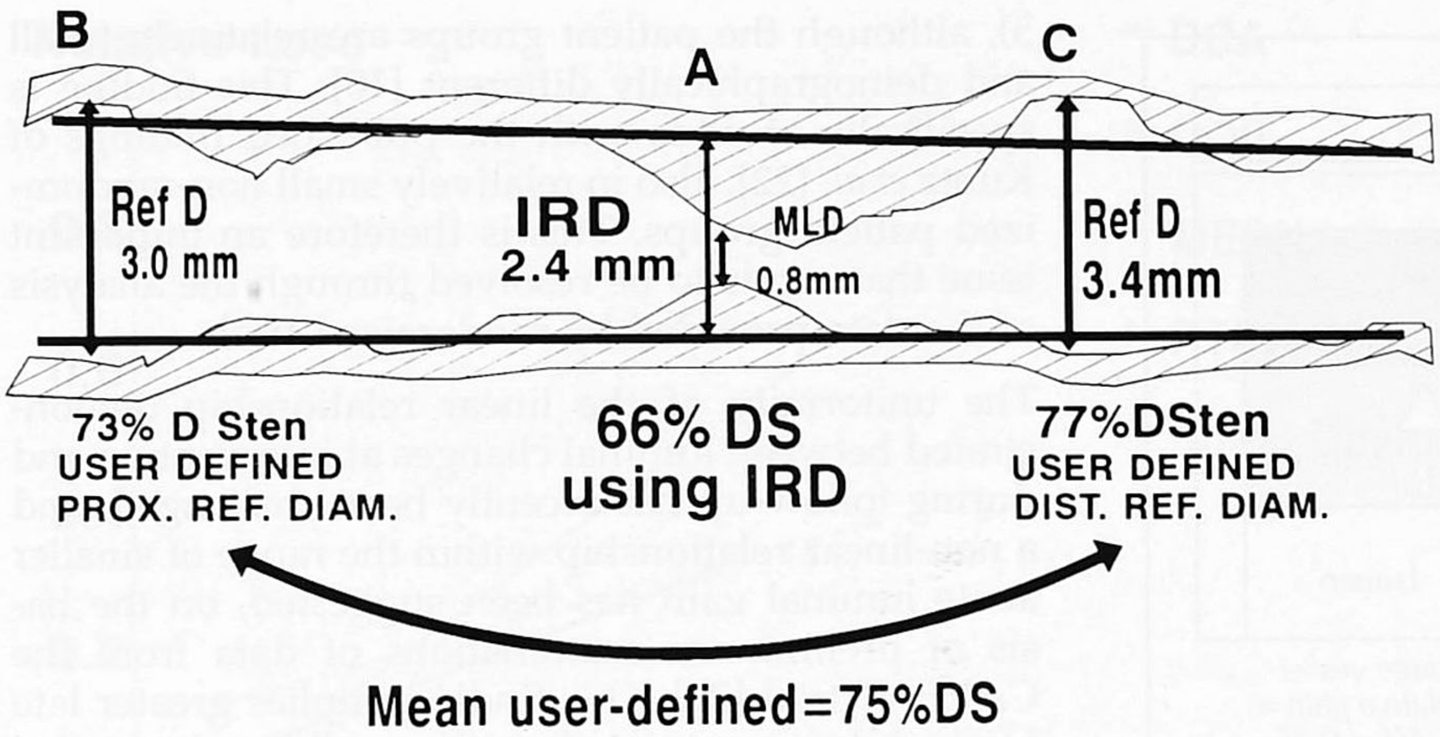


**Fig. 3.** Demonstration of the variability in per-cent diameter stenosis measurements of the same lesion resulting from arbitrary selection of the reference diameter by the user, and the more objective derivation of per-cent diameter stenosis by the user-independent method of the interpolated reference diameter. For a stenosis where the minimal luminal diameter (MLD) is measured as 0.8 mm, if a user-defined proximal or distal reference segment or mean of both is selected, then the resultant measure of % diameter stenosis for the obstructing lesion is 75%, 77%, or 76%, respectively. If the computer-determined interpolated reference diameter (shown as the upper and lower thick dark lines) is used, a diameter stenosis measurement of 66% is obtained. Prox. ref. diam., proximal reference diameter; dist, distal; %DS, % diameter stenosis. Published with permission [2].

(i.e. the measured late loss divided by IRD before intervention), as we have described in previous reports [2,6,10,17,27] (Fig. 4). Thus, with the IRD, there is an objective and user-independent point of reference which is, most importantly, constant. Per-cent diameter stenosis could thus be replaced by a measurement termed 'relative stenosis' or 'relative lumen', depending on whether there is a preference to focus on the 'doughnut' (the thickness of the arterial wall) or 'doughnut hole' (the lumen) [28]. Since the angiogram can really only provide information about the 'doughnut', perhaps 'relative lumen' would be most appropriate. As a new term, from the practical point of view, 'relative lumen' is not very attractive and can be confusing. However, perhaps it would be even more confusing to recommend changing the method of calculating percent diameter stenosis from the traditional and time-honoured method (comparing the narrowest point in the vessel with an apparently 'normal' proximal or distal point nearby), to the use of a constant point of reference: the interpolated reference diameter before intervention. At present, such calculations are clearly irrelevant to the practising non-academic clinician; however, it must be recognized that this will not be the case for much longer, with increasing availability of automated on-line QCA in the catheterization room. On-line QCA will have the facility to provide accurate luminal measurements and, specifically, objective estimation of the reference diameter (whether this is by an interpolated technique or not). It is our belief that clinicians must be informed of the uses and limitations and promises and pitfalls of QCA before diving headlong into the morass that awaits the unwary.

The use of per-cent diameter stenosis, to describe the outcome in important studies, is not therefore at present recommended. The need for relative luminal measurements in order to take account of the variability of the vessel size, must be addressed, and a more reliable measure than conventionally estimated per-cent diameter stenosis must be developed. For the time being, important clinical trials in this area must preferentially employ absolute luminal dimensions determined using quantitative angiographic analysis.

## Objective parameters for evaluation of randomized trials: process and outcome

For the purposes of the randomized clinical trial of interventional devices or combinations of intervention and biological agent, there are two quantitative angiographic approaches that must be considered, using the MLD as their core. On the one hand is the process of restenosis which must be measured so that information on its comparative inhibition or control can be evaluated. The measured loss in MLD can be used to this end; however, this measurement is unhelpful if devices that may be applied in vessels of different sizes and with differential immediate luminal effects are being compared. To this end, adjustment for the vessel size would be more useful; the relative loss may thus be used. Nevertheless, this still does not provide the full picture of the opposing forces at play which ultimately lead to the provision of the other important aspect: the residual lumen at follow-up. Thus, the relationship between relative luminal gain during intervention and relative loss during follow-up is the angiographic correlate or surrogate [2,10,17,27] for the vessel wall injury or intimal healing response [28], and provides useful information on the process of restenosis in a given population. Our experience with the ap-

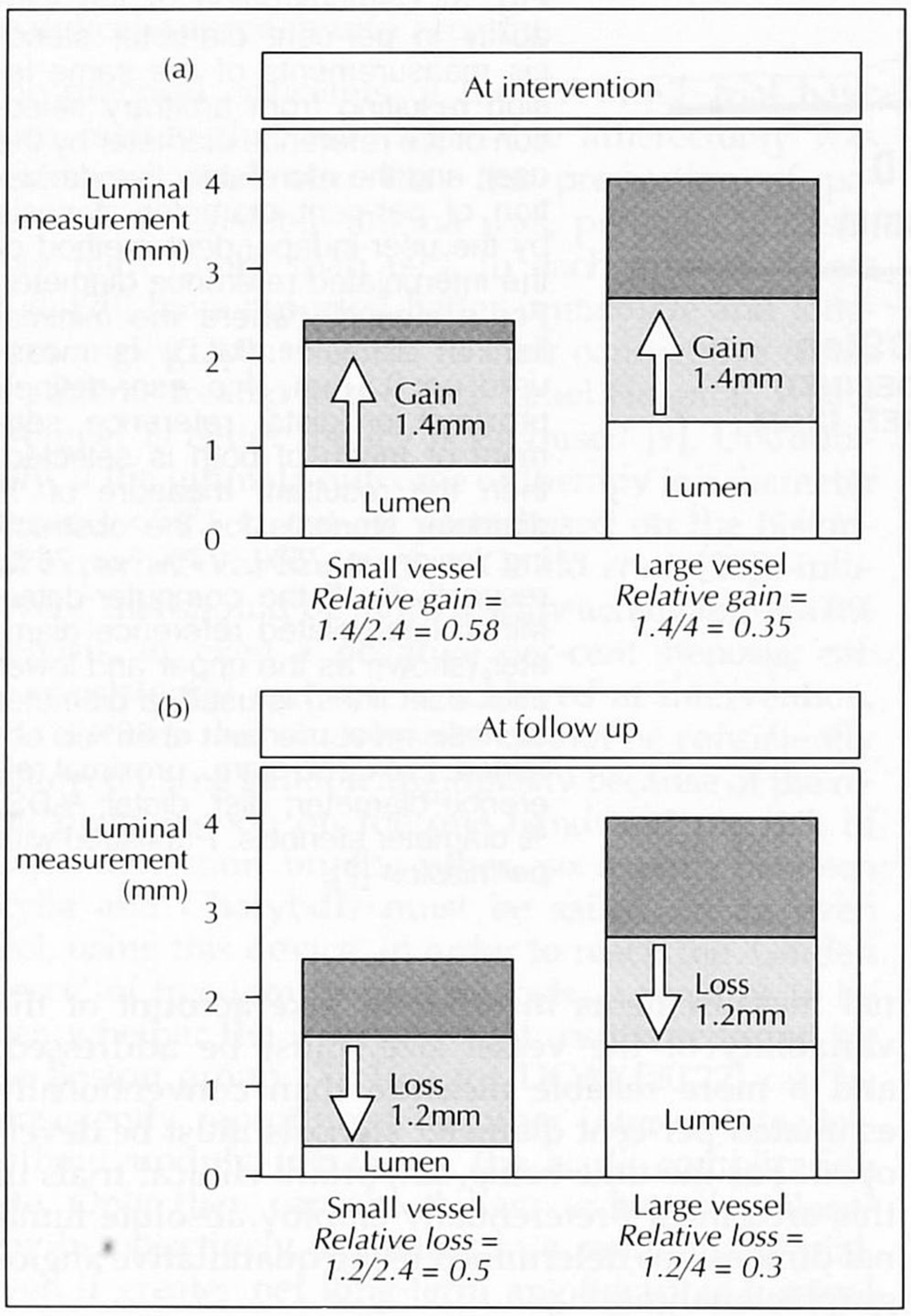


**Fig. 4.** Illustration of the measurement of, and justification for, 'relative gain' and 'relative loss'. (a) A severe lesion (66% diameter stenosis) is treated in each of a small and large vessel. Exactly the same degree of luminal increase is achieved (acute gain of 1.4 mm). Clearly, this amount of luminal enlargement carries completely different implications for the vessels: in the small vessel the 'lesion' is virtually obliterated, whereas, in the large vessel, only a moderate result of intervention is secured. Thus, normalizing the gain for the vessel size conveys the differential result of intervention in these vessels, with a relative gain of 0.58 in the small vessel and 0.35 in the large vessel. Similarly, in (b) we have the immediate and long-term angiographic measurements after a modest procedural result (but which is representative of clinical balloon angioplasty practice) in a small and large vessel. An exactly similar degree of luminal loss has developed during follow-up (measured at 1.2 mm) in each vessel. However, again the implications of this extent of renarrowing are clearly different, with virtual reocclusion in the small vessel but still a considerable patent lumen in the large vessel. The contrasting nature of these outcomes is much more usefully represented by adjusting the loss for the vessel size, which yields a relative loss of 0.5 in the small vessel compared with 0.3 in the large vessel. DS post, diameter stenosis.

plication of this approach to patients treated with balloon angioplasty in restenosis prevention trials showed an identical relationship in treatment and placebo groups, indicating no detectable treatment effect on the restenosis process [2]. Comparison with consecutive patient series treated with directional atherectomy or stent implantation has thus far suggested intrinsic differences between the devices (Fig. 5), although the patient groups are relatively small and demographically different [10]. This finding is specifically at odds with the published findings of Kuntz *et al.* [22], also in relatively small non-randomized patient groups. This is therefore an important issue that needs to be resolved through the analysis of the data provided by randomized trials.

The uniformity of the linear relationship demonstrated between luminal changes at intervention and during follow-up has recently been challenged, and a non-linear relationship within the range of smaller acute luminal gain has been suggested, on the basis of preliminary examinations of data from the CAVEAT trial [29]. This finding implies greater late luminal loss associated with smaller acute gains and proportionally less late loss after greater acute gain, which, if true, would support an aggressive interventional approach. In our large patient series treated with balloon angioplasty (3736 lesions in 3072 patients), the gain–loss relationship, although comparatively weak, is highly significant and is linear [30]. In addition, a personal communication from Simpson *et al.* demonstrates a linear relationship throughout the range of luminal gain, in patients treated with directional atherectomy. If a non-linear relationship as described above could be repeatedly demonstrated, then this clearly carries far-reaching implications for interventional practice and is an important issue to be resolved.

The ultimate outcome of intervention that must be evaluated in randomized trials is, undoubtedly, the MLD at follow-up. This is what remains for the patient after the healing process has attenuated the luminal increase achieved during intervention. Since randomized groups are assumed to be similar in all characteristics, except in the treatment under investigation, difficulties posed by differences in luminal changes during intervention, or those in vessel size are not relevant and any difference in the mean follow-up MLD between the groups can be assumed to be a consequence of therapy. Why not use the percent diameter stenosis at follow-up? This could be applied but, for the reasons already given, we consider this measurement to be imprecise and misleading and cannot recommend its use.

## Convergence of diverging philosophies: a two-sided coin

The MLD at follow-up certainly provides no information regarding the effect of therapy on the process of restenosis, just as the relative gain–relative loss relationship reveals nothing of the ultimate outcome. Therefore, these parameters must be considered complementary pieces of the jigsaw, or perhaps more appropriately, opposite sides of the same coin. Focusing on one or the other will only provide half the picture [27]. This observation may go a long

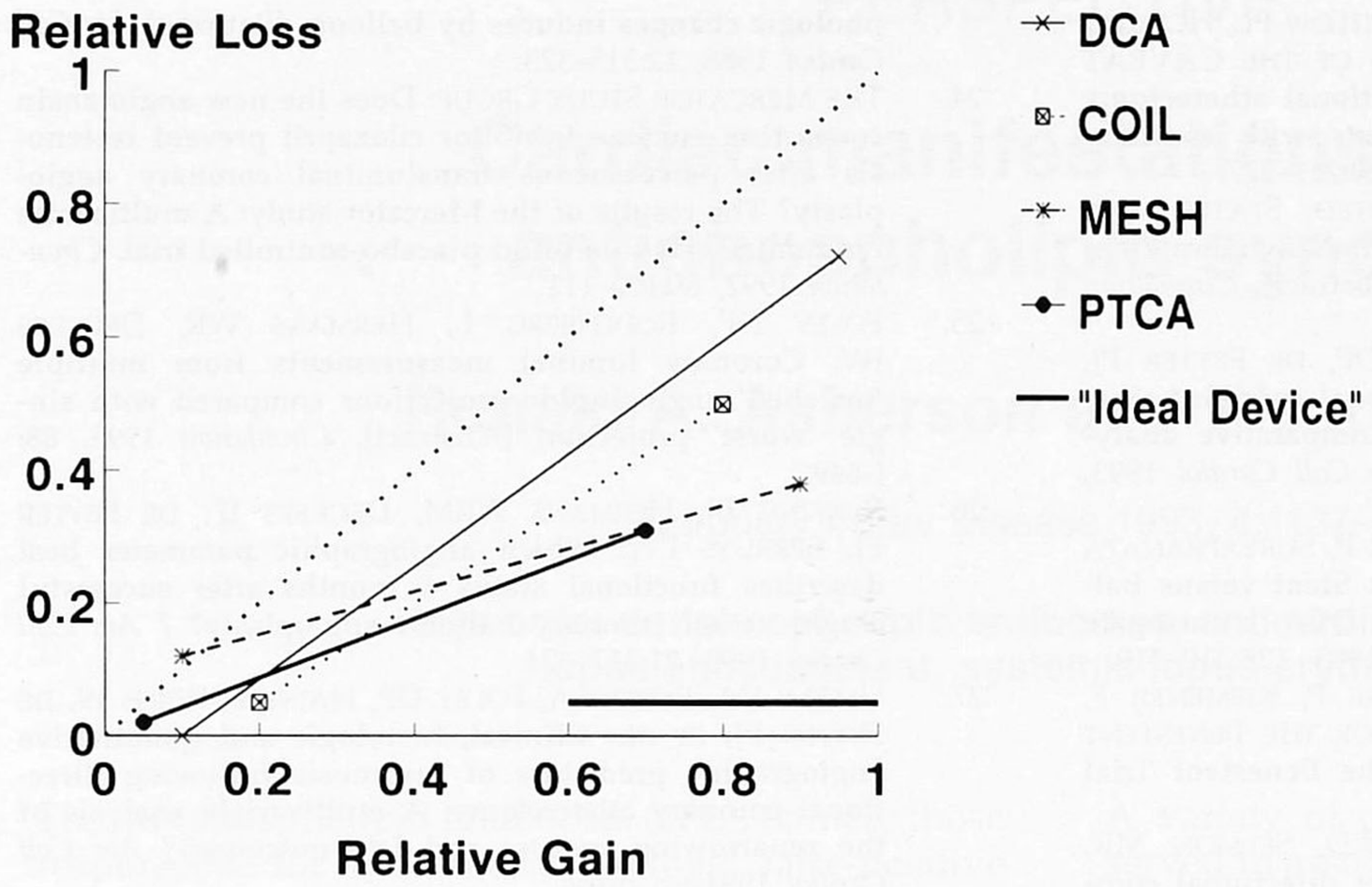


**Fig. 5.** Linear regression of relative gain–relative loss of patients who underwent therapy with four different interventional devices are shown with the line of identity. An imaginary regression line for the 'ideal' interventional device is included. It is clear that a device whose regression line crosses the identity line can be considered to be associated with a 'worse' angiographic outcome than one with a shallow gradient. The ideal device has a 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). Published with permission [2].

way towards explaining the apparently divergent philosophies associated with the Boston [9,20,22] and Thoraxcentre groups [2,10,17,27,30]. In reality, it would appear that there are more similarities than differences in these respective viewpoints.

The major points at issue are whether there are (Thoraxcentre) or are not (Beth Israel) innate differences between the devices with respect to the gain–loss relationship, as an indirect surrogate for the injury–hyperplasia relationship, whether the gain–loss relationship is linear (Thoraxcentre), or is non-linear (Beth Israel), whether the motto 'bigger is better' (Beth Israel) or 'the more you gain the more you lose' (Thoraxcentre) will prevail, or whether, in fact, they are mutually compatible, and finally, what exactly is meant by 'bigger is better' (Beth Israel: a bigger post-procedural lumen provides a better long-term result; Thoraxcentre: a better long-term result is obtained by treating bigger vessels). With imminent availability of large data sets collected during randomized trials of new devices, these hypotheses may be put to the test, and perhaps the apparently divergent philosophies may finally converge.

## References


1. MYLER RK, SHAW RE, STERTZER SH, HECHT HS, RYAN C, ROSENBLUM J, *ET AL.*: **There is no such thing as 'restenosis'.** *J Inv Cardiol* 1992, **4**:282–290.
2. SERRUYS PW, FOLEY DP, KIRKEEIDE RJ, KING SB III: **Restenosis revisisted: Insights provided by quantitative coronary angiography.** *Am Heart J* 1993, in press.
3. 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**:945–951.
4. REIBER JHC, SERRUYS PW: **Quantitative coronary angiography.** In *Cardiac Imaging, a Companion to Braunwald's Heart Disease.* Edited by Marcus ML, Schelbert HR, Skorton DJ, Wolf GI. New York: Saunders; 1991:211–280.
5. KEANE D, VAN SWIJNDREGT EM, HAASE J, DI MARIO C, SERRUYS PW: **Multicentre validation of computerized quantitative coronary angiographic (QCA) systems [Abstract].** *Circulation* 1993, in press.
6. 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.
7. 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**:939–945.
8. 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**:1493–1494.
9. FISHMAN R, KUNTZ R, CARROZZA J, POMERANTZ R, DIVER D, SAFIAN R, *ET AL.*: **Results of coronary atherectomy — Bigger is better [Abstract].** *Circulation* 1991, **84**:II-520.
10. FOLEY DP, HERMANS WR, DE JAEGERE PP, UMANS VA, VOS J, ESCANED J, *ET AL.*: **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.
11. SERRUYS PW, LUIJTEN HE, BEATT KJ, GEYSKENS R, DE FEYTER PJ, VAN DEN BRAND M, *ET AL.*: **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**:361–371.
12. SERRUYS PW, RENSING BJ, LUIJTEN HE, HERMANS WR, BEATT KJ: **Restenosis following coronary angioplasty.** In *Interventional Cardiology.* Edited by Meier B. Toronto, Lewiston, NY, Bern, Gottingen, Stuttgart: Hogrefe and Huber; 1990:79–115.
13. BEATT KJ, SERRUYS PW, HUGENHOLT PG: **Restenosis after coronary angioplasty: New standards for clinical studies.** *J Am Coll Cardiol* 1990, **15**:491–498.
14. BEATT KJ, SERRUYS PW, LUIJTEN HE, RENSING BJ, SURYAPRANATA H, DE FEYTER P, *ET AL.*: **Restenosis after coronary angioplasty: The paradox of increased lumen diameter and restenosis.** *J Am Coll Cardiol* 1992, **19**:258–266.

15. TOPOL EJ, LEYA F, PINKERTON CA, WHITLOW PL, HOFLING B, SIMONTON CA, *ET AL.* ON BEHALF OF THE CAVEAT STUDY GROUP: **A comparison of directional atherectomy with coronary angioplasty in patients with coronary artery disease.** *N Engl J Med* 1993, **329**:221–227.
16. THE CAVEAT INVESTIGATORS, UNITED STATES AND EUROPE: **The coronary angioplasty versus excision atherectomy trial preliminary results [Abstract].** *Circulation* 1992, **86**:I-1491.
17. 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**:1382–1390.
18. 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**:310–319.
19. SERRUYS PW, MACAYA C, DE JAEGERE P, KIEMENEIJ F, RUTSCH W, HEYNDRICKX G, *ET AL.*, FOR THE BENESTENT STUDY GROUP: **Interim analysis of the Benestent Trial [Abstract].** *Circulation* 1993, **88**:I-594.
20. 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**:1394–1399.
21. GOULD KL, LIPSCOMB K, HAMILTON GW: **Physiological basis for assessing critical coronary stenosis: Instantaneous flow response and regional distribution during coronary hyperaemia as measures of coronary flow reserve.** *Am J Cardiol* 1974, **33**:87–97.
22. 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.
23. BEATT KJ, LUIJTEN HE, DE FEYTER PJ, VAN DE BRAND M, REIBER JH, SERRUYS PW: **Change in diameter of coronary artery segments adjacent to stenosis after percutaneous transluminal coronary angioplasty: Failure of percent diameter stenosis measurement to reflect morphologic changes induces by balloon dilation.** *J Am Coll Cardiol* 1988, **12**:315–323.
24. 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 multicentre randomized double-blind placebo-controlled trial.** *Circulation* 1992, **86**:100–111.
25. FOLEY DP, RODENBERG L, HERMANS WR, DECKERS JW: **Coronary luminal measurements from multiple 'matched' angiographic projections compared with single 'worst' projection [Abstract].** *Circulation* 1993, **88**: I-649.
26. 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**:317–324.
27. UMANS VA, ROBERT A, FOLEY DP, HAINE E, WIJNS W, DE FEYTER PJ, *ET AL.*: **Clinical, histologic and quantitative angiographic predictors of restenosis following directional coronary atherectomy: A multivariate analysis of the renarrowing process and late outcome.** *J Am Coll Cardiol* 1994, in press.
28. 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**:267–274.
29. KUNTZ R, FOLEY DP, KEELER GP, UMANS VA, BERDAN LG, SIMONTON CA, HOLMES DR, ON BEHALF OF THE CAVEAT INVESTIGATORS: **Relationship of acute luminal gain to late loss following directional atherectomy or balloon angioplasty in CAVEAT [Abstract].** *Circulation* 1993, in press.
30. FOLEY DP, MELKERT R, SERRUYS PW; **Quantitative angiographic predictors of luminal renarrowing and late angiographic outcome after successful balloon angioplasty [Abstract].** *Eur Heart J* 1993, **14**:276.