SHORT AND LONG-TERM RESULTS OF TRANSLUMINAL CORONARY INTERVENTIONS: AN ANGIOGRAPHIC PERSPECTIVE

KORTE EN LANGE TERMIJN RESULTATEN VAN TRANSLUMINALE CORONAIR INTERVENTIES: EEN ANGIOGRAFISCH PERSPECTIEF

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Looking back now after 4 years at the Thoraxcentre, it is somewhat ironic to remember that the first kindling of my interest in the field of cardiology can be traced to my elective clinical attachment at the Beth Israel Hospital in Boston, which, during the course of my time at the Thoraxcentre, has been singularly our greatest rival in the area of quantitative angiography applied to the study of restenosis. My actual initiation to the Thoraxcentre, I also remember, was considerably facilitated by a rather fortuitous if somewhat painful occurrence (not so painful for me but rather for my promotor !). Professor Serruys, whose skills and dexterity in interventional therapeutics are virtually legendary, apparently was not genetically endowed with the same adroitness on a bicycle... a rather simple apparatus, which has made many a Belgian kinsman, such as Eddie Merckx, a household name. Not to put too fine a point on it, Patrick had been accidentally disengaged from his mount in full flight and suffered some physical trauma, which led to an unsolicited sabbatical period on the renowned 23rd floor of Erasmus University. I therefore had the rare (4 years later I now know how rare indeed !) pleasure of having him personally answer the telephone, when I first speculatively called to enquire for "positions vacant" ("looking for a start", as we say in Ireland). In his famous cavalier fashion he said, "come up and see me sometime", so I flew to Rotterdam the following day and in a one hour meeting we drafted a grant proposal to the Irish Heart Foundation and that, as they say, was that. I suppose it was at least a year after my commencement before I realised how rare was my smooth inauguration, having personally witnessed scores of hungry applicants, furiously and repeatedly phoning and faxing Patrick, vainly trying, like searchers of Bigfoot or the Yeti, to track him down. It would be tautological to say that this thesis would not have been possible without his vision, wisdom, guidance and incredible enthusiasm to discuss, dissect, explore and speculate on any subject at any time. Even when he falls asleep in the middle of a scientific discussion (not from being bored of course, but usually jet lag !), he can amazingly pick up the point where he left off, which leads me to conclude that, unlike some of his early morning conference audiences, whom he has impishly reprimanded for being still asleep and indulging in sexual fantasy (instead of listening to him !), Patrick not only lives, eats and breathes interventional cardiology, but also dreams it ! Salut Patrick, or "chin chin", as the Japanese say !!.

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INTRODUCTION AND OVERVIEW OF THE THESIS

General background to coronary angioplasty and introduction of new angioplasty devices

Percutaneous Transluminal Coronary Angioplasty (PTCA) is the original term describing the technique of alleviating coronary artery narrowings by inflating a short balloon (8 - 45mm long) mounted on a long hollow plastic catheter, which is introduced to the coronary artery over a thin (0.010 - 0.018 inch diameter) floppy tipped guidewire via a peripheral arterial puncture (the femoral artery in the groin being in modern times the most popular, then the brachial artery at the elbow and more recently, the radial artery at the wrist). Since its introduction in 1977, this non-surgical alternative to coronary artery bypass graft operation (with its attendant risks and unsavoury patient appeal) has undergone a metamorphosis from experimental clinical application into the medical specialty of "Interventional Cardiology". With its increasing clinical application, in addition to broadening indications and therapeutic possibilities, however, its limitations in consistently producing successful and uncomplicated results, have been exposed. Accordingly, a medical device industry rapidly burgeoned, hand-in-hand with the specialty of interventional cardiology itself, providing extensive refinements in guidewire and balloon catheter manufacture and design. Despite such advances in balloon technology and the increasing experience of physicians engaged in daily practise, procedural failure, or abrupt closure of the coronary artery, during or shortly after angioplasty, has remained an inherent complication in 5-10% of cases attempted.

Perhaps more vexatiously, recurrence of renarrowing, or "restenosis", of an initially apparently successfully treated artery, sufficient to require re-treatment or bypass graft surgery (or of a severity to cause myocardial infarction or even death) within the first 6 months, seems to have become an inevitable long term drawback in more than one in three patients treated. These two limitations of balloon angioplasty therapy have consequently precipitated a furious search by investigators worldwide for, on the one hand, a "magic bullet", in the guise of a biological, pharmacological or genetic panacea, which could be administered at the time of angioplasty, and perhaps for some months afterward, to control the problem of restenosis, and on the other hand, a "golden fleece", in the form of an alternative device, which would improve both immediate success rates and also reduce restenosis. In the last 15 years, a myriad of pharmacological and biological agents for restenosis prevention have been investigated in multicenter randomized clinical trials, with no convincing success. In addition, over the last decade, a larger number of new interventional devices for coronary revascularization have been progressively introduced to clinical practice, the principals among which have been endoluminal metal stents of varying composition and design, cutting devices, namely directional, extractional and rotational atherectomy and laser based devices, such as excimer laser coronary angioplasty. Each of these devices has staked a claim for a niche in the treatment of coronary artery disease and randomized clinical trials have been inaugurated to determine the clinical value of these new devices, compared with good old balloon angioplasty, which is still the mainstay of transluminal coronary intervention.

Directional atherectomy did not emerge from the multicentre randomized CAVEAT and CCAT trials with the type of superior acute and long term results over balloon angioplasty as had been perhaps expected by its champions. However, in the BENESTENT and STRESS trials, the Palmaz-Schatz stent has been perceived as providing superior acute and 6 month clinical and angiographic results compared with balloon angioplasty, although only patients with stable angina and target stenosis in a vessel larger than 3mm were included, which is an extremely circumscribed population, so that the conclusions may not necessarily be generalized to all clinical situations. Nonetheless, the excitement generated among interventionalists has led to Federal Drug Administration (FDA) approval of the device for general use in the United States and to new phases of clinical investigation. These include studies with increasing varieties of stent and specific studies aiming to reduce the need for rigorous treatment with anticoagulation medication (which has been associated with excessive incidence of bleeding complications), without increasing the risk of stent thrombosis and also to further improve the late results, by more optimal stent implantation and use of biologically active coatings or even biodegradable stents. Excimer laser angioplasty has allowed percutaneous treatment of previously untreatable lesions and registry reports indicate satisfactory acute success, although without impressive late angiographic results. The first reported randomized clinical trial evaluating excimer laser angioplasty with conventional balloon angioplasty, the AMROE trial (the angiographic aspects of which are reported in chapter 8 of this thesis), found no clinical or angiographic benefit of laser compared with balloon angioplasty, in terms of acute success or 6 month results. The field of new device angioplasty is thus developing rapidly, but must be vehemently considered to be as yet in its infancy.

Thoraxcentre contributions to interventional cardiology

The clinical and research activities of the department of interventional cardiology at the Thoraxcentre of the Academic Hospital and Erasmus University of Rotterdam, have firmly established this institution as a major source of continuing advances in both therapeutic approaches to percutaneous treatment of coronary artery

disease, as well as in understanding of the biological processes, triggered by instrumentation of diseased arteries. In particular, in the clinical arena, the imaging medium of contrast angiography has been harnessed to maximize its informative capabilities, through the development of computer algorithms which can automatically recognize the enhancement of the coronary lumen provided by the direct injection of contrast material. The possibility to accurately and precisely quantify luminal dimensions and serial changes therein over time, as a consequence of biological processes or mechanical interventions, has provided the physician with an opportunity to gain insight to these biological processes and reactions to coronary intervention, in the clinical setting. As early as 1982, the application of so called "Quantitative Coronary Angiography" (QCA) for evaluation of coronary angioplasty was already being demonstrated and recommended by the Thoraxcentre group. However, as with all new innovations, the enthusiasm of the inventors was not initially generally shared by their peers and it was some years later before the first major international clinical introduction of the Cardiovascular Angiographic Analysis System (CAAS) was witnessed, in the context of a multicentre randomized trial of a pharmacological agent for prevention of restenosis. Since then, quantitative angiography has really become the "gold standard" for investigation of biological and mechanical coronary artery interventions, and accordingly, forms the basis of the studies described in this thesis.

Purpose of this thesis

The purpose of this thesis was twofold; firstly, to investigate and demonstrate the appropriate applicability of angiography, particularly quantitative angiography, to the evaluation of the acute and long term effects of coronary angioplasty (chapters 1 - 6); secondly, to addresses one of the principal clinical issues in interventional cardiology today, namely, whether the type of device used for coronary angioplasty influences the potential for development of restenosis, or is it merely the magnitude of the result achieved at angioplasty alone which determines late outcome, regardless of the device used. As will emerge in this overview and in the thesis itself, our hypothesis has been that the device used does exert an independent influence on restenosis, as a consequence of the specific nature and extent of injury imparted to the coronary artery during intervention, which is characteristic of the mechanistic effect of each different device, as well as depending on the degree of luminal enlargement forced upon the diseased vessel. The finding of such a "device specific" influence on restenosis would carry practical implications for the future clinical use of the different devices. In chapters 7 to 11, the following devices are evaluated: balloon angioplasty, as already briefly described, the original and still predominantly used coronary intervention; coronary stent implantation, first introduced in 1986 and comprising a balloon-expandable or self-expanding, metal coil or mesh which can be permanently placed in a coronary narrowing using a balloon catheter (a number of designs of varying metal composition and geometry are now available, 3 of which are included in the studies in this thesis); directional atherectomy, introduced in 1989, and is essentially a cutting device intended to remove coronary atherosclerotic plaque by a hollow cone shaped cutter with a stabilizing balloon, which is introduced to the coronary artery over a guide wire, in similar fashion to balloon catheters; and finally, excimer laser coronary angioplasty, which is a method of vaporizing coronary artery disease using pulsed laser light, introduced through special layered fiber catheters.

Summary of the individual chapters

Chapter 1 of this thesis provides an extensive clinically relevant description of the technical aspects of automated quantitative angiography using the Cardiovascular Angiographic Analysis System (CAAS), including its evolution from research tool for evaluation of coronary artery disease to its widespread on-line clinical employment in interventional cardiology. Also explored are the challenges to its capacity to consistently provide reliable coronary artery luminal measurements, which have been encountered through its progressive application to evaluation of coronary angioplasty and intervention with new devices and how we have managed to address some of these limitations, by systematic introduction of standardized methods of angiographic acquisition by clinicians and off-line quantitative analysis in a designated core laboratory.

Chapter 2 introduces the clinical application of quantitative angiography to interventional cardiology. In particular, the nature and clinical relevance of the coronary luminal measurements provided by automated analysis is delineated and the biological insights to the process of restenosis provided by the serial application of quantitative angiography to clinical interventional investigations is presented. In addition, we expound the hypothesis of device specific differences in provocation of restenosis, which is the principle subject of the second part of this thesis, based on some previously published circumscribed studies and preliminary investigations of patient data which are comprehensively interrogated and presented in detail in chapter 10 of this thesis. Novel original approaches for comparative evaluation of restenosis propensity of interventional devices, using measurements provided by quantitative angiography are also proposed and form the basis for many of the studies presented in the second part of the thesis.

In chapter 3, the usefulness of angiography for evaluation of two of the major unwanted potential consequences of coronary angioplasty, namely, intracoronary thrombus and intimal dissection, is comparatively evaluated using intracoronary angioscopy (an investigation which allows direct visualization of the coronary lumen, but without the possibilities of quantification of the lumen dimensions). It emerges that although angiography both detected and outruled important intimal dissections reasonably reliably, considerable intimal disruption was missed angiographically and the presence of intracoronary thrombus was significantly underestimated by angiography, despite the absence of false positive findings. Thus, if non-obstructive coronary thrombus is an important nidus for development of restenosis, as is generally believed, this association must be studied by means other than angiography. Accordingly, angiographic thrombus is not considered in the later chapters of this thesis dealing with determinants of restenosis. Similarly, based on these findings, as well as our prior finding of no association between angiographically visible, non obstructive dissection with late restenosis (*J Am Coll Cardiol* 1992;20:767-80), this angiographic feature is also not further investigated in relation to restenosis in this thesis.

Chapter 4 investigates the possibility of routine use of a single angiographic projection for quantitative angiographic analysis, by comparing measurements obtained by automated edge detection and videodensitometry from orthogonal angiographic projections (angiographic recordings of the target coronary artery in perpendicular planes) before and after angioplasty and at 6 month follow up. If found to be as reliable as the use of multiple projections, this would obviously considerably facilitate interventional procedures and simplify the performance of serial angiography for quantitative analysis in clinical interventional trials. Our evaluation however, showed considerable variability between orthogonal measurements by both approaches at all stages of angioplasty, a finding which mitigates against the reliability of quantitative analysis from a single angiographic projection. Accordingly, all studies in this thesis are based on quantitative analysis from multiple angiographic projections serially identically repeated before and after intervention and at follow up. Our observation that the presence of angiographically visible dissection post angioplasty did not adversely affect the variability in orthogonal measurements, coupled with the superior agreement between orthogonal measurements pre-PTCA and at follow up, suggests that angiographically undetected changes in target lesion morphology or geometry as a consequence of balloon dilatation (as demonstrated in chapter 3) may be responsible for the poor agreement between orthogonal measurements post-angioplasty.

Chapter 5 deals with the important consideration of whether there are fundamental changes in the coronary artery luminal dimensions within the first 24 hours, which might invalidate quantitative analysis of the angiogram recorded after the procedure, as has been the routine approach over the years, and mandate the use of repeat angiography 24 hours after angioplasty, for any clinical studies investigating restenosis - a finding which would obviously have major repercussions for clinical practice, as well as research. The rigorous methodology applied (including, in keeping with the findings of chapter 3, the use of multiple projections identically repeated at 24 hours), provided highly reliable angiographic data and facilitated demonstration that no significant deterioration occurs at the dilated site during the first day after successful balloon angioplasty, so that the previously suggested phenomenon of delayed elastic recoil was not found to exist. However, because of a significant increase in the reference diameter of treated lesions over the 24 hours, a significant increase was consequently observed in derived percent diameter stenosis measurement. This finding confirms the potentially misleading information which may be provided by use of percent diameter stenosis and re-emphasises the need to focus on absolute coronary luminal measurements in clinical studies. In addition, the previously un-investigated post-angioplasty measurement variability of the CAAS system was found to be 0.20mm, which is eminently acceptable, in view of the potential difficulties with analysis of post-angioplasty angiography (as described in chapter 3). Accordingly, the post-PTCA angiogram could be considered to provide a reliable image of the end-result of the procedure, without recourse to further repeat angiography 24 hours later.

In chapter 6, subjective so-called "qualitative" angiographic coronary lesion morphological features, as well as automatically provided quantitative measurements are investigated, along with patient clinical factors, to determine their usefulness in predicting the occurrence of unfavourable outcome of coronary balloon angioplasty ie. occurrence of death or myocardial infarction or requirement for repeat angioplasty or for bypass graft surgery, during the same hospital admission. It is established that quantitative measurements were not at all helpful in predicting the occurrence of unfavourable outcome, but unstable angina at the time of angioplasty, target lesion located in the mid-segment of the artery or in a coronary bend $> 45°$, type C lesions and the presence of an angiographically visible dissection after angioplasty were independently predictive of a greater likelihood of adverse cardiac events. Of course, it is not surprising that dissection is predictive of unfavourable outcome, since virtually all acute and sub-acute occlusions occurring at the time of angioplasty are associated with the presence of more serious types of dissection (associated with obstruction to blood flow), invariably leading to one of the unfavourable outcomes listed. Quantitative measures were not predictive of unfavourable outcome, but perhaps study of larger numbers of patients with unfavourable outcome would be required to

definitively corroborate this finding.

Part two of the thesis is concerned with evaluation of late effects of intervention, specifically, comparison of the long term effectiveness of different devices with regard to their tendencies to provoke restenosis. Since different devices are more suitable for systematic use in large or small vessels, in chapter 7, the first fundamental aspect of the problem to be investigated was whether or not the size of the coronary artery itself could influence late renarrowing after angioplasty. A comprehensive investigation provided the information that larger vessels are independently associated with a lesser tendency to renarrowing than smaller vessels. Accordingly, failure to take account of the influence of vessel size in a comparison of devices might provide misleading results. When vessel size was controlled in multivariate analysis, the confounding influence was no longer evident. It is apparent therefore, that for comparative evaluation of angiographic results of intervention by different devices, whereby fundamental differences in coronary vessel size are evident, the comparison, in order to provide valid results, must take account of this important confounding factor. For this reason, in chapters 10 and 11, where 4 patient groups treated by different devices are compared, relative measures of luminal change are used, as introduced in chapter 2, whereby the CAAS provided interpolated reference diameter pre-intervention is used as the constant point of reference, rather than employ the unreliable method of percent diameter stenosis, as already shown.

Chapter 8 compares late angiographic results of excimer laser angioplasty and balloon angioplasty among patients who had been enroled in a randomized comparison of these devices for treatment of longer coronary lesions. Accordingly, in keeping with our proposals in chapter 2 and 5, we employ absolute coronary measurements, since the groups have been individually randomized and are well matched for baseline characteristics, particularly vessel size (in keeping with the findings of chapter 7). Focusing on angiographic restenosis propensity provides definitive findings that excimer laser is more provocative of restenosis than is angioplasty alone, both in the general inter-group comparison and also in the ancillary sub-group evaluations. We believe this finding may be due to inherent properties of laser induced vessel injury (as it was being clinically employed during the course of the Amsterdam Miami ROtterdam Eindhoven (AMROE) trial) compared with conventional balloon injury and that it supports our hypothesis of device specific differences in restenosis propensity.

In chapter 9, we compare what may be considered in some quarters as the "devices of the future", the potential "golden fleece". Proponents of directional atherectomy believe this device, when optimally applied, may be the ideal interventional device, by thorough removal of plaque, facilitating maximization of the coronary lumen. On the other hand, stent enthusiasts consider implantation of a permanent prosthesis, with its scaffolding and anti-recoil properties and potential to completely "normalize" the narrowed coronary segment, to be the ultimate panacea for restenosis. By individually matching patients to be compared for baseline clinical and angiographic characteristics, we provide a "surrogate for a randomized trial" and find that stent implantation, at least in our hands, provides superior acute results. This superiority is maintained in the long term (6 months follow up) and was associated with significant clinical benefit, in terms of reduction in frequency of major adverse cardiac events (as defined in chapter 6). To confirm that such superiority is not merely a function of the larger acute result, as has been the claim of other investigators, we performed a second comparison involving matching of patients for the post-procedural result, as well as baseline characteristics. In this manner it emerged that significantly less renarrowing developed in the patients receiving a stent, who consequently had a superior late angiographic result. This finding may be interpreted as a device specific effect, whereby achievement of similar luminal increase is associated with less vessel injury by stent implantation than by directional atherectomy.

Chapters 10 and 11 involve serial comparative evaluations of patient populations treated by different interventional devices, using the relative angiographic parameters introduced in chapter 2 and the multivariate modelling and graphic approach applied for the first time in a clinical study in chapter 7. The first comparative evaluation of 4 devices which we performed is described in chapter 10. At that time (1992), we had already prospectively collected patient data on 1452 patients treated by balloon angioplasty, 120 by directional atherectomy, 104 by Wallstent and 100 by Wiktor stent implantation, with serial quantitative angiography pre and post intervention and at follow up. Since chapter 7 showed the confounding influence of vessel size on outcome, relative angiographic parameters were employed to control for this. Significant differences were observed in angiographic restenosis propensity between the 4 devices, independent of baseline lesion severity, lesion location and luminal increase at intervention. Although the evaluations represent a novel and unconventional approach and, as such, require some digestion, the essence of the message can be gleaned from the 3 dimensional graphs, which, interpreted at their simplest, demonstrate differences in the slopes of the "planes" between the 4 groups and differences in the Y axis levels of the 3 points of comparison between the 4 groups. In basic terms, for a coronary lesion of given severity, location and vessel size, a given acute result will lead to differing late angiographic results, depending on the device. Unfortunately, the fact that

demographic differences existed between the 4 groups, could theoretically have influenced the findings, so definitive conclusions can be criticized, even though the findings are quite significant and support the hypothesis espoused in chapter 2. Other studies, referred to in this chapter and in chapter 11, which included clinical and histological as well as angiographic characteristics in evaluation of determinants of restenosis, did not find that inclusion of these additional characteristics altered the fundamental angiographic relationships described. However, although these findings would support the validity of the angiographic results of this study, the evidence is somewhat circumstantial. Accordingly, further comparison between more homogenous patient groups treated by different devices was considered necessary to further evaluate the hypothesis as described in chapter 11.

Chapter 11 involves comparison of angiographic restenosis propensity between a large group of patients treated by balloon angioplasty (the size of this group does not unbalance the comparison, but rather increases the statistical power to detect important inter group differences, due to the greater number of "observations") and relatively large (relative to single centre experience throughout the world) groups of patients treated by Palmaz-Schatz stent implantation, directional atherectomy or excimer laser angioplasty. Use of the previously established comparative methodology again demonstrated fundamental differences in angiographic restenosis propensity between the patient groups treated by different devices (again, independent of variations in lesion severity or location, vessel size or luminal increase).

Although critics may still point to possible unseen influences of subtle patient, procedural or lesion differences, these findings are in agreement with the findings of chapters 8, 9 and 10 and, considered together, convey the essence of "device specific" influences on late results of intervention and confirm the validity of our hypothesis formulated in chapter 2. Ultimately, to satisfactorily resolve the issue, randomized comparisons will be required between devices, with a prerequisite for optimization of acute results and with additional application of serial intravascular ultrasound, to possibly provide a mechanistic explanation for the findings. Appropriate methodology for suitable evaluation of restenosis propensity of coronary interventions is established in these studies. Superior devices for intervention my be considered to be those which provoke the lest degree of luminal renarrowing (relative luminal loss) with incremental luminal maximization (relative gain) during intervention. Useful adjunctive therapy should demonstrate a significant reduction in the relative loss response to increasing relative gain if it is to be accredited with a real influence on the process of restenosis. In the concluding chapter of the thesis, further interpretative consideration is given to these findings, with particular emphasis on the implications for clinical practice in the future.

CHAPTER 1

TECHNOLOGICAL CONSIDERATIONS AND PRACTICAL LIMITATIONS IN THE USE OF QUANTITATIVE ANGIOGRAPHY DURING PERCUTANEOUS CORONARY RECANALIZATION.

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Technologic Considerations and Practical Limitations in the Use of Quantitative Angiography During Percutaneous Coronary Recanalization

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ALTHOUGH the development of selective coronary arteriography[1] rapidly led to its acceptance by cardiologists as the "gold standard" in the diagnosis of atherosclerotic coronary artery disease (CAD), many authors have reported on the pitfalls associated with visual interpretation of the coronary angiogram.[2-9] The variability associated with visual quantification of stenosis has been shown to be related not only with the degree of compromise of the arterial lumen,[7] but also with the lack of uniformity in identifying the narrowest point of the lesion,[8] with the quality of the angiograms,[5] and with multiple anatomical factors, including lesion length, vessel irregularity, and branch overlap.[2] Selection of the angiographic view showing the stenosis at its most severe is equally affected by variability.[6] Although the variability associated with visual interpretation of coronary arteriograms can be reduced by a consensus panel,[9] it is self evident that such an approach is cumbersome, time-consuming, and cannot be applied during on-line analysis in cardiovascular interventions.

The advent of computerized image analysis and quantitative coronary angiography (QCA) has made possible the objective study of angiographic images over the past 15 years. During the same time period, the generalization in the use of percutaneous revascularization techniques using balloon angioplasty and other techniques such as coronary atherectomy and stenting has expanded the use of QCA in both the clinical and research fields. As a result of application of these interventional techniques, the data obtained have to be used to provide the operators with reliable information not only about the severity of the stenosis but also about aspects relevant to procedural decisions. Matching the size of the interventional device to the artery is required during recanalization to minimize vessel damage that may precipitate acute vessel occlusion and late restenosis.[10,11] Objective information on the changes in luminal dimensions obtained by the technique during the procedure may be required to decide whether discontinuation of the procedure or further recanalization is needed.[12,13] For the researcher, quantitative angiography has become the main tool to assess not only the primary efficacy of a particular technique but also the luminal renarrowing in the long term.[14]

The purpose of this article is to understand the advantages and limitations of QCA in the field of interventional cardiology. The Cardiovascular Angiography Analysis System (CAAS),

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developed at our institution and previously described in detail elsewhere,[15-18] will be used as an example, because it incorporates the two modalities of analysis that are more widely used, namely detection of luminal contours (so-called edge detection) and densitometry. These two types of analysis are discussed separately. A detailed comparison highlighting the similarities and differences between the CAAS and other QCA systems can be found in several reviews in the literature.[19,20]

CONTOUR-DETECTION QUANTITATIVE ANGIOGRAPHY

The first approach used in quantitative angiography consists of the analysis of the distances found between the leading edges of the luminal silhouette. From an historical point of view, this constitutes the first attempt to quantify vessel dimensions using calipers, either manual,[21,22] sometimes with optical magnification,[23] or digital.[24] Luminal diameters are widely used in quantitative angiography given the ease of measurement and probably because the fact that, at least at first glance, the information obtained with automated edge detection conveys information comparable with that used during visual interpretation of the angiogram or hand-held calipers (although this aspect has been questioned by the work of Fleming et al,[25] who found a better correlation between visual estimation of stenosis severity and luminal area derived from QCA analysis).

Despite its apparent simplicity, contour detection requires a sophisticated methodology for its adequate application. Because the borders of the luminal silhouette in the cineangiogram consist of a gradient of densities, identification of the true luminal borders is still uncertain and is a major cause of variability in the measurements. The problem posed to automated systems of edge detection is to establish at which level the transition between background and luminal densities of the opacified vessel occurs (Fig 1). In most automated systems, a two-dimensional analysis of the density observed in individual scanlines perpendicular to the vessel centerline solves this problem. Critical changes in brightness are detected by using the first and second derivatives of the density. The automated search is performed in consecutive scanlines that are repeated at close intervals over

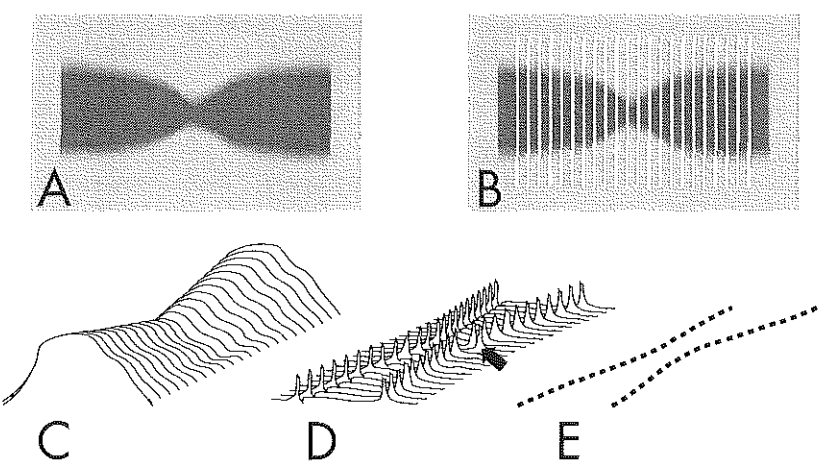

Fig 1. Steps followed during automated detection of luminal borders from the cineangiogram are shown. (A) The borders consist of a gradient of densities, posing the problem of establishing at which level the transition between background and luminal densities of the opacified vessel occurs. (B) A two-dimensional analysis of the density observed in individual scanlines perpendicular to the vessel centerline is performed. (C) The density observed in these consecutive scanlines is obtained. (D) Critical changes in brightness, corresponding to the transition between background and opacified lumen, are detected by using a combination of the first and second derivatives of the density. (E) The identification of luminal edges is based not only on individual scanlines but also on the overall information obtained from neighboring scan lines, which decreases the contribution of spurious variations in density that are observed a single scanline (arrow in D).

the studied segment. The information contained in an individual scanline may be influenced by local sources of error in edge detection, such as originating branches or overlying structures; therefore, the automated identification of luminal edges is based not only on individual scanlines but also on other neighboring scanlines. This identification is performed using so-called minimal cost algorithms, which facilitate edge detection over the length of the arterial segment being analyzed. By restricting the relevance of the information of each individual scanline, minimal cost analysis assumes that no drastic change in the contour of the vessel will occur in a very short segment. Thus, when complex angiographic morphologies with overhanging edges or abrupt changes are analyzed, errors derived from pitfalls in edge detection can occur. Finally, for a more precise detection of the luminal edges, an iterative method, which involves recalculation of the centerline and a new detection of the luminal contour, is applied. Each of these steps is fully automatic, and the only requirement for the user is the selection of the segment to be analyzed and the identification of a few arbitrary centerpoints within that segment.

Once the luminal diameters have been obtained, the distance between the edges at the level of each individual scanline can be easily calculated in pixel units. Calibration of the system with a structure of known dimensions, such as the filmed catheter, makes possible the transformation from pixels to absolute units. When the diameter values are plotted against the length of the analyzed segment, a so-called diameter function is obtained (Fig 2). Application of specific algorithms to the diameter function makes possible the calculation of a number of angiographic parameters. For example, in the CAAS system, the application of a curvature-detection algorithm to the diameter function identifies the location where a critical decrease in luminal dimensions (that is, one that is attributable to the stenosis and not to spurious variations in luminal diameter) occurs. The same principle is applied to identify both limits of the stenosis. Minimal luminal diameter (MLD) is easily identified in the diameter function as the point with the lowest diameter value.

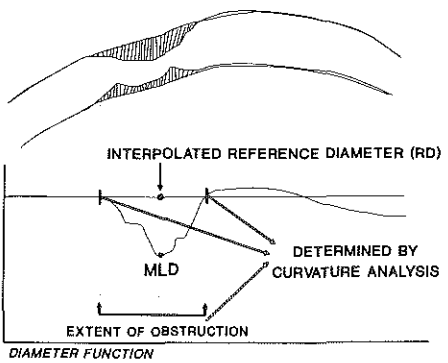

Fig 2. Schematic representation of a diameter function curve shows MLD, interpolated reference diameter, and the extent (or length) of the obstruction as determined by the curvature analysis.

For the calculation of relative measurements (percent diameter stenosis), MLD is compared with a reference segment. Although the latter can be defined by the user, it is obvious that visual identification of a reference segment would be associated with a similar variability as the point of minimal diameter, particularly in cases where the proximal part of the arterial segment shows a combination of stenotic and ectatic areas or in cases where a "normal" portion is just not clearly available. In an attempt to provide a solution to this problem, the CAAS system incorporates an interpolated reference diameter that is derived solely from the information conveyed by diameter function. In the CAAS system, the algorithm used for interpolation of the reference dimensions involves the calculation of a first degree polynomial, computed through the diameter values of the proximal and distal portions of the arterial segment, followed by a translation to the 80th percentile level (Fig 2). Interpolated reference diameter techniques are also useful when repeated measurements of the same segment are required, such as during follow-up studies after intervention. However, it is not possible to apply this technique when no reliable proximal or distal segment is present, such as in ostial lesions or in segments with incomplete opacification of the distal segment (Fig 3). In those cases, the selection of a reference segment by the user is justified (Fig 4).

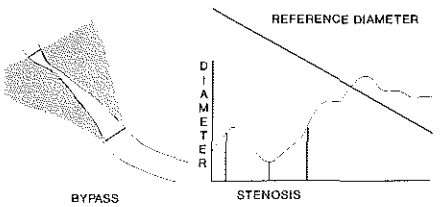

Fig 3. Measurement of the reference diameter for an ostial lesion is shown. The computer-defined reference diameter is inaccurate in situations where there is no reliable proximal or distal boundary (eg, ostial lesion or lesions located at the origin of a side branch). In this situation, the analyst must determine the reference diameter (user-defined).

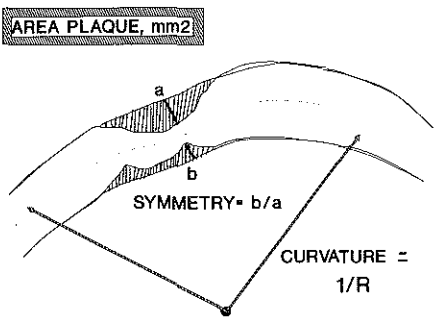

Fig 5. Determination of the area plaque, symmetry, and curvature values is shown (see text for details).

In the CAAS system, the combined use of the interpolated reference dimensions over the analyzed segment and the detected luminal edges yields an estimate of the protrusive area of the atheromatous plaque (Fig 5). Similarly, a symmetry index is calculated as the ratio of the angiographic plaque observed at both luminal edges.

The curvature value is an attempt to convey a measure of the degree of curvature or bending of the coronary segment being analyzed (Fig 6). The angiographic projection in which the vessel appears to be the least foreshortened (ie, where the measured absolute distance between the proximal and distal boundaries of the segment is greatest) is chosen for the curvature analysis. The inflow and outflow angles are derived from the slope of the diameter function at the descending and ascending limb of the diameter-function curve at the defined site of the obstruction (Fig 6). The information derived from these parameters may be relevant in characterizing the hemorrheologic behavior of the stenosis and has been helpful in studying the characteristics of coronary artery lesions at risk of thrombotic occlusion[26] and in assessing the modifications in stenosis morphology after coronary stenting.[27]

DENSITOMETRY

The basic principle on which densitometry is based is the existing relationship between the attenuating power of the lumen filled with contrast medium, which is a function of luminal area, and the x-ray image intensity.[28] From this information, a densitometric profile that is proportional to the cross-sectional area of the

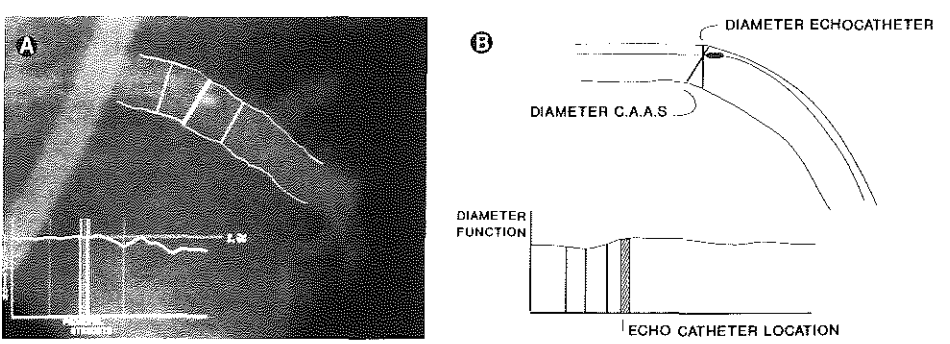

Fig 4. The user-defined reference diameter is also useful when the exact diameter is required at a specific location in the coronary artery. (A) In the validation studies of intravascular echo catheters, the tip of the echo-catheter is visible, and the diameter of the segment (3.26 mm) has been determined by the CAAS analysis. (B) It is also clear from the schematic diagram that different diameters are measured by the two methods, when the intravascular echo catheter is placed in a bend in the coronary artery.

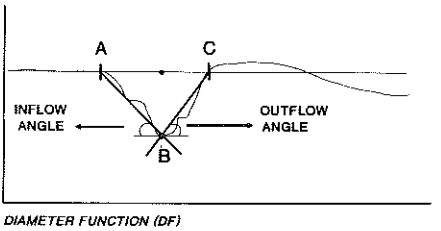

Fig 6. Determination of inflow and outflow angles from the diameter function is shown (see text for details). Inflow angle is the average slope of the DF between B and A; outflow angle is the average slope of the DF between B and C.

lumen is obtained, irrespective of its morphology. Thus, whereas edge detection analysis yields luminal diameters, densitometry provides an estimate of luminal area. A potential advantage associated with the use of area measurements is that it may yield more relevant physiologic information than luminal diameter measurements.[29-33] Furthermore, luminal area is calculated without making assumptions on lumen morphology and, theoretically, with independence from the angiographic angulation used.[28] On the other hand, the basic assumption of a correspondence between density and luminal area can be lost at every step of the collection, transfer, and analysis of data. Let us review some of these limitations.

To obtain a reliable correlation between luminal dimensions and videodensity, complete replacement of blood by contrast medium during each injection should be ideally obtained by the operator. Failure to do so may induce streaming of contrast that may affect the detection of the true luminal borders. Similarly, a decrease in concentration of iodine within the artery may cause errors during the calculation of luminal area from the densitometric profile. Perpendicularity of the x-ray beam to the analyzed segment is also important.

A major problem in videodensitometric analysis is derived from the presence of overlapping densities, corresponding to other anatomical structures, that can interfere with the calculation of luminal area. To correct for such patient structure noise, subtraction of the background has to be applied to obtain a net cross-sectional videodensitometric profile. Information obtained either from an identical image obtained before the injection of contrast (mask subtraction) or from the structures adjacent to the artery present in the same frame must be used for this purpose. Both systems of background correction present weak points. The former is affected by patient motion, particularly respiration, whereas the latter is affected by the structure-related variability, which cannot be fully replaced by the use of linear interpolation. Excessive background subtraction can occur when other vascular structures located close to the vessel contour are used by the subtraction algorithm or when the vessel is located in areas of rapid transition between dark and bright areas. In those cases, the subtraction can be so intense that the calculated cross-sectional area may even assume a negative value (Fig 7).

Not all brightness observed at the end of the cineangiogram-video chain can be attributed to the attenuation of the x-ray beam by the opacified vessel and anatomical structures. Both x-ray scatter and light reverberation within the optical systems, such as the image intensifier and video cameras (veiling glare), contribute up to 80% of the total light intensity.[34] When no correction is applied, these measured intensities are introduced in the calculation of luminal

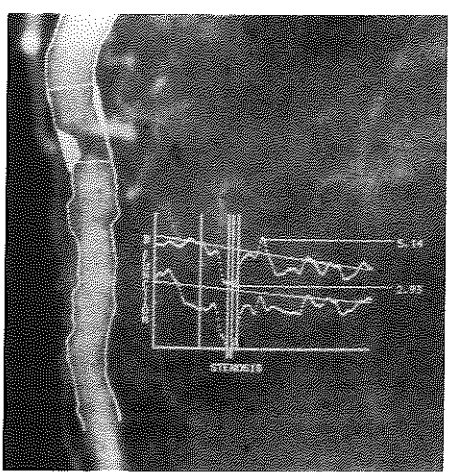

Fig 7. Densitometry measurements are affected and inaccurate in the presence of overlapping side branches. In this example, the upper curve (the diameter function) shows an MLD of 2.93 mm. However, because of interference from side branches from the background subtraction, the densitometric-determined MLCA (lower curve) is a negative value.

area . . . lay constitute an important source of error.[34,35] The contribution of scatter and veiling glare varies with the location across the thorax, reaching maximum values when the coronary arteries are projected in areas with a rapid transition between the cardiac silhouette and the lung field, and makes correct positioning of angiographic wedge filters mandatory during image acquisition to minimize this source of error.

In the CAAS system, a luminal area function is constructed in an analogous fashion to that described for the edge detection modality and can be used in the calculation of interpolated reference area. However, a critical difference in the calculation of absolute values with both techniques is that densitometry relies on the calibration of the system using a reference videodensitometric profile, which is obtained in a segment of known dimensions. In the CAAS system, this reference profile is usually obtained in a computer-defined disease-free segment, which serves as a reference area and in which luminal area is calculated simultaneously from the luminal diameter assuming that the lumen has a circular morphology (Fig 8). When this is not the case, such as in diffusely diseased vessels, errors in area calculation can occur.

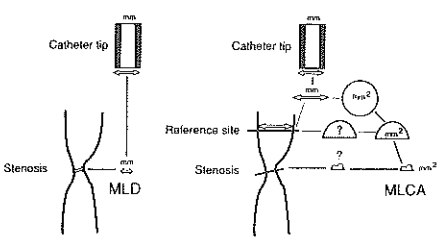

Fig 8. Calculation of absolute vessel dimensions by edge detection and videodensitometric analysis. In edge detection, the calculation of MLD is obtained by direct comparison with the diameter of the filmed catheter, which is used to calibrate the system. Videodensitometry yields a densitometric profile that has to be compared with a segment of known luminal area. This is achieved by automatic selection of a reference site where it is assumed that no occlusive atheromatous disease is present and that the lumen is circular. From the reference diameter (calculated from direct comparison with the coronary catheter as described above), geometric circular cross-sectional area at the reference site is calculated and compared with the densitometric profile at the same site. In this way, density units are transformed into area units (mm²). By direct comparison of the densitometric area, thus calculated at the reference site, and of the smallest densitometric profile in the stenotic segment, MLCA is derived.

Another potential source of error derived from the dependency on a reference segment for the calculation of absolute videodensitometric values can be found in the differences in the attenuating power of the opacified reference and stenotic segments. Most x-ray tubes are polychromatic and generate a spectrum of radiation with varying associated energy. It has to be remembered that the Lambert Beer law, which is used in most QCA videodensitometric systems,[20] requires a monochromatic source of x-rays. When the less energetic fraction of the radiation produced by the x-ray tube is selectively attenuated by a opaque structure, a substantial modification of brightness at the level of the image intensifier occurs because of the penetration of a "harder" x-ray beam (beam-hardening effect). Furthermore, because the column of contrast medium at this reference site has a higher attenuating power than that existing at the stenotic site, the characteristics of the densitometric profile can be modified by this so-called beam-hardening effect. Differences in the beam-hardening caused by the different attenuating power of the contrast column existing at the reference and stenotic segments can, when not corrected, affect all subsequent calculations of stenosis severity (Fig 8).

IMAGE ACQUISITION AND ANALYSIS IN CONTOUR DETECTION AND DENSITOMETRY

Edge detection and densitometry share common limitations and requirements that must be kept in mind during their applications. In the following paragraphs several of these aspects are discussed. At the present time, images for QCA are obtained from cineangiograms or digital systems. The main advantages of using cine films stems from the fact that they have a higher spatial resolution than digital images. Furthermore, by using adequate zooming with optical systems, a section of the image encompassed in the cine frame can be selected and digitized for further analysis. When digital systems are used, the spatial resolution of the images is currently hampered by the size of the matrix being used (512 × 512 pixels). The use of cineangiograms or digitally acquired images also has implications for the type of transfer function used during image analysis. In the

former, a semilogarithmic transfer function is needed, whereas, in digital angiograms, a linear relationship exists.[20] As discussed above, this may be advantageous when densitometry is applied.

During the acquisition of the cineangiogram, selective magnification of structures localized in the periphery of the image occurs. This phenomenon is termed "pincushion distortion," and can be minimized by the operator through proper manipulation of the table and gantry to ensure a location of the stenosis as close to the angiographic isocenter as possible. Pincushion distortion has been markedly decreased in new generation image intensifiers. In addition to the abovementioned precautions, correction for the images obtained can be performed during off-line analysis. For this purpose, a centimeter grid must be filmed in each mode of the image intensifier and later used by the CAAS system to calculate a correction factor for each intersection position of the grid wires so that the pincushion distortion can be corrected.[36]

An additional important practical point for the physician in all serial studies is the requirement for coronary vasodilation using agents of comparable efficacy for every study. In a recent study of 202 patients,[14] the mean diameter of a normal segment of a nondilated vessel prepercutaneous transluminal coronary angioplasty (pre-PTCA), post-PTCA, and at follow-up was analyzed (Table 1). Of these patients, 34 who received intracoronary nitrates pre-PTCA but not before the post-PTCA angiography showed a decrease of 0.11 mm in the reference diameter versus the small increase of 0.02 mm in the group that did receive postprocedural nitrate. Vasomotion should be controlled in QCA studies by means of a vasodilator drug that produces fast and complete vasodilation without significant effects on the peripheral circulation. At our institution, 0.1 to 0.3 mg of nitroglycerine or 1 to 3 mg of isosorbide dinitrate are used before angioplasty, after the last balloon inflation, and at follow-up angiography. Furthermore, the use of nonionic contrast medium is probably recommended because of its less intense effect on coronary vasomotion.[14] Warming of contrast medium to body temperature is also recommended to minimize potential vasomotor effects.

Table 1. Influence of Vasomotor Tone on QCA Measurements of Nondiseased Segments

Mean Diameter (mm)	Without Nitro Post-PTCA (n = 34)		With Nitro Post-PTCA (n = 168)
Pre-PTCA	3.12 ± 0.63		2.74 ± 0.63
Post-PTCA	3.01 ± 0.64		2.75 ± 0.59
F-Up	3.18 ± 0.55		2.82 ± 0.63
Δ Post-pre	−0.11 ± 0.27	↔	+0.02 ± 0.21*
Δ F-up–pre	+0.06 ± 0.22	↔	+0.07 ± 0.22†

Thirty-four patients did not receive intracoronary nitroglycerin post-PTCA. In the nondiseased segments adjacent to the dilated site, in these patients the mean diameter decreased by 0.11 mm after angioplasty compared with the pre-PTCA values (where nitroglycerine had been administered). This change was not seen in the group who received nitroglycerine post-PTCA. Such change in reference diameter will affect the determination of percentage diameter stenosis.

Abbreviations: Nitro, nitroglycerin; F-up, follow-up.

*$P < 0.001$.

†P value is not significant.

The ability to obtain reliable measurements from a single angiographic view would simplify enormously the use of on-line quantitative angiography. Although routinely applied in many laboratories, little information is available on the variability related with this approach. When edge detection is used, Lesperance et al[37] have suggested that restricting the analysis to the angiographic view in which the stenoses appears most severe fulfills the degree of accuracy required in clinical practice. However, the conclusions of this study were limited by the lack of a true standard for the assessment of precision and accuracy. Densitometry is an appealing alternative to edge detection, because the obtained measurements should not be influenced by the angulation used, a principle supported by experimental in vitro studies.[38-41] However, major controversy remains as to the application of this principle in the clinical field. The correlation for individual measurements obtained in orthogonal views both before and after balloon angioplasty has been found by different authors to be high,[42] moderate,[43] or poor.[44] It has also been found to be influenced by the stage of the intervention, deteriorating after balloon angioplasty to an unacceptable level.[45] In a recent study,[46] we have found that the variability of measurements obtained from two orthogonal views in a selected coronary segment was too high to recommend its application routinely. Although this was observed for both edge detec-

tion and videodensitometric data at all stages of balloon angioplasty, after balloon dilatation, densitometry showed significantly less variability between orthogonal measurements than did edge detection.

TECHNICAL ASPECTS OF QCA IN SPECIFIC RECANALIZATION TECHNIQUES

As stated in the introduction, the development of a variety of percutaneous recanalization techniques has introduced unexpected requirements for the analysis of vascular segments with conventional QCA systems. The different mechanisms of action associated with each technique have major implications for the performance and interpretation of QCA analysis. In the following paragraphs, we discuss some of these aspects in the case of conventional balloon angioplasty, stent implantation, directional atherectomy, rotational plaque ablation, and excimer laser angioplasty.

Balloon Angioplasty

Balloon angioplasty constitutes the most widely used percutaneous recanalization technique in the coronary arteries. The mechanism of action of angioplasty has been described in detail and involves tearing of the intima and atherosclerotic plaque, dehiscence of plaque from the tunic media, and variable degrees of medial and adventitia disruption.[47,48] From the point of view of this article, we can group the changes into three different categories: (1) the development of large disruption that can be visually identified in the coronary angiogram as dissection (Fig 9);[49] (2) the presence of intraluminal flaps and irregularities not actually identified angiographically but documented in angioscopic,[50-52] ultrasound,[53-55] and pathologic studies;[56] and (3) the change to noncircular lumen geometry secondary to balloon dilatation.[47] Several authors have suggested that these histopathologic changes are responsible for the decrease in angiographic accuracy observed after balloon dilatation.[57-61] When opacified during angiography, these irregularities may be wrongly identified as true luminal borders by edge detection algorithms, leading to a false estimation of luminal diameter.

Dissections are a frequent occurrence after PTCA, and the resulting haziness, irregular borders, or extravasation of contrast medium makes edge detection difficult (Fig 9). Few methodologic recommendations are available as to the QCA analysis of those cases. During the design of the MERCATOR trial, the Angiographic Steering Committee of the study decided that, during edge detection analysis, the automated mode of the computer "decides" whether the extraluminal defect is included or excluded from the analysis.[49] This is based on the assumption that if there is no clear separation between the lumen and the extravasation (because of the existence of large communicating channel), the application of minimum cost criteria during edge detection (see above) would incorporate the extravasation as part of the true lumen. On the contrary, the exclusion of the extravasation would be, presumably, caused by the presence of a steep difference in brightness

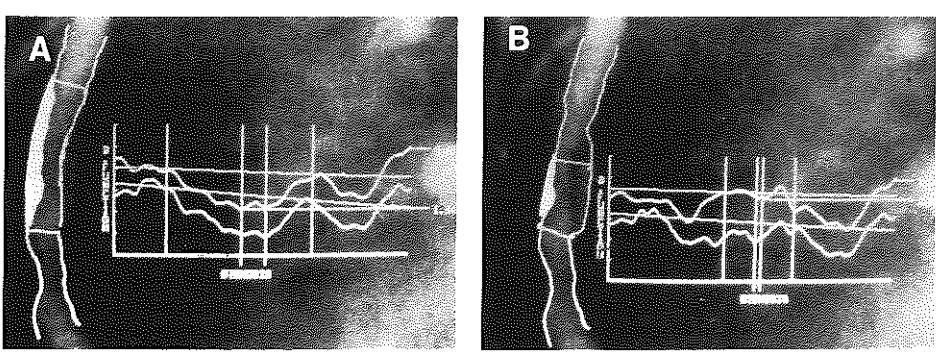

Fig 9. Edge detection of a lesion after PTCA has induced a large dissection. (A) Excluding dissection, the MLD is 1.34 mm. (B) Including the dissection, the MLD is 2.53 mm.

between the extravasation and the true lumen. The validity of these assumptions has yet to be shown and constitutes an empirical approach aimed to reduce subjective bias during angiographic analysis.

The reliability of videodensitometric measurements taken under circumstances similar to those found after balloon angioplasty has not been clearly established in an experimental setting. Such experimental settings have been based on the use of engineered phantoms either in vitro[38-41] or after percutaneous insertion in animal models.[62,63] This may explain the differences found with results obtained in clinical practice, where conflicting results suggesting a high variability in the obtained measurements have been reported (Fig 10).[57-60,64-69]

In a previous study,[46] we found, using edge detection before and after balloon angioplasty, that the agreement between single orthogonal measurements deteriorates significantly after balloon dilatation. However, this deterioration was not related to the presence of angiographically evident dissection. As mentioned above, we could also note that the variability between orthogonal measurements obtained with densitometry was less influenced by balloon dilatation than was that for edge detection. This observation may be related to the discussed theoretical independence from lumen morphology and to its relative insensitivity to imprecise border positioning[70] of videodensitometric measurements. Thus, although the application of densitometry may be currently hampered by the technical limitations discussed above, further progress in solving these problems may lead to a satisfactory application of the technique.

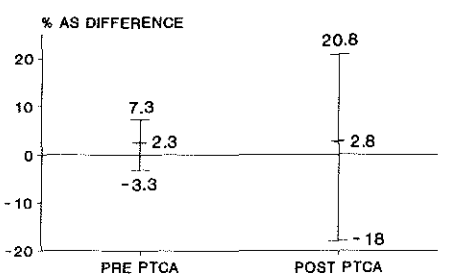

Fig 10. Agreement between densitometric percentage of area stenosis and the circular (edge detection) percentage of area stenosis pre- and post-PTCA is shown. The mean difference (and standard deviation) for percentage of area stenosis between the two methods was 2.3% ± 4.0% pre-PTCA and 2.8% ± 18% post-PTCA. Important discrepancies (ie, large standard deviation) between the two methods after PTCA are likely related to the noncircular, asymmetric configuration of the lesion after angioplasty.

Intracoronary Stenting

Three types of coronary stent (Wallstent, Wiktor, and Palmaz-Schatz) have been used in multicenter European clinical studies with angiographic follow-up and subsequent detailed QCA analysis at the Thoraxcenter Core Laboratory,[27,71-74] and a fourth (Gianturco-Roubin) is currently being evaluated in the "bail-out" setting. In all cases, the radiopacity of the stent has implications both for implantation and for the subsequent angiographic analysis, because its presence in the artery can interfere with edge detection algorithms.[61] The Wallstent and the Palmaz-Schatz stent are composed primarily of relatively radiolucent stainless steel, whereas clear, radiopaque tantalum is the principle constituent of the Wiktor stent (Figs 11A, B, and C).

A second problem with angiographic analysis of stented vessels is caused by the superior angiographic result immediately after stenting. Because routine mild oversizing of the stent has been recommended,[75] the stenosis may not only be completely corrected but also may be overdilated in comparison with the reference diameter before stenting. This may cause particular problems with the algorithms that measure lesion length and the calculation of the interpolated reference diameter. To bypass this problem, we arbitrarily define the length of the lesion after stenting as the actual length of the stent (which requires manual selection of the stent boundaries). Thus, the stented segment is defined for future follow-up analyses. An alternative to this type of analysis "per stent" is to perform a fully automated analysis "per vessel" by choosing landmarks located proximally and distally to the stented site (eg, branching points). In reporting our angiographic studies, we chose the pre- and post-PTCA frames to be analyzed "per vessel," and the post-stent and follow-up films to be analyzed "per stent." This ensures that we can obtain measurement data relating to the stent itself and its immediately adjacent segment, rather than obtaining measurement of

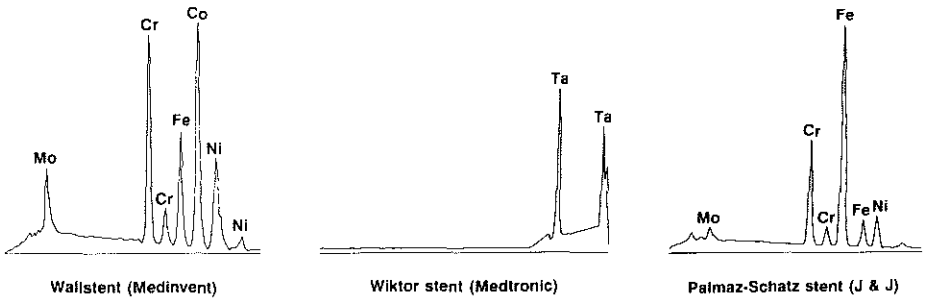

Fig 11. The metal composition according to x-ray energy dispersion spectrometry used in three currently investigated coronary stents. Ta, tantalum; Mo, molybdenum; Cr, chromium; Co, cobalt; Fe, iron; Ni, nickel. (Reprinted with permission.[76])

a more severe stenosis at a separate site in the coronary vessel.

Stenting has also highlighted a limitation of the CAAS system in determining a reference diameter in an overdilated segment. Theoretically, this should result in a negative value for diameter stenosis, because the MLD (which, as we already mentioned, was defined within the boundaries of the stent) was actually larger than the reference diameter (which is determined according to the diameter of the proximal and distal segments; see Figs 12A and B). However, for reasons that are unclear, a negative diameter stenosis has rarely occurred, and the reference diameter has virtually always remained larger than the MLD, in contrast to the post-stent measurements reported by other groups. This may be explained in many cases by detection of an MLD within the stent because of the protrusion of intima between the struts or at the articulation point. Thus, whereas the average diameter within the stent may appear greater than that of the adjacent segments outside the stent, detection of a single diameter measurement less than the reference diameter will provide a percentage of diameter stenosis greater than 0%. A further confounding factor in the determination of the reference diameter after stenting is that the marked vasospasm, occasionally seen immediately proximal and distal to the stent, may persist despite nitrate administration. This factor must be taken into account during "per vessel" analysis.

Stainless steel stents. The main problem with these stents is their poor radiographic visibility (Figs 13A and B). In particular, the Palmaz-Schatz stent, which is the most difficult stent to visualize, can be dislodged from the balloon catheter and embolize distally without radiographic evidence. Additionally, it can be quite difficult to ensure ideal placement of the stent across a lesion. For the analyst, it may be difficult or impossible to satisfactorily identify the stent boundaries, and the precise location of a recurrent lesion at follow-up angiography (within the stent or immediately adjacent) may be in some doubt. Careful review of the contrast-free cineframes may be needed to detect the position of the Wallstent. In our follow-up reports of stenting, we have always included lesions within and immediately adjacent to the stented segment to ensure that the degree of luminal renarrowing is not underestimated.[73]

Tantalum stents. Although the radiopacity of the Wiktor stent has greatly facilitated the implantation procedure (Fig 14A and B), this particular property severely limits the assessment of follow-up studies of the stent with the CAAS system. Several cases have now been documented in which the contour-detection program traces the radiopaque stent wires instead of the arterial borders of the narrowing within the stent (Fig 15). This invalidates the computer-derived data and requires manual correction of the contours by the analyst, which is also difficult in a segment containing radiopaque wires.

Densitometry in stented vessels. In contrast to the situation after PTCA, there is excellent agreement between minimal luminal cross-

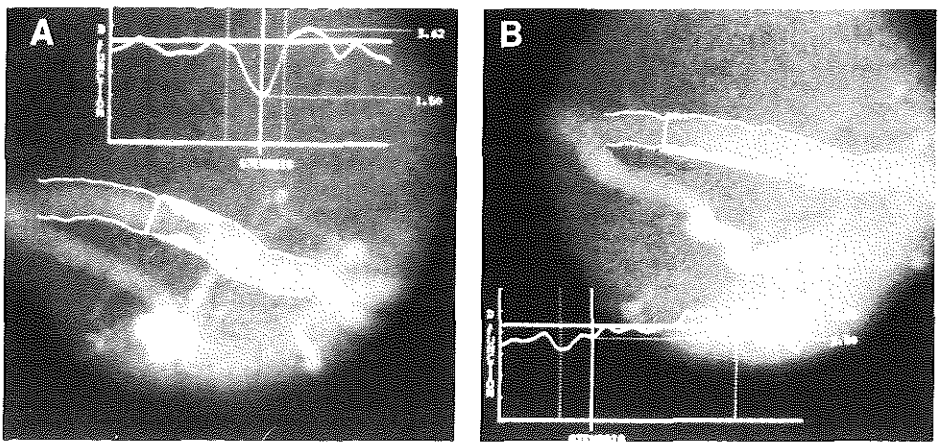

Fig 12. Coronary segment overdilated by a Palmaz-Schatz stent, (A) pre-stent (B) post-stent is shown. Although MLD in the stented segment should be greater than its reference diameter (which is determined for the stented segment by the algorithm, for the most part, from the smaller proximal and distal segments), the measurement given by the interpolated technique yields a reference diameter that is actually larger than the MLD, for reasons which are not entirely clear. Thus, the diameter stenosis within the stented segment after implantation of an oversized stent is positive (12%) rather than negative.

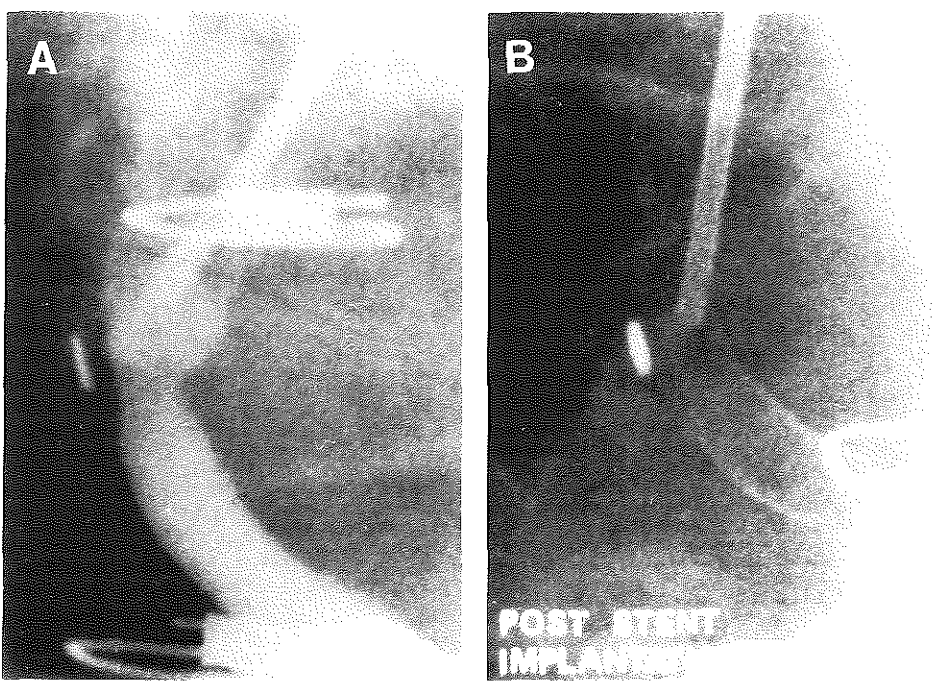

Fig 13. The Wallstent (poor radiopacity), after implantation in a saphenous vein bypass graft, is shown, on the left (A), in vessel opacified by contrast and, on the right (B), in vessel without contrast.

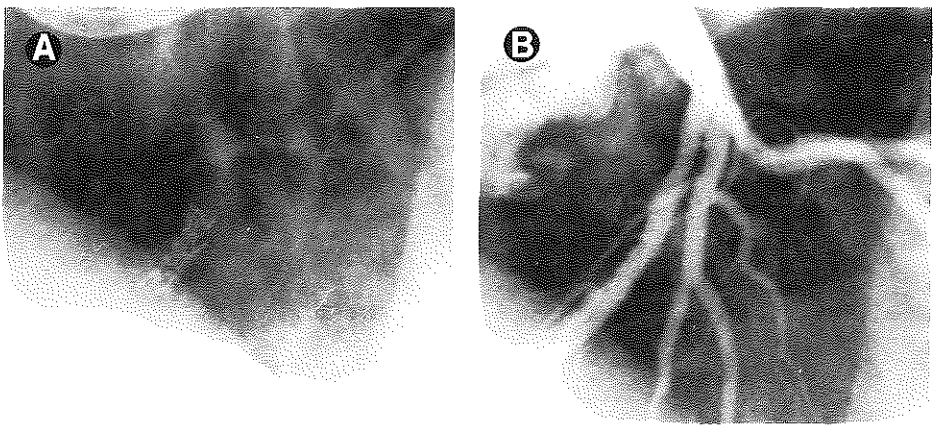

Fig 14. Wiktor stent after implantation in left anterior descending artery is shown (A) in vessel without contrast. (B) In vessel filled with contrast, the stent remains clearly visible.

sectional areas (MLCAs) determined by edge detection and by densitometry after stent implantation with the Wallstent.[61] The standard deviation of the mean differences between edge detection and densitometric determination of MLCA were 0.51 mm² pre-PTCA, 1.22 mm² after angioplasty, and 0.79 mm² after coronary stenting (Fig 16). This improvement is probably caused by smoothing of the vessel contours by

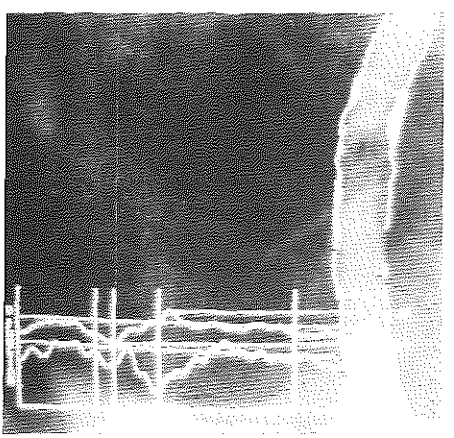

Fig 15. Restenosis within a coronary Wiktor stent not recognized by edge detection is shown. Graph shows the diameter function (upper curve) and the densitometric area function (lower curve). Outside vertical lines on the graph and two horizontal lines in the angiographic image are the corresponding boundaries of the analyzed segment. The inner two vertical lines on the graph represent the minimal points on the diameter and densitometric graphs respectively. The edge detection algorithm followed the outline of the stent and was unable to recognize the stenosis within the stent, giving an MLD of 2.17 mm. A discrepancy between the two functions is present and most notable at the vertical line that denotes the MLCA determined by densitometry. (Reprinted with permission.[76])

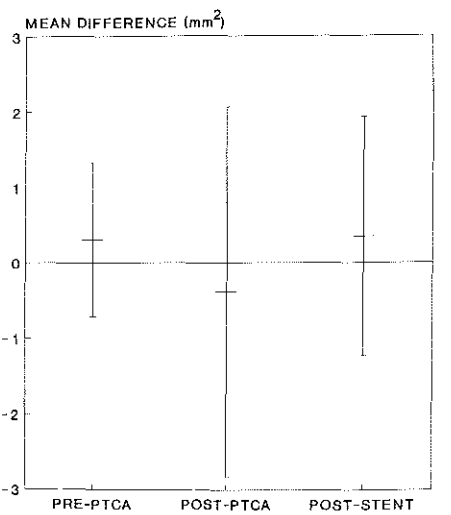

Fig 16. Mean difference (and 95% confidence intervals) between edge detection and densitometry before and after PTCA and after stenting. Mean differences were slightly positive (0.31, 0.35 mm²) before PTCA and after stenting, respectively, and slightly negative (−0.38 mm²) after PTCA. The widest 95% confidence interval was in the analysis after PTCA, indicating the poorest association between the two methods, compared with the analysis before PTCA and stenting.

the stent and remodeling of the stented segment into a more circular configuration (Fig 17). Therefore, we believe that both methods are appropriate to assess the immediate results after stenting. In a separate in vitro study in which stents were placed within plexiglass phantoms with known luminal dimensions, the Wallstent and Palmaz-Schatz stents caused minor interference with the densitometric determination of MLCA within the "stenoses" (Figs 18A and B)[76] that probably lack clinical relevance. Conversely, the radiopacity of the tantalum Wiktor stent led to overestimation of MLCA measurements in these same stenoses, which varied from 10% to 56% overestimation depending on the concentration of contrast medium used and on particular features of the stenosis (Fig 18C). Therefore, follow-up quantitative angiographic assessment of a lesion containing a vividly radiopaque stent may be subject to measurement imprecision because of this propensity for error, which appears to be inherent to both the edge detection and videodensitometric methods.

Directional Atherectomy

Few problems have been encountered in the angiographic analysis of lesions treated by directional atherectomy.[77] The radiopacity of the device, particularly when the support balloon is inflated, allows excellent visualization of the position of the eccentric cutting apparatus (Figs 19A and B). The vessel luminal contours are typically smooth and much less ragged than after PTCA, facilitating edge detection analysis. However, despite the apparent smooth contours, a discrepancy exists between analysis performed by edge detection and densitometry, similar to that which occurs after angioplasty (Fig 20),[78] suggesting that the vessel contour after atherectomy may not be as circular as it appears. It has been suggested that this may be caused by preferential expansion of the bases of the atherectomy cuts.[79] Furthermore, QCA of atherectomy-treated lesions has provided some insight into the mechanisms of lesion improvement. Penny et al[79] have shown that an average of approximately 28% of the effect of atherectomy could actually be attributed to tissue removal, although the individual values had a wide range (7% to 92%).[79] The correlation between the volume of tissue retrieved and the change in luminal volume was poor. The investigators concluded that the major component of luminal improvement was caused by "facilitated mechanical angioplasty" resulting from the high profile of the device and the low-pressure balloon inflations. Data from our angiographic core laboratory seem to support this hypothesis. In 10 patients who had angiography (with subsequent quantitative analysis) performed at baseline after the device had been threaded through the stenotic area and, again, immediately after the completion of the atheroma extraction pro-

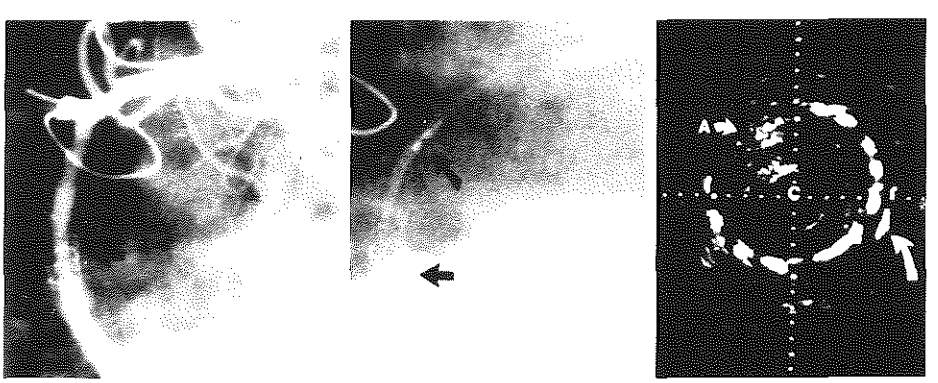

Fig 17. In vitro intravascular ultrasound examination of left anterior descending artery that was stented 24 hours earlier for a severe dissection during PTCA. (The patient died from intracerebral hemorrhage 12 hours after stenting.) The inner circle (c) is the actual intravascular probe itself. The outer echo-dense pattern is caused by the stent wires (large arrow). The lumen is the echo-free space inside the stent. The stent effectively tacked back the dissection and restored the circular configuration of the vessel. (Reprinted with permission.[61])

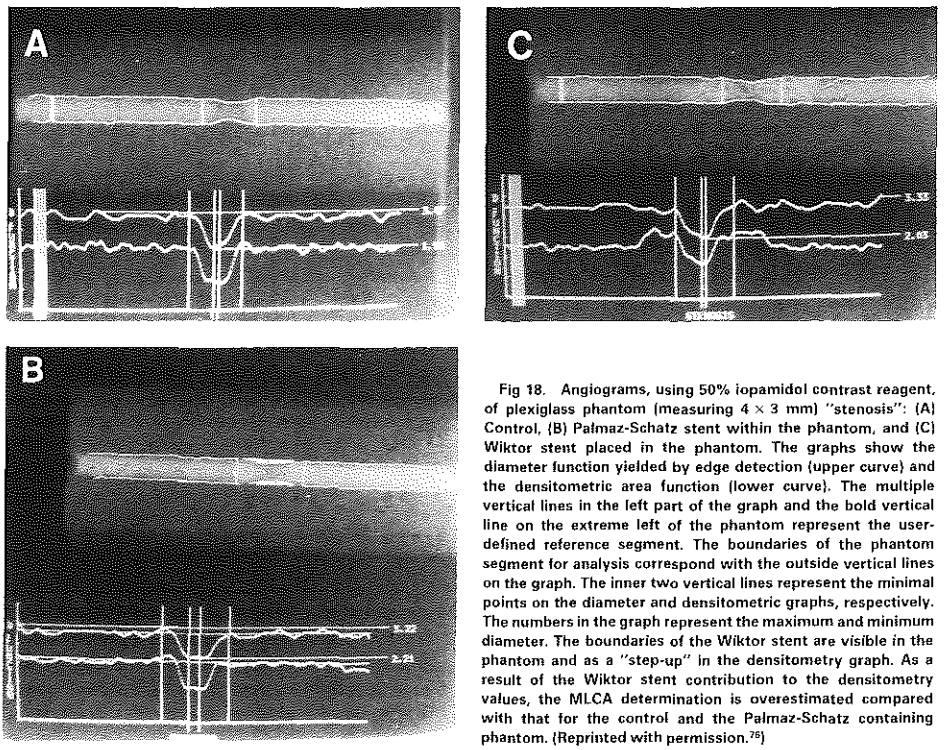

Fig 18. Angiograms, using 50% iopamidol contrast reagent, of plexiglass phantom (measuring 4 × 3 mm) "stenosis": (A) Control, (B) Palmaz-Schatz stent within the phantom, and (C) Wiktor stent placed in the phantom. The graphs show the diameter function yielded by edge detection (upper curve) and the densitometric area function (lower curve). The multiple vertical lines in the left part of the graph and the bold vertical line on the extreme left of the phantom represent the user-defined reference segment. The boundaries of the phantom segment for analysis correspond with the outside vertical lines on the graph. The inner two vertical lines represent the minimal points on the diameter and densitometric graphs, respectively. The numbers in the graph represent the maximum and minimum diameter. The boundaries of the Wiktor stent are visible in the phantom and as a "step-up" in the densitometry graph. As a result of the Wiktor stent contribution to the densitometry values, the MLCA determination is overestimated compared with that for the control and the Palmaz-Schatz containing phantom. (Reprinted with permission.[75])

cedure, the "Dottering effect" of the device accounted for 65% of the luminal improvement.[80]

Rotational Plaque Abrasion

To date, the Thoraxcenter experience with this device has been limited, with only 11 procedures performed.[81] A unique feature of the Rotablator (Biophysics International) is its usefulness as a calibration unit as an alternative to the guiding catheter. The device contains a burr of known size, and there is no question of completeness of expansion as with stents and PTCA catheters of specified sizes (Figs 21A and B). Precise measurement of the device at the lesion site has been useful to assess the extent of elastic recoil, which appears to be an important phenomenon, because the luminal dimension immediately after rotational abrasion is always smaller than the diameter of the burr used.[82] A unique feature of the Rotablator is that the optimal angiographic result is not realized until 24 hours later, because the intense vasoconstriction induced by the burr is largely attenuated at that time (Figs 22A, B, and C).

Excimer Laser

Excimer lasers have presented an attractive alternative to other forms of coronary intervention, based on the experimental finding that, in air, a focused, pulsed, UV laser beam can focally ablate targeted tissue with minimal adjacent tissue injury. However, in the clinical situation, where the vessel luminal surface is surrounded by a blood medium, catheter tip-tissue contact is required to avoid attenuation of the laser beam by the blood and to increase ablation efficiency. The effect of pulsed UV-laser light delivered through contact catheters on tissue ablation has been investigated in vitro and in vivo on human and porcine aorta.[83,84] Considerable temperature accumulation was found, as well as mechanical tissue damage caused by expansion of gaseous debris trapped

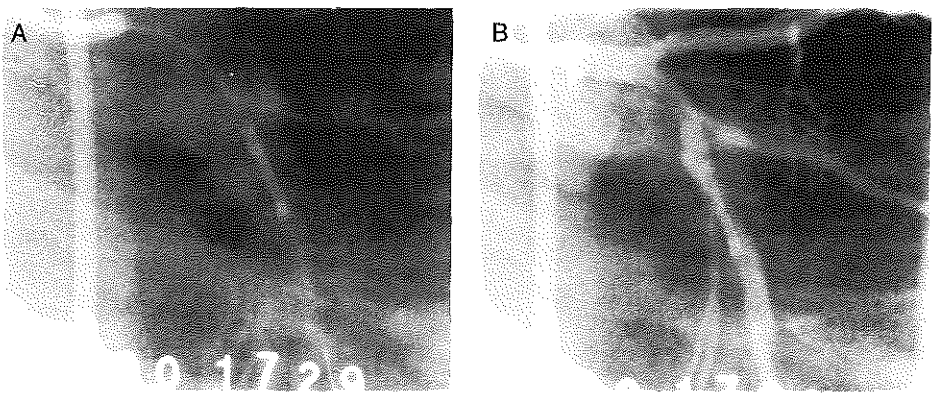

Fig 19. Radiopaque directional atherectomy device (Atherocath; Devices for Vascular Intervention, Redwood, CA) is shown (A) in circumflex artery without contrast and (B) in circumflex artery containing contrast.

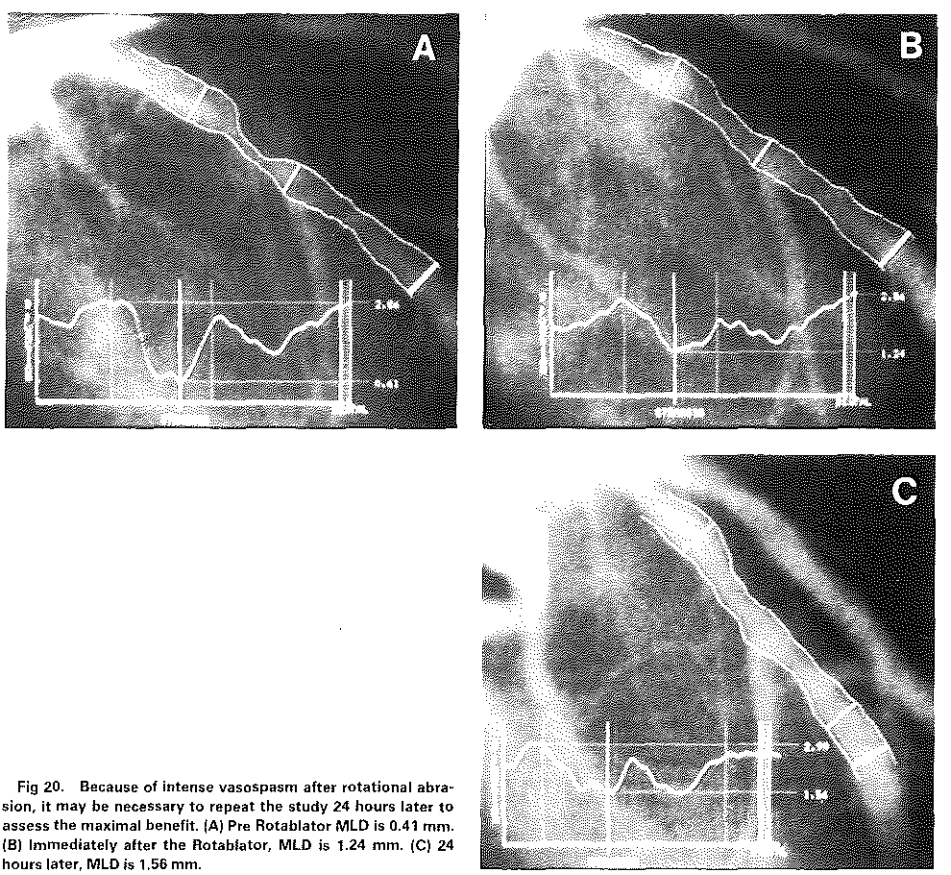

Fig 20. Because of intense vasospasm after rotational abrasion, it may be necessary to repeat the study 24 hours later to assess the maximal benefit. (A) Pre Rotablator MLD is 0.41 mm. (B) Immediately after the Rotablator, MLD is 1.24 mm. (C) 24 hours later, MLD is 1.56 mm.

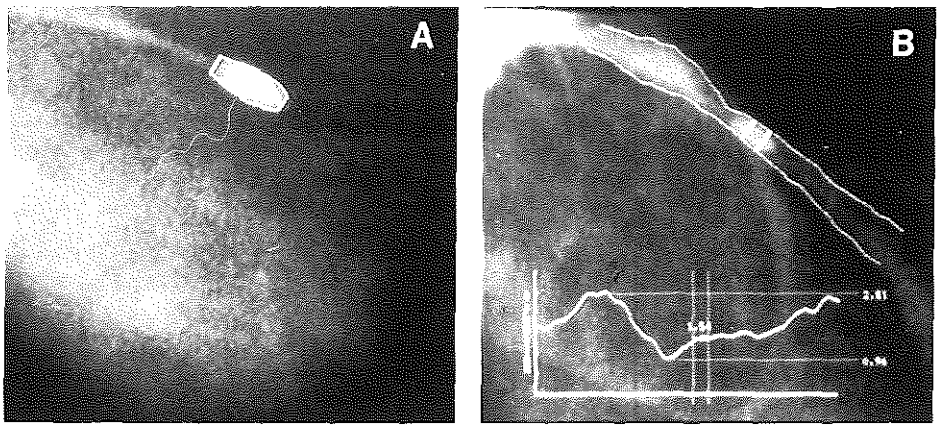

Fig 21. Rotational abrasion (Rotablator) in a coronary artery is shown (A) without contrast. Because the burr is nondeformable and of known diameter, calibration of the angiogram can occur at the site of the procedure in contrast to PTCA, stenting, or directional atherectomy, where we use the contrast-filled guiding catheter in one corner of the angiogram as the scaling device. In this case a 1.50-mm diameter burr was used. (B) In vessel containing contrast, the Rotablator is clearly visible.

under the tip of the delivery system.[83] In addition to thermal injury, dissections were observed that were attributed to pressure build-up and expansion of a vapor cavity within adjacent tissue.[84,85] The angiographic correlate of this phenomenon appears to be haziness of the contours of lesions treated with the excimer laser, with consequent complication of the immediate post-procedure analysis (Figs 23A, B, and C). The lesion has a typically "roughened" appearance and, therefore, may be particularly

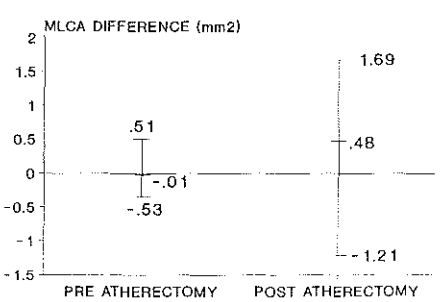

Fig 22. Agreement between densitometric MLCA and the circular (edge detection) MLCA before and after directional atherectomy. Despite apparent smooth contours after atherectomy, similar discrepancy exists between analyses performed by edge detection or densitometry as that which occurs after angioplasty. This may be because of preferential expansion of the bases of the atherectomy cuts, creating a less circular configuration.

well-suited to specific edge detection algorithms designed for the evaluation of very irregular luminal contours.[86] Whether densitometry should be preferred to edge detection in the assessment of the specific effects of the excimer laser in coronary interventions remains under investigation.

CONCLUSIONS

QCA clearly presents an objective and reliable technique to measure coronary luminal dimensions. This has been thoroughly shown for the edge detection analysis. Densitometry is theoretically attractive but remains practically limited for routine clinical application at this time. The geometric edge detection method is still limited by the need for angiography of suitable quality that must be performed in a standardized fashion. Fortunately, both the hardware and software used in QCA are under continuous evolution. New developments are being consistently produced because the broadening use of QCA in a spectrum of interventional situations shows technical and practical limitations of varying significance. In the second article of this series, the clinical application of diameter measurements obtained by automated edge detection is discussed, and important insights into mechanisms of intervention and of the restenosis process are presented.

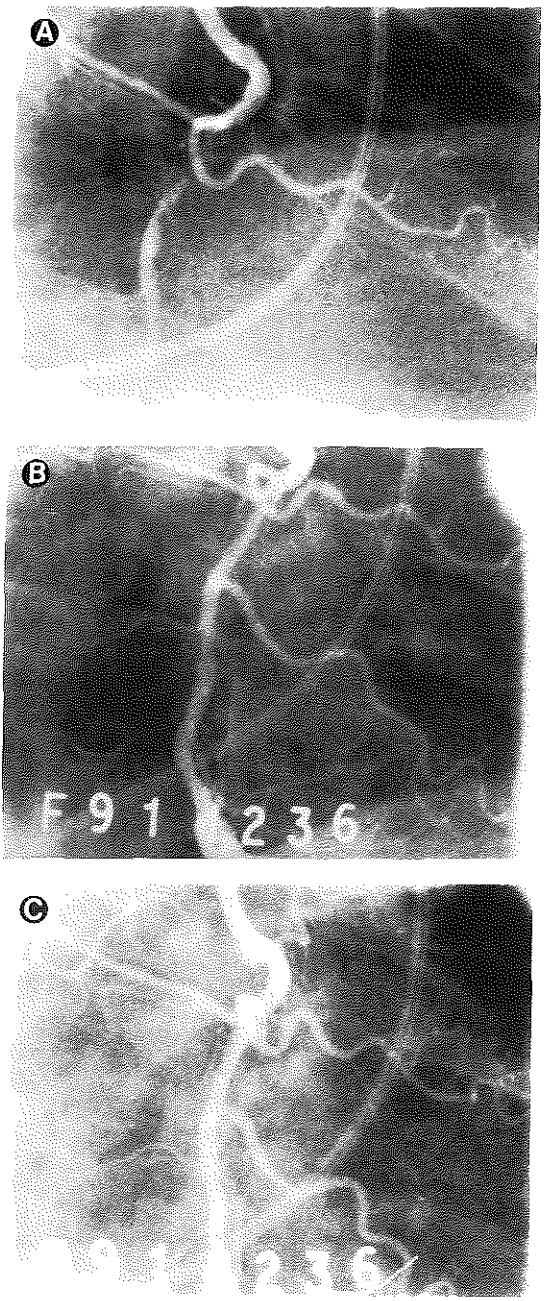

Fig 23. Excimer laser is shown. (A) Before laser treatment, long narrowing in left anterior descending artery (immediately distal to the sidebranches) is apparent. (B) After laser treatment, the arterial boundaries of the treated lesion show a roughened hazy appearance. (C) After balloon dilatation, luminal haziness is still present.

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CHAPTER 2

QUANTITATIVE CORONARY ANGIOGRAPHY IN INTERVENTIONAL CARDIOLOGY: APPLICATION TO SCIENTIFIC RESEARCH AND CLINICAL PRACTICE.

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Quantitative Coronary Angiography (QCA) in Interventional Cardiology: Clinical Application of QCA Measurements

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QUANTITATIVE coronary angiography (QCA) has had a tremendous impact in the field of interventional cardiology. Because of its superior accuracy and objectivity, QCA has supplanted visual and hand-held caliper assessments of coronary arteriograms and has improved interobserver and intraobserver variability.[1-3] QCA is now the "gold standard" for the assessment of the coronary tree in the context of scientific research,[4] although it has not yet gained widespread appeal for routine clinical use.[5] Until very recently, mainly because of the expense and time-consuming aspect involved in routine clinical application of sophisticated computer-based analysis, QCA has only been available for off-line use.[6-9] In addition, the extra precautions that must be taken by the angiographer in obtaining images suitable for quantitative analysis[10] imply that many angiograms routinely performed by busy clinicians or in acute or emergency situations may not be analyzable by an automated computer-based system.[5] However, with the progressively increasing number of clinics involved in multicenter restenosis prevention trials in which QCA plays an integral role,[11-13] perhaps these extra precautions may become routine clinical practice.

QCA has been particularly useful in interventional cardiology as the only objective and reliable means of assessing the immediate and long-term effects of coronary interventions. In particular, the phenomenon of restenosis has primarily been described and researched most extensively on the basis of sequential QCA studies. At the Thoraxcenter (Rotterdam, The Netherlands), we have been advocating the importance of QCA since the first report of its use by our group in 1978[14] and, subsequently, with renewed vigour after our initial experience with QCA in the assessment of coronary interventions, as reported in 1982.[15] The Cardiovascular Angiographic Analysis System (CAAS) has been extensively and rigorously validated,[16-18] and technical aspects are presented in the accompanying report. The entire angiographic database now consists of collected information from more than 5,000 patients who have undergone several different forms of nonoperative coronary revascularization. The principles of QCA, which were initially designed for diagnostic studies of coronary artery disease (CAD), have necessarily been adapted to more complex situations related to either the presence of a device or the effect of an intervention on the angiographic appearance of a damaged vessel. The introduction of several newer devices in the past 7 years, has presented a number of unique and unforeseen problems in image analysis and the subsequent interpretation of important quantitative data, as described in the accompanying report.

The emergence of digital subtraction angiography has allowed on-line performance of QCA measurements in the catheterization laboratory, so that a technique previously confined to research applications has been transformed into a powerful analytic tool, directly applicable to clinical decision making.[7,19] The immediate availability of QCA measurements during interventional procedures provides a unique opportunity for more accurate selection of appropriate interventional devices (eg, balloon, stent, or atherotome dimension) and for continuous monitoring and immediate evaluation of the result obtained. During the last 5 years at the Thoraxcenter, a large clinical experience has been accumulated through the application of the Philips Digital Cardiac Imaging (DCI) Automated Coronary Analysis System.[6,9] In vivo study of stenosis "phantoms" placed in porcine

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coronary arteries has confirmed that the accuracy and precision of the DCI on-line measurements are intimately comparable with those obtained off-line using the CAAS system, with a mean difference between true "phantom" stenosis diameter and DCI minimal luminal diameter (MLD) measurements of 0.08 ± 0.15 mm, for stenosis diameters ranging from 0.5 to 1.9 mm.[8] Therefore, we believe that the information presented here, mainly derived from the analysis of cine-film images, can now be immediately applied to guide the operator during diagnostic and interventional procedures.

In the preceeding article, the process and technical aspects of QCA are explained and described in detail, and it is now (we hope) evident to the reader that QCA analysis is more than just setting up the cine film and returning 20 to 30 minutes later for the data. Only close scrutiny of the analytic results, combined with ongoing communication between the clinician, the analyst, and the programmer, ensures that meaningful and useful data emerge from the use of QCA. The purpose of this review is to describe the insights into the short- and long-term sequelae of the various interventional devices already provided by the use of QCA in interventional cardiology and to explore its current and future applications in the comparative evaluation of interventional devices.

INFORMATION PROVIDED BY THE CAAS SYSTEM

The prime aim of QCA is to provide precise and accurate measurements of coronary anatomy. The CAAS system can provide this information by two different methods, (1) detection of luminal borders (so called "edge detection"), preferably in two (or more) orthogonal projections,[20] to provide a three-dimensional approximation of the diseased segment that can then be converted into absolute values after calibration with an object of known diameter, such as the shaft of the contrast-free guiding catheter and (2) videodensitometry, an approach that describes relative cross-sectional luminal area by measuring and comparing the density of contrast in a diseased and normal segment. The advantage of the information acquired by the densitometric method is that meaningful data can be obtained in a single projection, even if the cross-sectional shape is highly asymmetric or eccentric.[10] In contrast, area measurements derived from edge detection data (and specifically from MLD values), by definition, require an assumption of a circular cross-sectional lumen in the diseased arterial segment, which is at odds with the observations of several pathologic studies.[21,22] The intricacies and limitations of these respective techniques have been described in detail in the accompanying report and will not be discussed further here.

The important parameters which can be obtained by edge detection are listed below:

1. Direct measurements
   a) MLD (Fig 1)
   b) maximal luminal diameter
   c) mean luminal diameter
   d) lesion length
   e) minimal luminal cross-sectional area (MLCA)
   f) reference area

The calculation of cross-sectional area measurements (e, f) from the linear measurements obtained from the diameter function assumes a circular (single-plane view) or elliptic lumen (orthogonal biplane view).

2. Interpolated measurements
   a) reference diameter (RD; automatic computer reconstruction of the assumed disease-free or normal segment of the vessel; Fig 1)
   b) symmetry
   c) plaque area (mm^2)

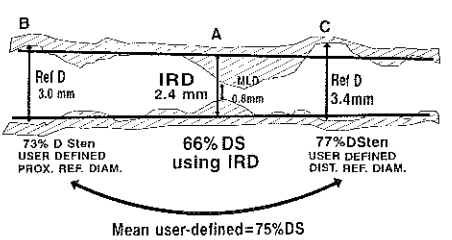

Fig 1. Graphic shows variability in percent diameter stenosis measurements of the same lesion caused by arbitrary selection of the RD by the user and also shows the more objective derivation of percent diameter stenosis by the user-independent method of the interpolated RD. For a stenosis where the MLD is measured at 0.8 mm, if a user-defined proximal or distal reference segment or the mean of both is selected then the resultant measure of percent diameter stenosis for the obstructing lesion is 75%, 77%, or 76%, respectively. If the computer-determined interpolated RD (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; MLD, minimal luminal diameter; %DS, percent diameter stenosis.

3. Derived measurements
   a) percent diameter stenosis (calculated from the MLD and RD; Fig 1)
   b) percent area stenosis (calculated from MLCA and reference area)
   c) curvature (calculated from the centerline of the vessel segment)
   d) inflow angle/outflow angle (calculated from the diameter function)
   e) roughness (calculated from the individual contour points, separately for the left- and right-hand vessel contour)
4. Hemodynamic measurements
   a) theoretical transstenotic pressure gradient
   b) calculated Poiseuille resistance
   c) calculated turbulent resistance

A WORD OF CAUTION IN THE INTERPRETATION OF ANGIOGRAPHIC DATA

The limitations of angiographic information in the evaluation of the extent of coronary artery disease have been well-recognized.[23] After all, coronary angiography is really just a two-dimensional profile or "shadowgram" of an opacified vessel lumen; it merely shows the effect of arterial wall disease on the contour of the arterial lumen. Moreover, atherosclerotic changes in the arterial wall are not reliably or precisely reflected by changes in the lumen, as shown by intravascular ultrasound and epicardial high-frequency echocardiography.[24-29] The variability of the atherosclerotic process, which may be smoothly and evenly distributed so that the entire lumen of a segment or vessel may be equally and diffusely reduced,[26] is sometimes beyond the scope of angiography, which may not detect its existence.[30,31] This pathologic fact is reflected in many necropsy studies, where coronary angiography frequently underestimated the severity of coronary artery lesions or even missed significant narrowings in the context of underlying severe diffuse atheromatous CAD.[32-35] Furthermore, elliptic or D-shaped lumens may, depending on the views obtained, be misrepresented on cineangiography, resulting in either underestimation or overestimation of true stenosis severity,[36] particularly if a single angiographic view is used.[10] The CAAS interpolated-measurement approach reconstructs the normal segment of the vessel at the site of the lesion[37] (Fig 1). Although there may be underestimation of the true diameter value by this presumed disease-free vessel contour, this approach is inherently more objective and accurate than the assumption of normality of an arbitrarily selected proximal or distal portion of the vessel as a reference segment.[10] In addition, it is obvious that the dimensions of the RD may change from before to after intervention, as a consequence of any intervention that stretches, dilates, or provokes dissection or coronary vasomotor changes. Moreover, during follow-up, the apparently normal segment adjacent to a treated lesion may be affected by the restenosis process.[38-41]

It is also important for interpreting the results of angiographic studies to know how the actual morphologic characteristics were measured. In a recent study,[42] we found quantitative angiographic morphologic features generally unhelpful in prediction of major procedural and in-hospital adverse cardiac complications among 1,442 patients undergoing balloon angioplasty (BA), in two major European multicenter restenosis prevention trials.[11,12] The only features associated with an increased likelihood of major cardiac complications, according to multivariable logistic regression analysis, were angiographically visible dissection after angioplasty, unstable angina, and lesion location in a tortuous segment, as estimated visually. No quantitative angiographic morphologic characteristics were helpful in this regard.

The predictability of restenosis (at 6-month angiographic follow-up) from baseline angiographic morphology has been widely investigated, and the data are extremely difficult to interpret, because of wide variations in methodological approach. Many studies have reported multiple, differing angiographic risk factors to be associated with a higher restenosis rate.[43-47] Part of the explanation for this diversity is that the definition of restenosis itself has varied widely, and there is still no universal consensus on the best methodological approach.[48] We shall elaborate on this particular application of QCA, as it is of widespread interest because of the exponential increase in the use of percutaneous devices for revascularization and because of the continued persistence of restenosis as the major limitation to maintained long-term success of therapy with these devices. In addition, this is the area to which our group has applied QCA most intensively over the past years.

MEASUREMENT VARIABILITY AND RELIABILITY

Before a discussion of the various devices used for coronary intervention, the utility of the information generated by QCA in general (and the CAAS system specifically) must be addressed. Geometric information, such as MLD, RD, and percent diameter stenosis, represent the most useful and reliable information obtained by this system. Angiographic morphologic features that may be important to the clinical outcome,[49,50] such as ulceration or complex, ragged morphology, have not been a focus of our research, in terms of their natural history in large populations undergoing coronary interventions. The newer intracoronary imaging modalities of intravascular ultrasound and angioscopy are better suited to such study.

The long-term lesion measurement variability of the CAAS system, under "worst case" or nonstandardized acquisition conditions, has previously been validated.[16] More recently, validation studies have been performed for the QCA system operating on-line on the Philips DCI system.[8,51] In addition, lesion measurement variability in the aftermath of coronary BA has also been investigated.[52] Our group has previously reported that a difference in MLD, between two catheterization sessions, of more than 0.72 mm represents an angiographically detectable change.[16] This does not infer physiologic significance. It merely represents twice the standard deviation (ie, the 95% confidence interval [CI]) of the mean difference between MLD measurements performed on angiograms recorded 3 months apart, under angiographic conditions in which no attempt was made to standardize the inspiratory level, the volume and rate of injection of the contrast agent, the vasomotor tone or technical characteristics, and/or the positioning of the x-ray system. Therefore, a measured deterioration in luminal diameter greater than 0.72 mm could be concluded, with 95% confidence, to be a real detectable change and, thus, a definite loss in lumen, under such conditions as prevailed in routine clinical practice at that time (1984). If a more standardized acquisition protocol is followed, the medium-term variability, as reported in that study, would be more applicable, ie, 0.44 mm. To put that index study in its proper perspective, it must be pointed out that the average RD was 3.7 mm, whereas the mean RD of lesions treated by percutaneous transluminal coronary angioplasty (PTCA), during the course of two recent, large multicenter clinical trials, was 2.6 mm.[11,12] Thus, the absolute measurement of 0.72 mm, as an index of detectable luminal change, is no longer relevant in modern studies, which use standardized angiographic protocols and intervene in smaller vessels. For this reason, in addition to the criticized lack of information on the post-BA measurement variability of the CAAS system,[53] our group has recently performed a clinical investigation to clarify these issues.[52] Quantitative analysis was performed on angiograms of 110 patients under optimal angiographic conditions obtained immediately after angioplasty and, again, 24 hours later. Vasomotion was controlled by intracoronary nitrate before each angiographic run, and angiographic projections after angioplasty were exactly repeated at 24 hours. At least two (orthogonal or near orthogonal) views were recorded for right coronary artery lesions, and at least three projections were recorded for left anterior descending or circumflex arteries; all patients were fully anticoagulated for 24 hours. There was no difference in mean MLD or cross-sectional area from postangioplasty to 24-hours postangioplasty, and the variability of the mean difference was 0.20 mm, which is not significantly different from the medium-term (1-hour) variability in the previously described study. This post-PTCA lesion measurement variability is eminently acceptible and shows that quantitative analysis of multiple matched views can provide extremely accurate and precise luminal measurements. RD increased significantly during the 24-hour period (presumably secondary to greater vasodilatory effect of the same dose of intracoronary nitrate at 24 hours relative to that immediately after PTCA); therefore, percent diameter stenosis was also found to increase significantly. This change in percent diameter stenosis without any change in actual MLD shows the limitations of preferential use of percent diameter stenosis measurements in clinical investigation.

LIMITATIONS OF PERCENT DIAMETER STENOSIS MEASUREMENTS AND VISUAL ASSESSMENT OF THE ANGIOGRAM

Percent Diameter Stenosis

As with all new developments, physicians may be somewhat reluctant to abandon the familiar

surroundings of the tried and trusted percent diameter stenosis measurement in favor of the apparently unreal environment of MLD measurement. However, it has long been our contention that percent diameter stenosis measurements are extremely unreliable, and, therefore, we have recommended the use of absolute luminal measurements.[38,54] Use of the term "percent diameter stenosis" connotes the assumption of the conventional measurement approach of selecting a normal-appearing segment, proximal and/or distal to the lesion of interest, as a point of reference. As already described above, this assumption of normality is frequently erroneous, particularly after intervention and at follow-up. Therefore, percent diameter stenosis measurements are prone to considerable variability (Fig 1).

This potential for imprecision and provision of misleading information was shown in the past by Beatt et al[38] and Serruys et al[54] and has been reiterated in two recent studies.[41,52] QCA morphologic features were examined before and after successful BA and at follow-up in 778 lesions in an investigational study (as an ancillary to the Multicenter European Research Trial with Cilazapril after Angioplasty to Prevent Transluminal Coronary Obstruction and Restinosis [MERCATOR][12]) that showed that the restenosis process affects the entire vessel segment which was dilated and not just the target lesion.[41] This finding confirmed the previous findings of Beatt et al,[38] who contended that changes in RD occurring during follow-up invalidated the use of percent diameter stenosis measurements as an accurate estimate of lesion severity. Similarly, the previously mentioned study that used angiography after angioplasty and at 24 hours after angioplasty showed that changes in RD occurring during the 24-hour period had analagous implications for calculation of percent diameter stenosis. The change in percent diameter stenosis from after angioplasty to 24 hours that was observed in this study, if evaluated alone, would have produced the misleading conclusion of significant deterioration in lesion severity during the first day after successful BA. Such a conclusion would have far-reaching consequences. For example, the deterioration could be interpreted as delayed elastic recoil, implying that this might play an important role in the process of restenosis (which is clearly not the case). In addition, the routine application of 24-hour angiography might be recommended in clinical trials to evaluate the true result after angioplasty, after delayed recoil. Use of absolute luminal diameter measurements allowed a clearer and less ambiguous interpretation of the results of this study; no change in lesion severity was detected in the first 24 hours after successful BA, and, therefore, routine angiography at 24 hours is not clinically indicated.

Visual Techniques

Visual and other observer-dependent, nonquantitative approaches of estimating percent luminal obstruction are known to be greatly associated with high intraobserver and interobserver variability.[2-4] In general, visual assessment leads to overestimation of the degree of narrowing in severe lesions and to underestimation of the severity of mild or moderate lesions.[55] Among 1,445 lesions treated by BA during the course of two multicenter European restenosis prevention trials, apart from totally occluded or subocclude vessels, quantitatively derived percent diameter stenosis measurements greater than 74% were extremely rare and accounted for only 5% of all lesions undergoing PTCA.[56] The most severe lesion encountered had a measured diameter stenosis of 86%. The logic of this is shown in Fig 2, which shows

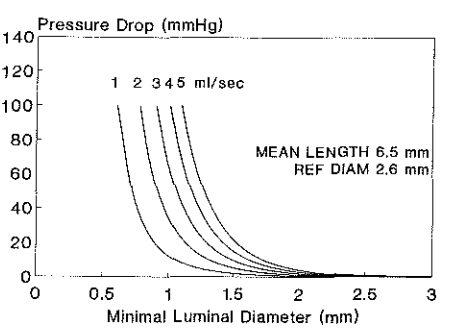

Fig 2. Theoretic pressure gradient calculated from the fluid dynamics equation, derived by Gould et al[59] and Kirkeeide et al,[60] at assumed flow rates of 1 to 5 mL/s is shown. Vessel size (2.6 mm) and lesion length (6.5 mm) were taken as the means for the combined patient populations enrolled in two European multicenter clinical, restenosis prevention trials.[11,12] It is readily appreciated that when MLD is less than 0.5 mm (diameter stenosis more than approximately 81%), the pressure gradient across the stenosis is well beyond the physiologic range at an assumed resting flow rate of 1 mL/s. (Reprinted with permission from the American College of Cardiology.[56])

the pressure gradients (as calculated using the fluid dynamic equations devised in the past by Gould et al,[57] Young et al,[58] Gould et al,[59] and Kirkeeide et al[60]) across a stenosis with a length of 6.5 mm and an interpolated RD of 2.6 mm, the mean values observed during these trials, at assumed flow levels ranging from 1 mL/s at rest to 5 mL/s at maximal hyperemia. It is clear that the pressure gradient necessary to maintain rest flow at 1 mL/s is moving beyond the physiologic range when the MLD is less than 0.5 mm, which, for a 2.6 mm vessel, represents a diameter stenosis value of greater than 80%. Anterograde flow through lesions approaching this severity will tend to decrease below that required to maintain patency, and the lesion becomes occluded, as opposed to a gradual, incremental progression of stenosis over time to eventual occlusion.

To clinicians unfamiliar with QCA, these values for critical lesions may appear low, but in fact, a quantitatively measured diameter stenosis of 74% corresponds with an area stenosis of approximately 93%.[56] Fleming et al[55] have suggested that visual overestimations of percent diameter stenosis arise because of the observer perceiving the area stenosis but calling it diameter stenosis. It has been shown that an area stenosis greater than 70% is associated with a reduction in coronary flow reserve to less than 1,[61,62] ie, when the ability of the vessel to dilate and increase blood flow to the area of myocardium supplied, in response to various stimuli (reactive coronary hyperemia), is abolished. A simple clinical quantitative angiographic study from our group[63] explored the reliability of visual estimates of coronary artery stenosis in the 90% range and asked the clinically relevant question of whether the 90% stenosis actually exists. The conclusion was that, excluding lesions where the anterograde blood flow was Thrombolysis in Myocardial Infarction (TIMI) grade I or in occasional cases, TIMI grade 2 (ie, subtotal or functional occlusions), authentic 90% diameter stenoses probably do not exist. In this study, interventionalists were asked to estimate the percent diameter stenosis of and TIMI grade blood flow through the target lesion before BA. Blood flow was again recorded after guidewire insertion across the target lesion. The likelihood of flow reduction or occlusion after insertion of the guidewire was predicted on the basis of the visual estimation of stenosis severity (percent diameter stenosis) and the quantitatively measured vessel size (interpolated RD) and was compared with actual blood flow. For example, if the observer estimated a 90% diameter stenosis and the vessel diameter was quantitatively measured at 3 mm, the residual lumen diameter, according to the visual estimate, would be 0.3 mm. Thus, introduction of an 0.018-in guidewire (0.48 mm) should cause total occlusion of the vessel, and this stenosis grading was classified as a "predicted occlusion." Although observers frequently provided estimates of stenosis severity corresponding with predicted occlusion, actual occlusion or flow reduction by one or more TIMI grades rarely occurred. In all cases where guide wire insertion across the target lesion caused flow reduction, baseline flow had been classified as TIMI grade 1 or, occasionally, grade 2. Thus, it could be concluded that, where anterograde blood flow is normal, lesion severity never reaches a diameter stenosis of 90%. Therefore, angiographic evaluation systems that allow classification of lesions of such severity do not reflect actual lesion dimensions and describe lesions that are not physiologically possible and, thus, are unsuitable for important studies. Specific training in quantitative coronary analysis can actually improve the discriminant ability of the observer in visual estimation of the severity of coronary stenosis, as observed by Fleming et al[55] and also recently reported by Danchin et al.[64]

PHYSIOLOGIC CORRELATIONS OF MINIMAL LUMINAL DIAMETER

The physiologic significance of a coronary obstruction will depend on a number of factors, but the absolute MLD has been shown to be the most important of these.[60-62,65-68] Rensing et al[69] have reported that recurrence of (or freedom from) angina can be predicted, with 72% accuracy, by MLD threshold of 1.45 mm at 6-month angiographic follow-up after single-lesion BA. Similarly, the likelihood of a positive or negative exercise test by bicycle ergometry could be predicted with 62% certainty by a measured MLD of 1.46 mm. In other words, a patient with MLD at follow-up of greater than 1.45 mm will probably be free from anginal symptoms with 72% certainty, and a symptomatic patient has a 72% chance of having an MLD of less than 1.45 mm. Of course, this measurement will have different relevance in smaller or larger vessels,

and this important aspect was also investigated. It was found that the relevant MLD threshold in smaller vessels (vessels less than the median value of 2.63 mm) that predicted anginal recurrence or ischemia on exercise testing was 1.37 mm and that the corresponding value in larger vessels (>2.63 mm) was 1.53 mm. Corresponding measures of percent diameter stenosis were also provided, but, considering what has already been stated regarding the reliability of these measurements, they must be cautiously interpreted. Thus, simple quantitative angiographic luminal measurements can provide important and clinically useful, functional information.

The significance of the degree of change in lumen dimensions during follow-up after angioplasty was also investigated in this study but is, however, much more difficult to interpret. Clearly, a deterioration in MLD of 0.72 mm, for example, is likely to have greater functional importance in a 2.6-mm diameter vessel than in a 5-mm diameter vessel, but the functional significance of the change ultimately depends on the final luminal diameter (as well as the amount of myocardium at risk and the level of physical performance required by the individual patient). Thus, loss of as much as 2 mm in MLD may cause no functional deterioration, if the final lumen diameter at follow-up is more than 1.53 mm (obviously such changes would only be possible in vessel larger than 3.5 mm). By contrast, loss of as little as 0.5 mm during follow-up may be of definite clinical relevance, if the final MLD is 1 mm. These findings might reflect either a suboptimal initial angiographic result in a 2.5-mm vessel or a reasonably good, immediate result in a 1.5- to 2-mm vessel.

The degree of absolute luminal change necessary to cause a physiologically significant effect is, therefore, impossible to accurately categorize because of the relative importance of other factors. Thus, the phenomenon of luminal renarrowing after interventions can be most objectively and definitively evaluated using a continuous and purely anatomic approach. Ultimately, the real value of QCA is the provision of objective and reproducible measurements of luminal dimensions, which facilitates the study of the natural history of both atheromatous coronary disease[23] and long-term outcome after interventions,[48] in populations of patients rather than in individual patient management decisions. The impending widespread availability of QCA for routine on-line use in the catheterization room[7,9] may allow such an application.

QCA AND SPECIFIC CORONARY DEVICES

Percutaneous Transluminal Coronary Angioplasty

Insights Into the Therapeutic Mechanism of Balloon Angioplasty

Although our initial analytic approach to serial angiographic studies in patients treated by BA was restricted to repeated measurements of the lesion site, the development of several new concepts related to mechanisms of balloon dilatation required extension of our measurements to include the inflated balloon. These included stretch (theoretic maximal gain in diameter or area during the angioplasty procedure), elastic recoil (which clearly affects the immediate result after angioplasty), and balloon-artery ratio (which affects both the extent of recoil and the likelihood of dissection). Before these assessments, the inflated balloon was used as a scaling device and (incorrectly) assumed to be uniform along the entire balloon length, at a diameter according to the manufacturer's specifications. Monson et al[70] have previously reported that the nominal balloon size is almost never achieved over the entire balloon length. Measuring the balloon diameter over its entire length in 453 patients, during an average inflation pressure of 8.3 ± 2.6 atm, Hermans et al[71] observed a difference between the nominal balloon diameter of 0.3 ± 0.29 mm with the measured mean diameter and of 0.66 ± 0.32 mm with the minimal balloon diameter. In addition, a difference of 0.59 ± 0.23 mm in diameter was found between the minimal and maximal balloon diameter (Fig 3). These differences resulted in large variations in the calculated stretch, elastic recoil, and balloon-artery ratio, depending on the balloon measurement chosen. It was concluded that, for clinical studies, it is essential to measure the actual diameter of the inflated balloon (minimal, mean, and maximal diameter), because the theoretic inflated diameter cannot be assumed and will provide unreliable results. It was recommended that stretch be calculated as the minimal measured diameter (or cross-sectional area) of the largest, fully inflated balloon used during the procedure minus the MLD before angioplasty then corrected for the vessel size, for which

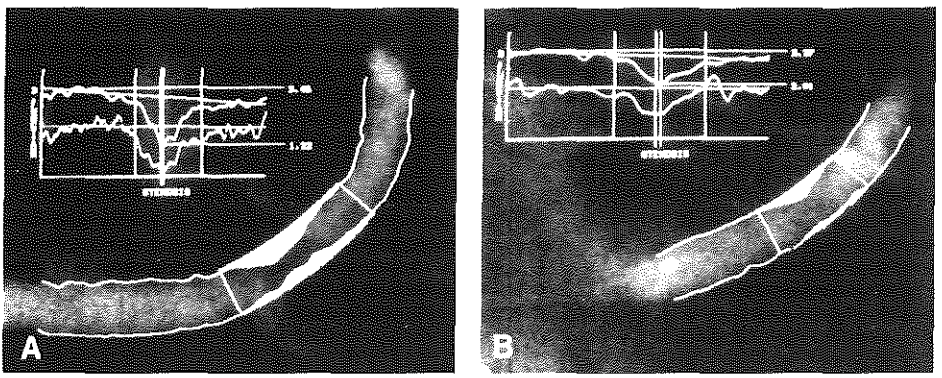

Fig 3. Nonuniform balloon inflation during BA is shown. (A) Pre-PTCA MLD of 1.22 mm is shown. (B) During balloon inflation with a 3.5-mm (manufacturer specification) balloon, the minimal balloon diameter is 2.01 mm, and the maximal balloon diameter is 3.27 mm. (Reprinted with permission.[71])

purpose the interpolated RD before angioplasty should be used. Elastic recoil should be calculated as the difference between the MLD (or cross-sectional area) after angioplasty and the minimal balloon diameter (or cross-sectional area) at the highest inflation pressure, corrected for vessel size, and balloon-artery ratio is best calculated as the ratio of the RD (or reference area) of the inflated balloon (calculated by the automatic contour detection program) and vessel size. The equations used are as follows: stretch = MLD (MLCA) inflated balloon − MLD (MLCA) pre-PTCA/vessel size; recoil = MLD (MLCA) inflated balloon − MLD (MLCA) post-PTCA/vessel size; and balloon/artery ratio = MLD (MLCA) inflated balloon/vessel size where vessel size is the interpolated RD (or reference area) pre-PTCA.

The immediate result of PTCA is influenced by both plastic (dissections, intimal tears) and elastic changes in the vessel wall. Experimental studies have shown that part of the angioplasty mechanism consists of stretching the vessel wall with a resulting fusiform dilation or localized aneurysm formation.[72] However, recent intravascular ultrasound studies have clearly shown that the major effect of balloon dilatation is plaque rupture and compression and vessel wall tearing, with stretching of the nondiseased vessel wall playing only a minor role.[29] This group has also previously reported that, in lesions where no ultrasonographically assessed plaque rupture was produced by angioplasty, a significantly higher restenosis rate, evaluated angiographically using a categoric definition, was subsequently found.[28]

Rensing et al[73] have noted that elastic recoil after coronary angioplasty results in a mean decrease of 50% in luminal cross-sectional area immediately after balloon deflation. A follow-up study showed that asymmetric lesions, lesions located in less angulated parts of the artery, and lesions with a low plaque content showed more elastic recoil.[74] Furthermore, lesions located in distal parts of the coronary tree were also associated with more elastic recoil, probably because of relative balloon oversizing. However, although elastic recoil appears to be an important component of the initial response of the vessel to balloon dilatation, 24-hour angiographic study showed no additional delayed recoil,[52,74] a finding which has been confirmed by other groups.[75-77] More importantly perhaps, multivariate analysis in a large patient group has shown no relationship between the extent of elastic recoil at the time of PTCA and late luminal renarrowing.[78] Conversely, recent preliminary investigations using intravascular ultrasound in small patient groups have concluded that chronic elastic recoil during follow-up after successful transluminal intervention may have a more considerable effect on luminal renarrowing than does intimal hyperplasia,[79,80] and an angiographic study has reported that luminal loss during the first 24 hours is associated with a significantly higher incidence

of late restenosis.[81] However, these studies can be criticized for using a categoric definition of restenosis, therefore, the results are difficult to evaluate in terms of reliability in describing an association between two phenomena. Undoubtedly, some lesions do deteriorate markedly during the first day; however, a similar number undergo additional luminal increase, and the vast majority display minimal change, so that the overall mean change in MLD is essentially zero (Fig 4). It has been shown by Rensing et al[56] and by Kuntz et al[82] that luminal diameter measurements before and after angioplasty and at follow-up, as well as the change in lumen during follow-up, are normally distributed; thus, a continuous statistical approach is appropriate when examining angiographic phenomena. In the 24-hour angiographic study, the combined use of quantitative measurement of the luminal dimensions in millimeters and a continuous statistical approach showed a more complete picture than would have been provided by the use of percentage of diameter stenosis measurements and a categoric analytic approach, permitting a clearer interpretation of the data and a better understanding of the underlying processes. Thus, it could be properly concluded, in agreement with our previous findings[73,74] and those of other investigators,[75,76] that elastic recoil is an instantaneous phenomenon occurring immediately after balloon deflation with no further luminal deterioration within the next 24 hours. Ultimately, these conflicting conclusions need to be further evaluated and reconciled, and serial studies using intravascular ultrasound and quantitative angiography in parallel would be of major interest in laying the matter to rest.

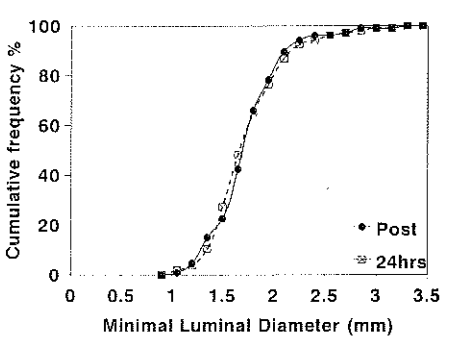

Fig 4. Cumulative distribution curves of MLD immediately after BA and 24 hours later, in 110 successfully dilated lesions, show that there was no deterioration in lesion severity over the 24-hour period.

Insights to the Restenosis Process Through Application of QCA to Clinical Trials

The largest experience in the Thoraxcenter database consists of serial angiographic studies in patients treated by PTCA, which have shown several important aspects of QCA. Firstly, the reproducibility of the CAAS system is extremely high. In several large trials, comparable values have been obtained in the determination of MLD pre-PTCA, post-PTCA, and at 6-month follow-up.[11,12,54,83] Based on data obtained from these QCA studies, a number of important observations on restenosis after BA has been made.

It became apparent that the process of restenosis tends to affect all treated lesions to some degree and that this process could be detected angiographically as progressive luminal renarrowing, which was detectable as early as 1 month post-PTCA and did not appear to advance beyond 4 months after the procedure.[54] These findings were corroborated by Nobuyoshi et al.[39] Restenosis rate was shown to depend most on the actual criterion used and, thus, varied accordingly.[54] In addition, the RD of treated vessels was found to decrease significantly during follow-up after BA, leading to the conclusion that percent diameter stenosis measurements fail to detect true changes in luminal dimensions.[38] Measurements of MLD and RD were noted to be normally distributed,[38] which would justify a continuous rather than categoric approach to description of the long-term outcome. It was recommended that restenosis should be assessed by repeat angiography and ascertained according to the change in absolute quantitative measurements of the luminal diameter.[54] Differences between findings of angiographic restenosis-prevention trials were suggested to arise from three important sources: 1) insufficient patient numbers and incomplete angiographic follow-up; 2) use of inherently variable user-dependent angiographic measurement techniques; and 3) inconsistencies in the approaches used to evaluate restenosis, which do not distinguish between the result of angioplasty and the restenosis process.[84,85] The need for full angiographic follow-up in all clinical studies examining the restenosis issue was advo-

cated,[84] and a continuous rather than categoric statistical approach was recommended[86] to provide a more sensitive evaluation of the effect of a therapeutic agent on the renarrowing process. Moreover, a continuous approach was shown to require considerably fewer patients to reflect a significant treatment effect than would the use of categoric criteria.[86]

Application of a continuous approach to 1,445 lesions treated in the aforementioned European trials confirmed that luminal renarrowing during follow-up is undoubtedly normally distributed in the treated population.[56] This finding contrasts sharply with the conventional clinical belief of an all-or-nothing phenomenon, supported by the findings of King et al[87] through the use of clinical evaluation of angiograms, that luminal renarrowing occurs in some lesions but not in others (ie, a bimodal distribution). In agreement with the report by Rensing et al[56] of a Gaussian distribution for luminal changes after BA, Kuntz et al[82] reported the finding of a normal unimodal distribution for late loss in patients treated by directional coronary atherectomy (DCA) or stent implantation. In addition, contrary to popular belief, Hermans et al[88] found no differences in restenosis between coronary segments, using either a categoric definition of greater than 50% diameter stenosis at follow-up or a continuous approach that compared absolute changes in MLD adjusted for the vessel size. These results collectively show that restenosis is an ubiquitous and normally distributed biologic phenomenon without any predilection for a particular site in the coronary tree and also show the limitations of the use of the term "restenosis rate" to adequately describe long-term outcome after intervention. However, in contrast to the findings of Hermans et al,[88] Kuntz et al[89] have recently reported the finding of a higher restenosis rate and loss index (late loss in lumen diameter divided by acute gain) in left anterior descending compared with right or circumflex artery lesions treated by DCA or stent implantation. The results of this study must be cautiously interpreted because the patient group treated by stent implantation was small (n = 90) compared with that treated by atherectomy (n = 310). The distribution of treated vessels was different in the two groups; lesions were mainly located in the proximal segments, clinical characteristics were not reported or included in the analyses, and angiographic follow-up was incomplete (82%). Although this study raises an interesting question and uses a comprehensive, continuous analytic approach to challenge previous findings by Hermans et al,[88] we believe that the Hermans et al analysis, in a homogenous patient group treated by BA with 94% angiographic follow-up of 1,452 lesions (which were widely distributed throughout the coronary tree), carries more weight at this time. Of course, the conflicting findings of these studies may reflect differing consequences of DCA or stent implantation and BA. Intuitively, it is difficult to reason why one coronary artery should have a greater propensity for neointimal response than another, regardless of how the injury is imparted. Nevertheless, these conflicting conclusions clearly require further study and resolution.

QCA has been useful to clarify conflicting data in the literature regarding angiographic risk factors associated with restenosis. Previous studies using univariate or multivariate analysis with restenosis rate as the dependent factor have provided conflicting reports of risk factors for restenosis.[47,86] Our group has applied a continuous approach to studying the long-term outcome after BA, and we have found, in a number of separate studies, that the proportional luminal increase at angioplasty, or relative gain in MLD (MLD post-PTCA − pre-PTCA, adjusted for vessel size), to be the strongest predictor of absolute luminal loss during follow-up.[78,85,90,91] Other factors were also found to be independently associated with greater lumen renarrowing, namely lesion severity before angioplasty, lesion length, angiographic evidence of thrombus, and total occlusion before PTCA.

Our interpretation of this data is that a large luminal improvement after PTCA imparts deeper arterial injury and provokes a more aggressive fibroproliferative vessel wall reaction, resulting in greater luminal renarrowing. This observation concurs with previous pathologic and experimental findings,[92-98] in particular with the Mayo Clinic model that used endoluminal stent oversizing to induce graded arterial injury in porcine coronary arteries.[99] Other groups, using various methods of quantitation of luminal dimensions, have also reported a direct relationship between angio-

graphic luminal increase at intervention and the subsequent renarrowing.[100-103]

Alternative Devices for Percutaneous Revascularization

QCA Evaluation of the Immediate Therapeutic Effects of Devices

Stent implantation. The ability of an endoluminal prosthesis to maintain luminal patency after failed BA was the original indication for implantation of these devices.[104] Serruys et al[105] investigated serial geometric changes in stenosis morphology in 19 patients after BA and then after stent implantation by quantitative angiographic measurements of luminal dimensions, of the theoretic transstenotic pressure gradient, and of Poiseuille and turbulence resistance. The self-expanding stainless steel mesh stent produced additional immediate luminal dilatation resulting in decrease in both the Poiseuille and the turbulence resistance and in theoretic transstenotic pressure gradient, in addition to the expected scaffolding effect. Puel et al[106] reported a deterioration in MLD and MLCA at 3 months, among 11 patients similarly studied and followed up; however, this change was not associated with any significant increase in transstenotic pressure gradient at assumed flow rates of 1 to 3 cm/s. The conclusion of these studies was that this device had a dilating function, in addition to its stenting role, that might be of value in preventing abrupt closure and restenosis after conventional BA. Further studies of luminal geometry after stent implantation by Strauss et al[107] showed that both the agreement and mean difference between luminal cross-sectional area measurements obtained by edge detection and videodensitometry deteriorated markedly from before to after BA, but were then considerably reimproved after stent implantation. This effect of stenting was attributed to smoothing of the vessel contour after stent implantation and also to vessel remodelling toward a more circular configuration. Beatt et al[108] reported an extra feature of the self-expanding stainless steel mesh stent, namely additional luminal improvement during the first 24 hours, clearly indicating its negation of elastic recoil and justifying its description as self-expanding. However, evaluation of the early clinical experience with this device was unduly disconcerting because of an unacceptably high frequency of acute and subacute stent thrombosis,[109] temporarily quelling the early enthusiasm of some of its proponents.[110] Nevertheless, persistence with the clinical application of endoluminal stents, incorporating increasing attention to control of coagulation, to refinement in stent composition and design, and to deployment techniques has yielded progressive improvements in early clinical success.[111-115]

Morphologic changes brought about by the balloon-expandable tantalum coil (Wiktor) stent were investigated by Serruys et al,[116] with the additional aspect of examining recoil after implantation. This prosthesis was found to produce geometric improvements similar to those previously reported for the self-expanding stainless steel mesh stent. The smaller mean diameter of the stented segment (2.88 ± 0.43 mm) compared with the mean diameter of the fully inflated balloon (2.98 ± 0.44 mm) suggested some minor recoil in the stented segment (3% diameter reduction, compared with a mean of approximately 33% diameter reduction after conventional BA).[73] In addition, it was noted that the balloon did not achieve the diameter specified (3.35 ± 0.36 mm) at the recommended inflation pressures for stent deployment, perhaps because of the opposing forces of both the stent and the arterial wall itself.

Haude et al[117] have recently investigated the occurrence of elastic recoil immediately after sequential BA and Palmaz-Schatz stent implantation and found that this device almost completely eliminated recoil (31% diameter recoil [48% area recoil] for BA, compared with 3.5% [5.1% area] after stent implantation), thus, decreasing the impact of long-term intimal hyperplasia on the residual lumen dimensions.

An experimental in vitro study investigated the interference caused by stainless steel and tantalum stents to the densitometric measurement process and found that only tantalum stents were prone to produce serious overestimation of the MLCA within the stent, which would be accentuated by incomplete vessel opacification by radiographic contrast.[118] For this reason, edge detection has been the preferred quantitative analytic method applied to assessment of angiographic results of stenting with this prosthesis.

Directional coronary atherectomy. DCA may cause luminal improvement by a combination of

dilatation and plaque removal.[119-121] In a cohort of 10 patients (among a total series of 113 patients), Umans et al[119] examined quantitative angiographic lesion morphology before and after passage of the atherectomy device and after activation of the device with plaque retrieval to determine the degree of luminal increase achieved by the procedure, which may be attributed to lesion stretching or dilatation merely by the passage of the device (so called "Dotter" effect). The MLD increased from 0.97 ± 0.32 mm before atherectomy to 1.85 ± 0.37 after crossing the lesion and then to 2.38 ± 0.33 after plaque removal. Among a selected matched patient group undergoing BA, MLD increased from 1.10 ± 0.30 mm to 1.9 ± 0.40 mm, showing that the Dotter effect produced a luminal increase virtually equivalent to that achieved by BA and accounted for 62% of the total luminal increase achieved by DCA. After DCA, the agreement between edge detection and videodensitometry measurements was found to deteriorate somewhat compared with that before DCA, although there was minimal discrepancy between the mean cross-sectional area measurements obtained by each approach (0.28 mm^2), in agreement with previous reports.[120,122] As will be evident from the accompanying report on the technical aspects of these measurement techniques, discrepancy (edge detection/videodensitometry mismatch) is most likely to be explained by the presence of a noncircular lumen morphology. The improved agreement after stent implantation, as described above, is believed to be because of the fashioning of a circular lumen by the device; thus, it was concluded that the finding of a reasonable level of agreement after DCA may imply lumen morphology that is close to circular.[119,122] This interpretation is at variance with the report by Penny et al[121] who postulated a clover-leaf–shaped luminal configuration after DCA. However, the two studies are in accordance regarding the relative contribution of dilatation and plaque removal to the luminal improvement achieved by DCA. Our group has not specifically examined elastic recoil after DCA, but a recent report from Kimball et al[123] suggests significantly less elastic recoil after DCA (23.5% ± 16%) than after BA (41.6% ± 13.8%).

COMPARATIVE EVALUATION OF LONG-TERM THERAPEUTIC EFFICACY OF DEVICES

The safety and immediate efficacy of alternative devices for percutaneous coronary revascularization have now been satisfactorily proven by many investigators. The next logical step is critical evaluation and comparison of the various devices to determine long-term benefit in terms of degree of luminal renarrowing provoked by intervention. Comparison between devices is hampered by a number of clinical and angiographic factors that are most objectively surmounted by randomized clinical trials, a number of which are in progress or are already completed.[124,125]

Because of the difference in vessel size among lesions treated by these respective devices, it has been our contention that direct comparisons could not validly be made without taking this factor into consideration. In fact, comparison of acute and late angiographic results of any intervention between individual patients is similarly ambiguous unless vessel size is comparable. Two possible solutions have been applied by our group to surmount this obstacle. The first involves the selection of lesions; lesions to be compared should be selected according to vessel size and lumen diameter before intervention so that the baseline lesion characteristics are similar, hence the matching process by which unmatchable lesions will be excluded from the comparison. The second approach is to include all patients in the comparison but to adjust or normalize absolute luminal changes at intervention and during follow-up for the individual vessel size for each lesion, as explained further below.

Matching

According to this comparative method, lesions to be compared are selected from baseline angiograms by an independent observer who is unaware of clinical or procedural details or of the 6-month angiographic outcome. The technique[126] is based on three principles. 1) The angiographic dimensions of matched lesions are assumed to be "identical"; 2) the observed difference between the two identical lesions must be within the range of the CAAS analysis reproducibility of 0.1 mm (1 SD); and 3) the size (RD) of the matched vessels are selected within a range of ±0.3 mm (3 SD; ie, 99% CI) (Tables 1

Table 1. Quantitative Comparison of the Immediate and Long-Term Results of DCA Versus BA (Matched Data)

Measurement	DCA	BA	*P* Value
RD (mm)			
Pre	3.03	3.07	NS
MLD (mm)			
Pre	1.08	1.15	NS
Post	2.61	1.92	10^{-5}
F/U	1.69	1.57	NS
ΔIn MLD (mm)			
Post-Pre (gain)	1.53	0.77	10^{-6}
Post-F/U (loss)	0.92	0.35	10^{-3}

Matching of lesions to compare interventions is shown.
Abbreviations: NS, not significant; F/U, follow-up.

and 2). Thus, two comparable groups of lesions treated by different devices are derived. The acute and long-term clinical and angiographic effects of intervention may then be compared. We have, thus far, applied this technique in comparing DCA and stent implantation with conventional BA.[126-128] DCA was found not only to achieve greater luminal increase than BA but also to be attended by greater luminal loss during follow-up, so that the ultimate angiographic outcome was similar in each group (Figs 5A and B). Stent implantation also achieved significantly greater luminal improvement than did BA; however, although attended by greater luminal loss than that for BA, the MLD at follow-up in lesions treated by stent implantation was significantly greater (Figs 5C and D).[127] Important lessons have been learned from these studies that may be considered as surrogates for randomized trials. In fact, the angiographic findings in the matched comparison of DCA and BA could be interpreted as predicting the angiographic outcome of the CAVEAT study.[124]

Table 2. Matched Preprocedural Stenosis Characteristics of Patients With Successful Directional Coronary Atherectomy Versus Balloon Angioplasty

Measurement	DCA	BA	*P* Value
RD (mm)	3.03	3.07	NS
MLD (mm)	1.09	1.15	NS
D-STEN (%)	64	63	NS
A PLAQ (mm^2)	9.5	8.4	NS
Curvature	15.9	22.2	<.02
Symmetry	0.6	0.5	NS
Length (mm)	6.8	6.5	NS

No significant differences exist between the two groups before the procedure except for a lower curvature value for lesions treated by DCA.
Abbreviations: D-STEN, diameter stenosis; A PLAQ, area plaque; Length, length of lesion.

The final results of the Benestent trial[111] are eagerly awaited, and, among the findings, it will be interesting to note whether the matching study mentioned here provided an equally close prediction of the angiographic outcome.

Independent of the vessel size treated, DCA and stent implantation are both clearly capable of greater luminal increase than is conventional BA. Each of these new devices also provokes a greater loss in lumen during follow-up that, according to the injury/hyperplasia hypothesis, is likely to be a direct consequence of the greater luminal increase. Moreover, studies using multivariate analysis techniques in patients treated by stent implantation[129] and DCA[130] have shown the strongest determinant of luminal narrowing during follow-up to be the luminal gain achieved at intervention. Other groups have reported a direct association of luminal gain at intervention with late luminal loss after DCA or stent implantation or after BA.[82,101-103] Greater loss observed after use of the new devices compared with that for conventional BA is generally attributed to the greater luminal increase achieved by these devices, which presumably cause deeper vessel wall injury in the process.

Kuntz et al have gone a step further and concluded that the greatest determinant of long-term angiographic outcome after intervention is the immediate postprocedural result, and this determinant is independent of the device used to achieve this result.[100,101] Our findings in the matching studies would suggest that stent implantation is associated with a better long-term angiographic outcome than BA[127]; however, DCA did not appear to provide a superior long-term benefit.[128] To adequately address the dilemma further, studies matching DCA with stent implantation are underway. In addition, more sophisticated matching techniques may be used to provide specific answers to questions, such as, if the baseline vessel size and lesion severity and the immediate postprocedural result are similar in patients treated by different devices, does the fibroproliferative hyperplastic response vary according to the device used?

Relative Gain, Relative Loss, and Net Gain Index

These indices of luminal change are derived by normalizing absolute gain, loss, and net gain, respectively, for the individual vessel size. To

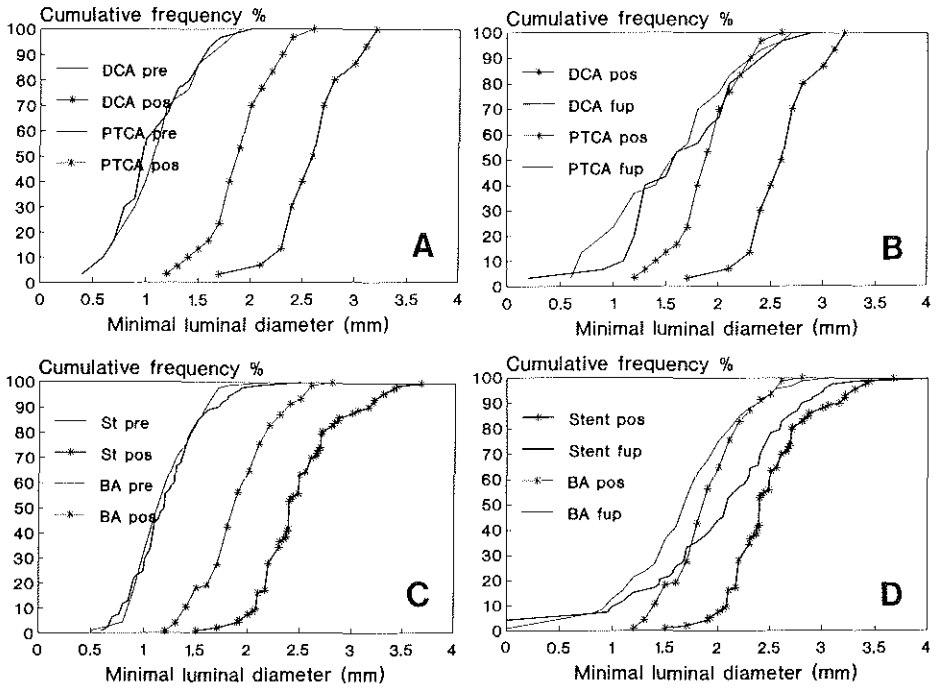

Fig 5. Comparison of immediate and long-term angiographic outcome of BA with DCA and stent implantation using cumulative distribution curves applied to matched patient groups. The x-axis represents the measured MLD, and the y-axis represents the cumulative frequency (in percentage of the total) of lesions corresponding to a given MLD measurement. (A) Preprocedure and immediately postprocedure results for PTCA and DCA (n = 90 lesions); (B) postprocedure and follow-up results for PTCA and DCA; (C) preprocedure and immediately postprocedure for PTCA and the Wallstent (n = 93 lesions); and (D) postprocedure and follow-up for PTCA and the Wallstent.

provide a constant and objective point of reference, the interpolated RD before intervention is used for the vessel size. As mentioned previously, this is the closest angiographic approximation of the disease free or normal vessel diameter. These relative measurements are not interchangable with changes in conventional percent diameter stenosis, because selection of the RD is quite different, as explained earlier (Fig 1). The matching procedure, as described above, is inherently selective, and many lesions cannot be compared because of lack of a suitable partner. However, by normalizing for vessel size, any lesion may be compared with any other with respect to changes at intervention and during follow-up. Using this approach, applied to patient groups treated by DCA, BA, or implantation of a self-expanding stainless steel mesh stent or of a balloon-expandable tantalum coil stent, we have reported, in all of the groups, a direct linear relationship between relative luminal increase at intervention and subsequent deterioration during follow-up; however, this relationship differs considerably among the groups (Fig 6).[131] Although there were definite demographic variations, which may partly explain the observed differences, we believe sufficient evidence was presented to speculate that the findings reflect device-specific variations in the injury/hyperplasia relationship that need to be further investigated. According to these findings, the stainless steel mesh stent and BA display a better profile than DCA or tantalum coil stent implantation, in terms of provoking less relative luminal loss at increasing levels of relative luminal gain. These findings are in conflict with the previously mentioned reports of Kuntz et al,[100,101] perhaps because of differ-

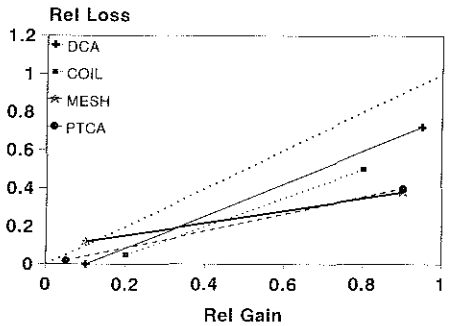

Fig 6. Linear regression relationship of relative gain/relative loss of patients treated by 4 different interventional devices are shown with the line of identity. It can be appreciated that a device whose regression line has a steep slope (eg, DCA) could be considered to be associated with a worse profile than could one with a gentle line-slope (eg, the MESH stent), insofar as a greater relative loss is associated with any given relative gain. It is additionally clear that each device is associated with the achievement of progressively increasing net gain index (the perpendicular distance from the regression line to the identity line) at increasing levels of relative luminal gain. DCA (n = 118 lesions); COIL, balloon-expandable tantalum coil stent (n = 101 lesions); MESH, self-expanding stainless steel mesh stent (n = 110 lesions); PTCA (n = 1435 lesions).

ences in methodological approach, whereby they have used absolute (not adjusted for the vessel size) luminal measurements. In these studies, their conclusion of no difference in proliferative response to the devices is based on the finding of similar loss index for each patient group and of absence of an independent influence of the device used on late loss in multivariate analysis of the patient groups combined. However, possible effects of specific interactions between the individual device and the gain achieved, on the late loss, were not taken into account as independent factors.

Despite these differences in approach and final conclusions, it is clear that the immediate aim of intervention must be to safely achieve as great an angiographic luminal improvement as possible with each device, because it can be extrapolated from Fig 7 that progressively greater, relative luminal gain yields proportionally increasing net gain (each regression line is beneath and diverging from the identity line so that a greater net gain index is associated with increasing relative luminal gain, despite the concomitantly increasing, relative luminal loss). A proviso to this general recommendation is that the achievement of great luminal improvements is obviously more safely possible by stent implantation than by BA or DCA. Aiming to obliterate the target lesion by balloon dilatation is not a legitimate endpoint of intervention with this device, because of the inevitable elastic recoil and the risk of vessel wall dissection. Similarly, by its very nature, aggressive DCA is attended by some risk of vessel perforation. In addition, Umans et al have suggested that DCA should not be used in smaller vessels (<2.5-mm RD), even if smaller cutters are used, because of the apparently aggressive, intimal response as a likely consequence of deeper vessel wall injury in these vessels. However, Kuntz et al[132] have reported a general trend toward an improved long-term angiographic result when medial or adventitial tissue is retrieved; this contrasts with previous reports by Garratt et al.[133] Nevertheless, it is becoming increasingly apparent that, in general, interventions in larger vessels may be associated with a better long-term outcome. Our group has reported that relative luminal deterioration during follow-up after DCA, BA, and balloon-expandable tantalum-coil stent implantation is greater in smaller vessels, which appears to be a consequence of increasing relative luminal gain achieved at intervention (Fig 7).[134] In addition, Kuntz et al

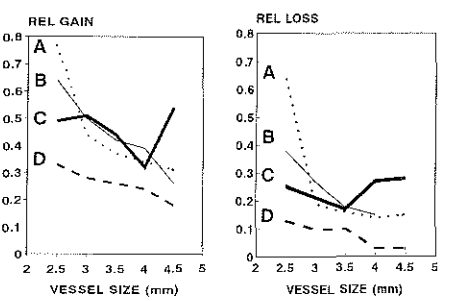

Fig 7. Relative luminal gain (REL GAIN; left panel) and loss (REL LOSS; right panel) according to vessel size in increments of 0.5 mm, for the patient groups described in Fig 6. A pattern of decreasing relative luminal loss with increasing vessel size is apparent for each device except for the MESH stent, and a similar pattern is observed for relative luminal gain. This finding would suggest that previous observations of lower tendency to restenosis in larger vessels is, in fact, a consequence of less relative luminal increase at intervention in these vessels compared with that for smaller vessels. A constant relationship between relative gain and relative loss at all vessel sizes, for each device, can be appreciated. Thus the restenosis process would appear to be independent of vessel size but strongly dictated by the degree of relative luminal gain at intervention, as shown in Fig 6.

have reported lower restenosis rates in larger vessels treated by DCA or stent implantation.[100] Thus, the "bigger is better" philosophy may be more properly interpreted to mean that intervention in a bigger vessel is associated with a better long-term outcome as opposed to the initially reported intention that a bigger lumen after intervention is associated with a better long-term outcome, because larger postprocedural and follow-up lumen are naturally associated with larger vessels.

ANGIOGRAPHIC EVALUATION IN RANDOMIZED TRIALS COMPARING INTERVENTIONAL DEVICES

Important multicenter trials, examining the impact of various pharmacologic agents, or new interventional devices on restenosis are now being assessed in core laboratories[135-137] using quantitatively derived parameters, particularly MLD.[138] In addition, increasing attention is being paid to the use of intracoronary nitrate and replication of the angiographic projections before and after intervention and at follow-up.[115]

However, many studies continue to report results in terms of percent diameter stenosis measurements and restenosis rates. We have already described our strong reservations concerning the use of percent diameter stenosis measurements in important clinical trials. Similarly restenosis rates are, as explained, inherently misleading and inaccurate and have little relevance to the description of the ubiquitous and dynamic process of luminal renarrowing.[56,82] If long-term clinical outcome is to be reported, the frequency of occurence of lesion severity at follow-up angiography of more than 50% diameter stenosis is entirely inappropriate because it yields no information on actual lesion deterioration intervention and, also, because this approach equally categorizes patients with a diameter narrowing of 50% and those with a totally occluded vessel. Similarly, those with a completely normal artery, 0% stenosis, would be classified in the same group as those with a 49% diameter narrowing. Reporting on the occurrence of major cardiac complications or major adverse cardiac events (death, myocardial infarction, coronary artery bypass graft surgery, reintervention[42]) in the follow-up period, a technique used in many current multicenter trials, presents considerably more relevant and useful clinical information regarding long-term clinical success of therapy than the so-called clinical restenosis definition.

Angiographic outcome must be evaluated using a continuous approach to provide sensitive evaluation of the usefulness of new therapeutic strategies. In addition, 100% QCA follow-up is desirable to measure absolute luminal dimensions before and after intervention and at follow-up in all patients. In randomized trials the baseline characteristics of the treated groups are assumed to be similar, so that the acute and long-term effects of intervention may be directly compared, as has been presented in restenosis prevention trials after BA,[11,12,83] in the recently completed CAVEAT,[124] and in the soon-to-be completed Benestent[111] trials. There are three important angiographic aspects of interventional results that need to be considered for thorough comparative evaluation of these trials.

First, the long-term angiographic outcome should reflect patient status at follow-up. To this end, the MLD at follow-up has been shown to have relevant clinical correlations[69] and is the most unambiguous comparative measure of this aspect both for the individual patient and the treated group. Second, the net angiographic benefit of the intervention (the angiographic balance of relative luminal improvement at intervention and relative luminal loss during follow-up) may be considered to convey a comparative measure of the ultimate effectiveness of the device, in providing luminal improvement from before intervention to follow-up. We would suggest that the net angiographic benefit, normalized for the vessel size (what our group has termed the net gain index), is the most useful index in this regard. Finally, the overall effect of the device on the process of restenosis within the treated population may be evaluated using the relative gain/relative loss relationship as an angiographic surrogate for the wall injury/fibroproliferative response relationship and may be compared between groups. Within a randomized trial, whereby all baseline characteristics are comparable, any differences in this relationship may be attributed to real device effects.

Kuntz et al have proposed the use of a loss index[82,89,100,101] (absolute loss corrected for absolute gain) as a measure of the proliferative potential of an instrumented vessel to evaluate the effectiveness of a therapeutic strategy. In essence, this is the regression coefficient of the

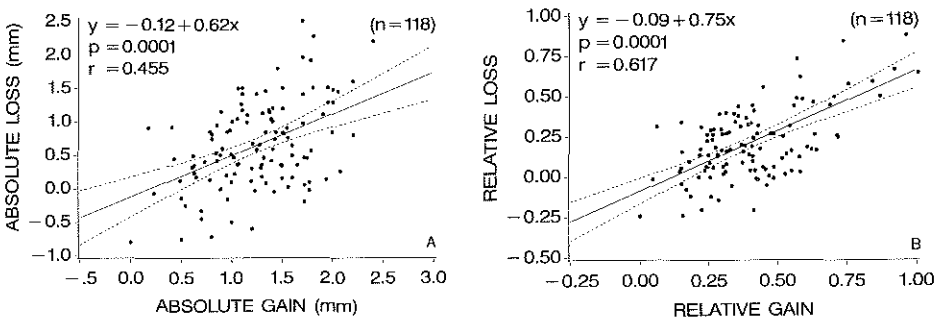

Fig 8. (A) Linear regression (y = a + bx) of absolute loss on absolute gain and relative loss on relative gain for the DCA group shown in Fig 6, with the individual data points included (n = 118), is shown. In the relative gain/relative loss graph (B), the denominator is the same for the calculation of relative measurements (ie, the interpolated RD before DCA), and, thus, the loss/gain relationship will be exactly the same as the relative loss/relative gain, for each lesion; however, the resultant population relationships are clearly not identical. This is because of changes in spatial orientation of individual lesions, with respect to each other, on normalization for the vessel size, as shown. For the reasons given in the text as well as for the obviously stronger correlation (r), we consider the relative loss/relative gain relationship to be more meaningful and useful for comparative purposes between patient groups treated by different interventions. The loss index would be 0.62, whereas a relative loss index would be 0.75. r, Pearson's product moment correlation coefficient; p, statistical certainty of a linear relationship between the dependent (loss, relative loss) and independent (gain, relative loss) variables.

gain/loss relationship, which is similar (but not identical) to the relative gain/relative loss relationship (Fig 8), and may be a useful simple index. However, we have reservations regarding its sensitivity, because two widely separated population responses of luminal loss to luminal gain may be described by the same loss index, which would misleadingly convey similar proliferative response to a given level of injury (Fig 9). In addition, the potentially wide and variable range of individual responses cannot be communicated by the simple loss index. Thus, because we consider normalization of luminal changes for vessel size to be an integral step to comparative evaluation, we believe the linear regression display of relative luminal loss on relative luminal gain (Figs 6 and 8) to be the most informative angiographic exploration of the restenosis

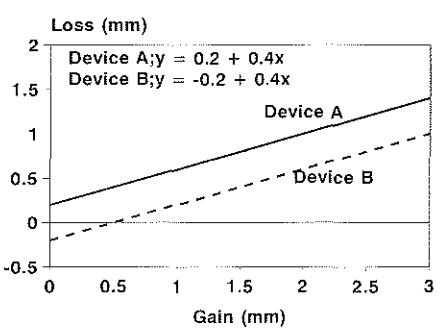

Fig 9. Schematic drawing shows potential limitations of the loss index. Both device A and device B would have a loss index of 0.4, yet it is clear that in the achievement of acute gain of 2 mm, device A would provoke a late loss of 1.2 mm, whereas device B would provoke a loss of 0.8 mm. This is a purely hypothetical example whereby other factors, not considered in the analysis, are likely to explain the different population responses; however, it must be remembered that, in reality, the restenosis phenomenon is clearly multifactorial, and such a scenario may not be completely unrealistic.

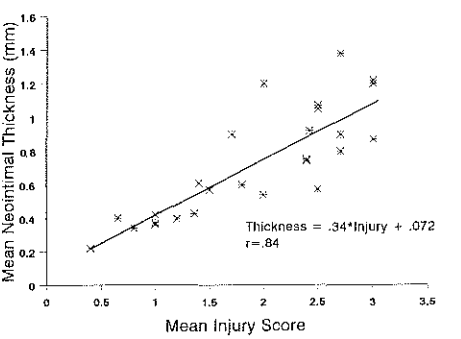

Fig 10. The relationship between wall injury score and measured neointimal thickness, in a stented porcine model, as reported by Schwartz et al,[99] is shown. Compare this with the relative gain/relative loss relationships displayed in Figs 6 and 8. Certain similarities are apparent that stimulate the speculation that these QCA indices may represent relevant correlates of arterial wall injury and neointimal response, which may be of some value for clinical restenosis studies. (Reprinted with permission.[99])

process (arterial wall injury/hyperplastic response; Fig 10).

CONCLUSION AND EPILOGUE

Through the extensive application of QCA to large patient populations undergoing transluminal interventions, with comprehensive scrutiny and analysis of the data provided, our group and others have developed and continue to explore pertinent and contributory concepts to the understanding of the immediate and long-term responses to coronary vessel intervention. Rapid advances in alternative imaging techniques should not be visualized as competing with QCA but, rather, as mutually complementary methods of providing increasingly comprehensive assessment of coronary luminal obstructions and the outcome of therapeutic interventions. Correlations between the information provided by these techniques and quantitatizve angiographic data will be of major clinical interest.

Although in clinical practice, most of these techniques are, as yet, investigational and tend to be used mainly in large academic institutions, increasingly sophisticated QCA analysis programs have been adapted for on-line use and produce rapid, accurate, and precise measurement of luminal dimensions in the catheterization room, as well as off-line in the analysis room or core laboratory. These continuing developments, together with universal use of cineangiography or digital angiography by interventionalists, are likely to cement the position of QCA as the "gold standard" in coronary luminal examination for the forseeable future. Thus, the clinical use of QCA on-line during intervention has barely been explored but presents exciting and fascinating prospects. We hope that this and the accompanying report will provide some general and specific, theoretic and practical guidance for the interventionalist embarking on the fantastic voyage into the realms of QCA.

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CHAPTER 3

ANGIOSCOPIC VERSUS ANGIOGRAPHIC DETECTION OF INTIMAL DISSECTION AND INTRACORONARY THROMBUS.

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Angioscopic Versus Angiographic Detection of Intimal Dissection and Intracoronary Thrombus

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Objectives. **This study was undertaken to compare coronary angioscopy with angiography for the detection of intimal dissection and intracoronary thrombus.**

Background. **It has been demonstrated previously that coronary angioscopy provides more intravascular detail than cineangiography. Both imaging methods have to be compared directly to assess the additional diagnostic value of angioscopy.**

Methods. **The angiograms and videotapes of 52 patients who had undergone angioscopy were reviewed independently by two observers unaware of other findings. Classic angiographic definitions were used for dissection and thrombus. Angioscopic dissection was defined as visible cracks or fissures on the lumen surface or mobile protruding structures that are contiguous with the vessel wall. Angioscopic thrombus was defined as a red, white or mixed red and white intraluminal mass.**

Results. **Angiography and angioscopy were in agreement in 40.4% of cases in the absence of thrombus and in 11.5% in the presence of thrombus. No fewer than 25 (48.1%) angioscopically observed thrombi remained undetected at angiography. With angioscopy as the standard, although the specificity of angiography for thrombus was 100%, sensitivity was very low at 19%. Angioscopic dissection was present in 40 patients (76.9%) versus angiographic dissection in 15 patients (28.8%). With regard to dissection, there was no correlation between the two imaging methods ($r_\phi = 0.15$, $p = 0.29$).**

Conclusions. **Coronary angiography underestimates the presence of intracoronary thrombus. Angioscopy and angiography are complementary techniques for detecting and grading intimal dissections.**

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Coronary angioscopy is a relatively new technique for imaging the vascular inner surface and intraluminal structures of the coronary arteries (1–3). The recent introduction of a small, flexible, wire-guided, high resolution coronary angioscopy system has led to an increasing acceptance of this imaging method for clinical and investigational purposes (4–8). From the beginning of its clinical application, it has been recognized that angioscopy provides more intravascular detail than can be detected with angiography. The presence of intracoronary thrombus and intimal dissection has been clearly documented in angiographically unremarkable vessels (9–15).

Coronary angiography, by contrast, is accepted as the standard for imaging the coronary arteries and is irreplaceable for routine patient care in diagnostic and interventional cardiology. However, with the increasing availability of angioscopy and its potential for rapid and comprehensive direct visualization of the coronary lumen, the definition of intracoronary thrombus and intimal dissection by angiography must be questioned. The purpose of this study was to compare and contrast imaging information obtained in 52 patients undergoing coronary angioplasty, using a combination of angiography and angioscopy, with specific attention to the detection of intracoronary thrombus and intimal dissection.

Methods

Patients. At the catheterization laboratories of the University Hospital Groningen and the Thoraxcenter, Rotterdam, the Netherlands, 52 patients (mean age 60.5 years, range 40 to 76) underwent coronary angioscopy before (15 patients) or after (37 patients) coronary balloon angioplasty.

Coronary angioscopy. Angioscopy was performed with the ImageCath system (Baxter, Interventional Cardiology Division). Visualization of the coronary lumen is facilitated by low pressure inflation of a proximal cuff (maximal diameter 6 mm) and continuous flushing of prewarmed normal saline solution at 40 ml/min through the irrigation channel of the angioscope. Specific features of the angioscope include a mobile fiber bundle allowing 5-cm longitudinal movement after cuff infla-

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Table 1. Classification System for Angioscopic Thrombus and Dissection

Dissection	
0	Not assessable, not applicable
1	None
2	Small surface disruptions (flaps)
3	Large dissection
Red thrombus	
0	Not assessable, not applicable
1	None
2	One lining thrombus
3	Multiple lining thrombus
4	Protruding thrombus, <⅓ of lumen
5	Protruding thrombus, ⅓–⅔ of lumen
6	Protruding thrombus, ⅔–⅓ of lumen
White thrombus	
0	Not assessable, not applicable
1	None
2	One lining thrombus
3	Multiple lining thrombus
4	Protruding thrombus, <⅓ of lumen
5	Protruding thrombus, ⅓–⅔ of lumen
6	Protruding thrombus, ⅔–⅓ of lumen
Mixed red/white thrombus	
0	Not assessable, not applicable
1	None
2	One lining thrombus
3	Multiple lining thrombus
4	Protruding thrombus, <⅓ of lumen
5	Protruding thrombus, ⅓–⅔ of lumen
6	Protruding thrombus, ⅔–⅓ of lumen

tion. All angioscopic images were recorded on Super-VHS videotape.

Coronary angiography. Coronary angiography was performed according to the normal routine of both catheterization laboratories, with multiple projections of the treated coronary artery segments both before and after angioplasty. The angiograms were recorded at 12.5 to 25 frames/s on cinefilm.

Data acquisition and definitions. The angioscopic videotape recordings were reviewed in a predetermined random order by two interventional cardiologists with ample experience in angioscopy. The presence of dissection and thrombus was scored with the use of a classification system to provide grading scales for these diagnoses (Table 1). Presence of thrombus was subclassified as red, white or mixed red and white. The angioscopic definition for a thrombus was as follows: red, white or mixed red and white, intraluminal, superficial or protruding mass, adherent to the vessel surface but clearly a separate structure. A white thrombus should fulfill the additional criterion of a shaggy, irregular and cotton wool–like appearance. The magnitude of a protruding thrombus, classified as grades 4 to 6, was determined by visual estimation. Angioscopic dissection was defined as visible cracks or fissures on the lumen surface or mobile protruding structures that are contiguous with the vessel wall and of homogeneous appearance with the vessel wall. These definitions and classifications of thrombus and dissection are part of an angioscopic classification system that was developed and evaluated by the European

Table 2. Modified National Heart, Lung, and Blood Institute Classification of Angiographic Dissection

No dissection	
Type A	Small radiolucent area within the lumen of the vessel disappearing with the passage of contrast material
Type B	Filling defect parallel to the lumen of the vessel disappearing with the passage of contrast material
Type C	Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material
Type D1	Spiral-shaped filling defect with normal runoff of the contrast material in the anterograde flow
Type D2	Spiral-shaped filling defect with delayed runoff of the contrast material in the anterograde flow
Type E	Persistent lumen filling defect with delayed runoff of the contrast material in the distal vessel
Type F	Filling defect accompanied by total occlusion

Working Group on Coronary Angioscopy (16). Intraobserver and interobserver agreements of angioscopic recordings, evaluated by this working group, were considered acceptable. Intraobserver and interobserver agreements for the angioscopic presence of red thrombus were found to be 91% and 81%, respectively. For dissection, intraobserver agreement was 87% and 73% for interobserver agreement.

The cineangiograms were scored off-line by the same observers in blinded manner in a different random order. Intimal dissection was defined as intraluminal filling defects, extravasation of contrast material or linear lumen density staining and was categorized according to modified National Heart, Lung, and Blood Institute criteria (Table 2) (17–20). Angiographic evidence of intracoronary thrombus was defined as the presence of an intraluminal central filling defect or lucency surrounded by contrast material, seen in multiple projections and with absence of calcifications within the defect (21).

Statistical analysis. The angioscopic and angiographic absence, presence or degree of dissection and thrombus was scored by consensus of the two observers. If they differed in their judgment, consensus was reached by the opinion of a third, independent observer. The observers were uninformed of all patient data to allow for independent, unbiased review of angioscopic images and angiograms.

Cross-tables were made to compare angioscopic and angiographic scores. Correlations were calculated using the Spearman rank-order correlation coefficient r_s and the phi coefficient for 2 × 2 tables (r_ϕ). These correlations were computed using the SPSS statistical package, version 5.01. Statistical significance was set at the 5% level ($p < 0.05$).

Results

There were no major complications caused by angioscopy in this patient cohort. There was one case of ventricular fibrillation, which was easily cardioverted, resulting from an excessively long period of ischemia during our learning curve. Severe coronary spasm, air embolism, angiographic evidence of dissection caused by angioscopy, balloon or wire entrapment

Table 3. Angioscopic Thrombus Grade Versus Angiographic Thrombus Presence

Angiographic Thrombus	Angioscopic Thrombus Grade					
	1	2	3	4	5	6
Absent	21 (40.4%)	7 (13.5%)	11 (21.2%)	4 (7.7%)	2 (3.8%)	1 (1.9%)
Present	—	1 (1.9%)	3 (5.8%)	1 (1.9%)	—	1 (1.9%)

Data presented are number (%) of patients.

or trauma caused by the occlusion cuff did not occur in this patient group.

Coronary angioscopy revealed both intracoronary thrombus and dissection in many angiographically unremarkable vessels.

Intracoronary thrombus. All intraluminal filling defects fulfilling the criteria for thrombus that were observed with angiography were confirmed by angioscopy as representing intracoronary thrombus. The angioscopic score of thrombus versus the absence or presence of thrombus at angiography is presented in Table 3. Angiographic evidence of thrombus was reported in only six cases. Angioscopy, by contrast, revealed 31 (59.6%) cases of intracoronary thrombus, varying from a single lining thrombus to large occluding thrombi. The distribution of the colors of the thrombi that were detected was as follows: 24 cases of red thrombus, 6 cases of mixed thrombus and 1 purely white thrombus.

Table 4 shows the presence or absence (angioscopy grade >2) of thrombus in a 2 × 2 cross-table. There is agreement between angiography and angioscopy in 21 cases (40.4%) with regard to the absence of thrombus and in 6 cases (11.5%) with regard to the presence of thrombus. However, no fewer than 25 (48.1%) angioscopically observed thrombi remained undetected at angiography. This underdetection was independent of the thrombus color; in other words, white or mixed thrombus was missed by angiography as often as red thrombus. Compared with angioscopy, there were no false negative angiographic thrombus observations. There was a weak but significant correlation between angiographic and angioscopic presence or absence of thrombus (r_ϕ = 0.30, p = 0.03). A typical example of intracoronary thrombus formation detected by angioscopy but obscured by angiography is presented in Figure 1.

Sensitivity and specificity. On the basis of these findings, as well as on previous publications (9,14,22–24), angioscopy can be regarded as the most reliable means of in vivo detection of intracoronary thrombus. Accordingly, to enhance the interpretation of our data, we used angioscopy as the standard to calculate the sensitivity and specificity of angiography for thrombus. Although the specificity of angiography for thrombus was 100%, sensitivity was very low at 19.4%. The positive predictive value was 100%; the negative predictive value 45.7%. It can be argued that the angiographic criteria for thrombus (intraluminal filling defect surrounded by contrast in multiple projections) allow detection of only larger, lumen space-occupying thrombi (25). Furthermore, although the angioscopic presence of red thrombus has been validated in a postmortem study by Siegel et al. (14), it can be argued that wall hemorrhage after angioplasty may be misinterpreted as lining red thrombus. Therefore, we recalculated these variables counting only protruding thrombi (grade 4 or more) as positive angioscopic thrombus observations, disregarding mural, lining thrombi. This had only a minor influence on the outcome: Sensitivity of angiography for thrombus using angioscopy as the standard was 22.2%, specificity 90.7%, positive predictive value 33.3% and negative predictive value 84.8%.

Table 4. Angioscopic Versus Angiographic Thrombus

Angiographic Thrombus	Angioscopic Thrombus (≥grade 2)	
	Absent	Present
Absent	21 (40.4%)	25 (48.1%)
Present	—	6 (11.5%)

Data presented are number (%) of patients.

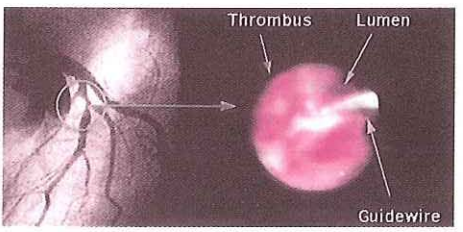

Figure 1. Coronary angiogram (left anterior oblique view with cranial angulation) showing a significant stenosis in the left anterior descending coronary artery. The lesion has a smooth angiographic appearance, without filling defects suggestive of intracoronary thrombus. Coronary angioscopy reveals two fairly **large red thrombi** located on the proximal side of the eccentric narrowing.

Dissection. Table 5 represents the comparison of angiographic and angioscopic dissection. Type A, B and D1 dissections were seen with angiography in these patients. There appeared to be no relation to angioscopic intimal dissection grade (Spearman correlation coefficient 0.21, p = 0.14). The variables were dichotomized to test whether the angioscopic

Table 5. Angioscopic Dissection Grade Versus Angiographic Dissection Type

Angiography	Angioscopic Dissection Grade		
	1 (no dissection)	2 (small disruptions)	3 (large dissection)
No dissection	10 (19.2%)	9 (17.3%)	18 (34.6%)
Type A dissection	—	1 (1.9%)	2 (3.8%)
Type B dissection	2 (3.8%)	—	9 (17.3%)
Type D1 dissection	—	1 (1.9%)	—

Data presented are number (%) of patients.

Table 6. Angioscopic Versus Angiographic Dissection

Angiographic Dissection	Angioscopic Dissection (≥grade 2)	
	Absent	Present
Absent	10 (19.2%)	27 (51.9%)
Present	2 (3.8%)	13 (25.0%)

Data presented are number (%) of patients.

presence or absence of dissection had a relation to any type of angiographic dissection (Table 6). These data show angioscopic dissection in 40 patients (76.9%) versus angiographic dissection in 15 patients (28.8%), again without any correlation ($r_\phi = 0.15$, $p = 0.29$). There were two cases of angiographic dissection that were not detected by angioscopy. Surface disruptions are typically seen with angioscopy after balloon angioplasty (4,12), as was the case in all postangioplasty observations in this study. Small surface disruptions, like small thrombi, may easily be missed with angiography and may not have clinical consequences. These small flaps may even be regarded as the "normal" aspect of the vascular wall after balloon angioplasty. For this reason the analysis was repeated, comparing only large angioscopic dissections with all types of angiographic dissections, but, again, it did not yield a significant correlation between the two imaging methods ($r_\phi = 0.23$, $p = 0.10$). Figure 2 shows an example of a dissection found with angioscopy that was not visible on the angiogram.

Discussion

Contrast cineangiography is accepted as the standard imaging method for the coronary arteries. Although angiography provides indispensable anatomic information and has set the standard for quantifying stenotic lesions (26) both before and after angioplasty (27), it can be questioned if it still should be regarded as a sufficient means of imaging for studies that require a reliable detection of intracoronary thrombus and intimal dissection. The value of such angiographic studies must be open to question, particularly if they address the sequelae of intracoronary thrombus (28–32).

Implications. Adequate angioscopic evaluation of intracoronary thrombus can have an impact on routine patient care as well, for instance, in the determination of the optimal management in cases of suboptimal angioplasty result or abrupt reclosure. All nine patients in this study with protruding thrombi (≥grade 4) at angioscopy were treated with adjunctive intracoronary thrombolysis. Intracoronary thrombus was present in 8 of the 15 patients who underwent angioscopy before angioplasty (six cases grade 3, and two cases grade 4 thrombus). All of these eight patients had unstable angina, as opposed to two of seven patients without intracoronary thrombus before angioplasty. This higher incidence of thrombus in patients with unstable angina is in accord with other angioscopic studies (5,6,24). Sassower et al. (33) and Knopf et al. (8)

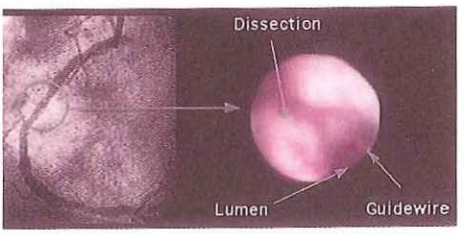

Figure 2. Postangioplasty coronary angiogram (left anterior oblique view) of the right coronary artery with an angiographically optimal result, without evidence of dissection. At angioscopy, a large intimal dissection with **white mobile flaps** is observed.

have identified the clinical relevance of reliable angioscopic thrombus detection during coronary angioplasty in cases of abrupt closure, unstable angina and acute myocardial infarction. We previously reported two cases of subacute stent occlusion where angioscopy helped to distinguish dissection from thrombosis as the primary cause (34).

The high sensitivity of angioscopy for the detection of thrombus potentially has clinically relevant implications. Used before the intervention, angioscopy may predict a high incidence of acute or abrupt closure if intracoronary thrombus is detected. Another potentially useful application of angioscopy is in the emergency situation: when an acute occlusion occurs or threatens to occur after angioplasty, it is of utmost importance to be able to differentiate between thrombus and dissection as the primary cause for this adverse outcome. The selection of the optimal emergency strategy, such as stent implantation, prolonged inflation of autoperfusion balloon catheters or intracoronary thrombolysis, could be facilitated by angioscopy.

This study was undertaken to compare objectively the usefulness of angioscopy and conventional angiography for detection of intracoronary thrombus and intimal dissection. Contrasting conclusions may be drawn from the findings with respect to these respective diagnoses. The sensitivity and specificity of angiography for thrombus detection clearly indicate that angiography underestimates the presence of thrombus. The vast majority of angioscopically observed thrombi remain obscured at angiography. For dissection, however, angiography and angioscopy appear to be complementary imaging techniques. There were two cases in which angioscopy missed the dissection although it was evident on the angiogram. Both were type B dissections, with a filling defect parallel to the lumen that must have remained hidden from angioscopic view. Dissection was not seen on angiography in the 15 patients who were studied before angioplasty. With angioscopy, dissection was scored in nine of these patients (six cases grade 2 and three cases grade 3 dissection). It is likely that angioscopically observed dissections in this preangioplasty situation represent spontaneous dissections or ruptured plaques.

Study limitations. Our study has the limitations of a retrospective investigation. Not all types of dissection were present

in this group, which included patients with both preangioplasty and postangioplasty lesions. As a result, a positive correlation between angiographic dissection type and angioscopic dissection grade may not be excluded but may merely not have been confirmed with this limited number of 52 paired observations.

We found a considerable angiographic underestimation of thrombus. This may result in part from the strict angiographic criteria for thrombus. More liberal criteria undoubtedly would result in increased sensitivity at the cost of a much lower specificity. Another problem, which may result in inaccurate estimation of angiographic sensitivity and specificity for thrombus and dissection, arises from the difficult angiographic distinction between these two diagnoses. Thrombi may have been misinterpreted as dissections, and vice versa. In five of six cases of angiographic thrombus, dissection was present as well. There were four cases of angiographic thrombus that correlated with angioscopic lining thrombus. By contrast, because lining mural thrombus is not very bulky, in general it would not be detected by angiography (25), so it is highly probable that the lumen filling defects that were observed in these cases were caused by concomitant dissection. In fact, there proved to be a large angioscopic dissection (grade 3) in three of these four cases, and small surface disruptions (grade 2) in one case. Thus, an even lower angiographic sensitivity for thrombus may have been found if a different patient group, with intracoronary thrombus but without dissection, had been studied.

Intravascular ultrasound imaging is another new imaging tool for intraluminal structures (as well as for vascular wall properties). Although it does not have ideal properties for thrombus detection, intraluminal ultrasound imaging has the potential for superior imaging of intimal dissection (35–38), with the ability to discern plaque fracture from more extensive disruption that includes the internal elastic lamina. Future studies should address the combined use of all available coronary imaging techniques.

Conclusions. Coronary angiography considerably underestimates the presence of intracoronary thrombus. In studies that require reliable detection of thrombus, coronary angioscopy is the imaging tool of choice. Angioscopy and angiography are complementary techniques for detection and grading of intimal dissections.

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CHAPTER 4

QUANTITATIVE CORONARY ANGIOGRAPHY DURING CORONARY ANGIOPLASTY WITH A SINGLE ANGIOGRAPHIC VIEW: A COMPARISON OF AUTOMATED EDGE-DETECTION AND VIDEODENSITOMETRIC TECHNIQUES.

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AM HEART J 1993;126:1326-33.

Quantitative angiography during coronary angioplasty with a single angiographic view: A comparison of automated edge detection and videodensitometric techniques

Little information is available on the reliability of coronary luminal measurements obtained from quantitative analysis of a single angiographic view, an approach that is central to the practical use of on-line quantitative angiography. In the present study we investigated the contribution of two different techniques of quantitative angiography, edge detection (ED) and videodensitometry (VD), to the application of this concept during coronary angioplasty. Forty-six balloon angioplasty procedures were included in this study, all of them performed in a stenosis located in the mid right coronary segment. This coronary location was chosen to optimize data collection on luminal morphology and to minimize the number of factors that may adversely affect quantitative analysis with both techniques. In all cases two orthogonal angiographic projections were obtained before, after balloon dilatation, and at follow-up. Correlation coefficients and differences between orthogonal measurements obtained with each technique were used to evaluate the agreement between orthogonal readings at every stage of the procedure. The obtained correlation coefficients and mean differences (MD) between orthogonal measurements were as follows: before percutaneous transluminal coronary angiography (PTCA), 0.67 (MD 0.01 ± 0.47 mm^2) and 0.57 (MD 0.05 ± 0.64 mm^2) for ED and VD, respectively (Pitman's test for SD, $p < 0.05$); after balloon dilatation, 0.32 (MD −0.56 ± 1.53 mm^2) and 0.53 (MD −0.15 ± 1.43 mm^2) for ED and VD, respectively (paired t test for MD, $p < 0.05$); and at follow-up 0.79 (MD −0.15 ± 0.97 mm^2) and 0.73 (MD 0.17 ± 1.16 mm^2) for ED and VD, respectively (p = NS). The presence of coronary dissection did not influence the variability in measurements observed after balloon dilatation. A considerable variability between orthogonal cross-sectional area measurements obtained with ED and VD was observed at all stages of coronary angioplasty, a finding that does not support the clinical application of area measurements with ED or VD from a single view. Similar observations were made after the exclusion of angiographically evident dissections. However, after balloon dilatation the agreement between orthogonal area measurements was significantly better with VD than with ED. Our results provide new insights into the problems posed by coronary intervention with respect to the on-line angiographic assessment of such intervention and to the potential solution of these problems. With either of these two quantitative techniques, area measurements obtained from a single angiographic view should be interpreted with caution. (Am Heart J 1993;126:1326-33.)

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The growing demand for the use of on-line quantitative angiography during interventional procedures is currently hampered by two major limitations. First, although averaging of measurements obtained in different angiographic views is accepted as the optimal method for quantifying coronary stenosis,[1-3] this approach appears too cumbersome for its application during coronary intervention. Second, quantitative analysis of intervening segments appear to be less reliable than that performed in nonintervening segments.[3-7] It remains unclear whether either of the two main alternative techniques of quantitative analysis, namely videodensitometric and edge detection, can offer a distinct solution to these problems. The routine use of quantitative angiography would be facilitated and more widely applied during interventional procedures if accurate measurements could be ob-

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tained from the analysis of a single angiographic view. To that end, videodensitometry might be the most preferable technique since, at least theoretically, measurements are independent of the angiographic projection used. Other authors[8] have suggested that analysis of a selected single angiographic view, using edge detection, may also be accurate enough for clinical purposes. With respect to the loss of accuracy of quantitative angiography postintervention, no clear agreement has been reached on the mechanisms causing increased variability of measurements in the intervening segment. If this is the result of complex changes in luminal geometry, videodensitometry might be the method of choice, since luminal area measurement by this technique is independent of lumen morphology. However, up to now videodensitometric studies in the context of balloon angioplasty have yielded conflicting results.[4-7, 9, 10]

To shed further light on these topics, we investigated the degree of agreement between cross-sectional area measurements obtained in two orthogonal angiographic projections during balloon angioplasty. Our first objective was to test whether the use of a single angiographic view is sufficiently accurate for its clinical use. Furthermore, we wanted to test whether in this regard videodensitometry is superior to edge detection analysis. Finally, we investigated whether the agreement between measurements obtained in two orthogonal views changes significantly during the different stages of coronary intervention. By limiting the study to a selected coronary segment with ideal characteristics for both videodensitometry and edge detection, the effect of luminal changes caused by balloon dilatation on both types of quantitative analysis was highlighted. Edge detection and videodensitometry analysis were performed separately. Qualitative analysis of the dilated segment was also performed to assess the impact of angiographically evident dissection on single-plane analysis and on both modalities of quantitative angiography.

METHODS

Study population. The study population consisted of 653 patients having balloon angioplasty procedures who were included in the efficacy analysis of the Multicenter European Research trial with Cilazapril after Angioplasty to prevent Transluminal coronary Obstruction and Restenosis (MERCATOR).[11] The study showed that cilazapril, 5 mg twice a day, does not influence the development of restenosis or of patient clinical outcome during the first 6 months after balloon angioplasty. All 653 patients had had a successful procedure and underwent follow-up angiography at 26 ± 3 weeks after the procedure or earlier if symptoms had recurred. All 72 percutaneous transluminal coronary angioplasty (PTCA) procedures performed in a mid right coronary artery stenosis were initially considered. This segment was chosen as presenting the ideal anatomic characteristics for quantitative angiographic analysis: minimal foreshortening in the right and left anterior oblique views, few side branches, and virtual absence of vessel overlap. Lack of orthogonal angiographic projections or follow-up angiography, and total coronary occlusion at any stage of the study were exclusion criteria.

Image acquisition. Image acquisition was standardized to ensure exact reproducibility of the measurements before PTCA, after PTCA, and at follow-up. The same angiographic angulations were used throughout the study. Intracoronary nitrates (nitroglycerine, 0.3 mg, or isosorbide dinitrate, 1 mg) were given before image acquisition to ensure full vasodilation of epicardial vessels. So that they could be used as a scaling device during quantitative analysis, all catheter tips were filmed empty of contrast medium before each injection and were stored after the procedure for future micrometric measurement.[12]

Quantitative angiographic analysis. All 35 mm films were analyzed at a core laboratory (Cardialysis, Rotterdam, The Netherlands) using the Cardiovascular Angiography Analysis System (CAAS). The automated edge detection and videodensitometric techniques used in this system have been described in detail elsewhere,[13-16] as has its validation in vitro[13] and in vivo using precision-drilled acrylic plastic models inserted percutaneously in a in vivo swine model.[17, 18] All measurements were performed in end-diastolic frames with optimal vessel opacification. Before quantitative analysis, all contour positions of the catheter tip and arterial segment were corrected for pincushion distortion induced by the individual intensifiers.

Edge detection. After a region of interest measuring 512 × 512 pixels was selected and digitized using a high-fidelity charge-coupled device (CCD) videocamera, luminal edges were detected using a weighted sum of the first and second derivative functions of the brightness profile of each vessel scan line. A diameter function was determined by computing the shortest distance between the left and right contour positions. Conversion of these measurements to absolute values was achieved by using the catheter tip as a scaling device. From the diameter function, a computer-derived estimation of the original arterial dimension at the site of obstruction or an interpolated reference diameter was also calculated.

Videodensitometry. Videodensitometry is based upon the existing relationship between the attenuating power of the lumen filled with contrast medium and the x-ray image intensity. From this information a densitometric profile that is proportional to the cross-sectional area of the lumen was obtained. Subtraction of patient structure noise was applied after computing the linear regression line through the background pixels located left and right of the detected luminal contours. A cross-sectional area function on the analyzed segment was obtained by acquiring consecutive densitometric profiles in all scan lines perpendicular to the vessel. From this area function an interpolated reference area was calculated in a similar way to that described in the edge detection algorithm. Conversion of the individual videodensitometric profiles to absolute values was performed after a transformation of the videodensitometric profile found at the reference diameter with the corre-

sponding geometric area (calculated from the reference diameter and assuming a circular cross section at that point). The cross-sectional area at the narrowest point was identified and was expressed in square millimeters. No correction for veiling glare was introduced.

Assessment of dissection. Coronary dissection following balloon angioplasty was recorded by two independent observers using a modification of the criteria defined by the National Heart, Lung, and Blood Institute.[19] A dissection was classified as a small radiolucent area within the lumen of the vessel (type A), a nonpersisting or persisting extravasation of contrast medium (type B or C, respectively), a spiral-shaped filling defect with or without delayed antegrade flow (types E and D, respectively), or a filling defect causing total coronary occlusion (type F). The presence of angiographic dissection may constitute a source of variability during quantitative analysis. Following the recommendations of the angiographic committee of the MERCATOR study, identification of the luminal borders in vessels with evident angiographic dissection was performed always using the automated edge detection mode with no manual correction by the analyst. In this way, subjective bias was minimized.

Statistical analysis. Mean values ± standard deviation were calculated for all measurements obtained before PTCA, after PTCA, and at follow-up. Pearson's product moment correlation coefficients were calculated for orthogonal measurements. The agreement between orthogonal measurements was also studied using the mean (accuracy) and the standard deviation (precision) of the differences between measurements obtained in orthogonal views.[20] Quantitative data were compared using one-way analysis of variance. Paired two-tailed t tests were used when required to compare mean values. Comparisons between standard deviations were performed using Pitman's test. A p value <0.05 was considered statistically significant.

RESULTS

Of the 72 successful PTCA procedures performed in the midsegment of the right coronary artery, eight were total occlusions at baseline or follow-up and were excluded. In addition, 18 cases lacked satisfactory orthogonal angiographic assessment and were also excluded. The remaining 46 cases constitute the population of this study. Orthogonality between right and left anterior oblique views was 90.00 ± 14.43 degrees. Coronary dissection immediately after PTCA was documented in 16 cases. The dissection was classified as type A in six cases, type B in nine cases, and type E in one case. Negative videodensitometric measurements were obtained in two cases before PTCA and in one case at follow-up. The cause of negative readings may be found in an excessive background subtraction when bright areas are close enough to the analyzed vessel to fall within the region of interest. These cases were excluded only from the analysis at that particular stage of the study (pre-PTCA and follow-up, respectively).

The mean minimal luminal cross-sectional areas (±SD) obtained by averaging videodensitometry values from orthogonal views were 1.00 ± 0.96, 3.1 ± 1.68, and 2.6 ± 1.50 mm^2 before PTCA, after PTCA, and at follow-up, respectively. Averaged edge detection measurements were 1.11 ± 0.53, 3.17 ± 1.05, and 2.63 ± 1.31 mm^2, respectively.

Fig. 1 shows the correlation between pairs of orthogonal measurements obtained by using either videodensitometry or edge detection. The degree of agreement between these values is further illustrated with the mean difference between both measurements and its standard deviation (Fig. 2). Before angioplasty, the accuracy of measurements obtained from a single view is similar using videodensitometry or edge detection (mean difference −0.05 and −0.01, respectively), although the precision of edge detection was significantly higher than that of videodensitometry (standard deviations 0.47 and 0.64 mm^2 for edge detection and videodensitometry, respectively, $p = 0.023$).

After balloon dilatation, the agreement between orthogonal measurements decreased for both videodensitometry and edge detection. The mean difference between orthogonal values was −0.15 ± 1.43 mm^2 and −0.56 ± 1.53 mm^2 for videodensitometry and edge detection, respectively ($p < 0.05$). To investigate the contribution of vessel dissection to the observed loss of agreement between orthogonal measurements, the same analysis was applied separately to vessels with and without dissection (Fig. 3). No significant difference in the mean value or in the standard deviation of the difference between orthogonal values was found between groups.

At follow-up, the difference between orthogonal views was 0.17 ± 1.16 mm^2 and −0.15 ± 0.97 mm^2 for videodensitometry and edge detection, respectively. There was no significant difference in the precision of these measurements.

To study the contribution of recorded vessel dissection to the loss of agreement between orthogonal views after balloon dilatation, a separate analysis of the between-projection differences in minimal luminal area was applied to vessels with and without dissection (Fig. 3). The mean difference in cases without dissection was −0.62 ± 1.21 mm and −0.19 ± 1.49 mm^2 for edge detection and videodensitometric measurements, respectively. In those cases with angiographically detectable dissection, the differences obtained were −0.46 ± 2.04 mm and −0.06 ± 1.35 mm^2 for edge detection and videodensitometric measure-

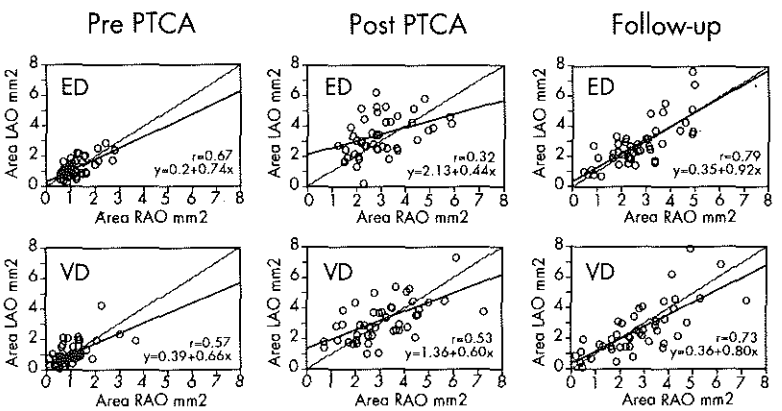

Fig. 1. Correlation between minimal luminal cross-sectional area measurements obtained in two orthogonal projections. The results obtained with automated edge detection and videodensitometric analysis in each stage of the study are shown separately. *ED*, Edge detection; *VD*, videodensitometry; *LAO*, left anterior oblique view; *RAO*, right anterior oblique view.

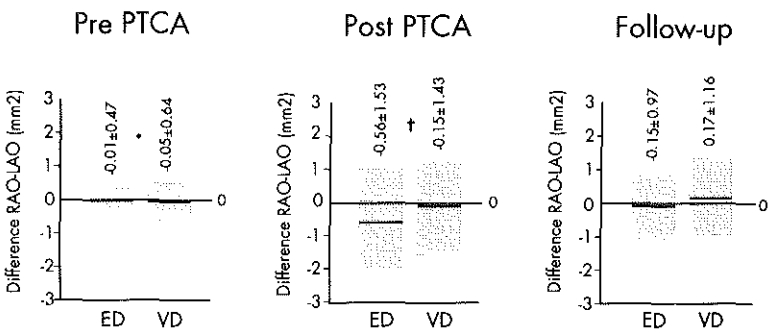

Fig. 2. Mean differences between minimal luminal cross-sectional area measurements obtained in two orthogonal projections with automated edge detection and videodensitometric analysis ± 1 standard deviation *(shadowed area)*. The results obtained during the different stages of the study are shown separately. *ED*, Edge detection; *VD*, videodensitometry.

ments, respectively. No significant differences in accuracy or precision were found with respect to the type of analysis applied (edge detection or videodensitometry) or to the presence or absence of recorded coronary dissection.

DISCUSSION

Edge detection and videodensitometric algorithms are built-in features of most new digital angiographic systems, a fact that may contribute to the widespread use of on-line quantitative coronary angiography in the near future. Although the performance of quantitative analysis from a single angiographic view is central to the practical use of these systems during routine procedures, little information is available on the variability between measurements obtained from orthogonal views. It has been argued that a significant variability would be expected when noncircular lumens are measured from different angiographic projections. Two main alternatives have been put forward to solve this problem. Lesperance et al.[8] suggested that limiting the analysis to the angiographic view in which the stenoses appears most severe might fulfill the degree of accuracy required in clinical

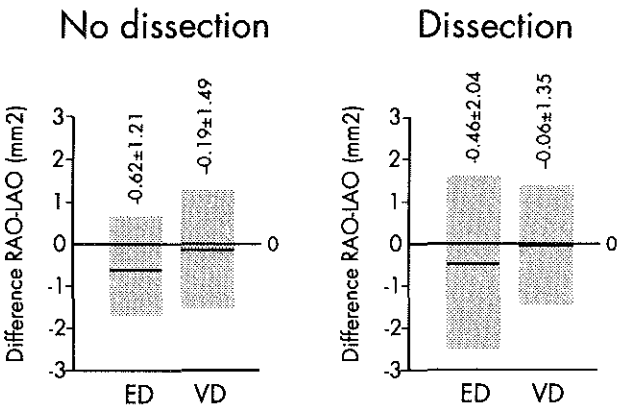

Fig. 3. Mean differences between minimal luminal cross-sectional area measurements obtained in two orthogonal projections immediately after balloon dilatation. Results obtained in cases with and without angiographically detectable dissection are shown separately. The mean difference ± 1 standard deviation *(shadowed area)* is shown. *ED*, Edge detection; *VD*, videodensitometry.

practice. A second approach, based on initial results obtained in in vitro phantoms, suggested that the use of videodensitometry would be advantageous, since accurate measurements were obtained independent of angiographic projection and lumen morphology.[5, 21, 22] Validation studies of videodensitometry in conditions closer to those found in clinical practice have been performed, including videodensitometry in postmortem specimens[23] or in engineered angiographic phantoms implanted in animal models.[18, 24] However, conflicting results have been reported when videodensitometry was used during coronary angioplasty. The correlation for individual measurements obtained in orthogonal views both before and after balloon angioplasty has been found by different authors to be high,[8] moderate,[5] or poor.[4] The deterioration caused by balloon angioplasty in the agreement of videodensitometric measurements obtained from different angulations has also been reported in one study and was found to be unacceptably large.[6]

Two of the objectives of the present study were to test whether the use of a single angiographic view is sufficiently accurate for clinical use, and whether in such regard the use of videodensitometry offers any advantages over edge detection. We found that in the postangioplasty period videodensitometry yields a significantly better agreement between orthogonal measurements than edge detection. However, further analysis of the results obtained (Fig. 1, *left panel* and *center panel*) demonstrated that the clinical relevance of this difference may be negligible. This conclusion was arrived at by setting the limits of agreement as the standard deviation of the differences observed between orthogonal measurements, according to the method proposed by Bland and Altman.[20] It led us to conclude that the overall variability between orthogonal measurements of cross-sectional area observed before and after coronary angioplasty makes single-plane quantitative angiography with either edge detection or videodensitometry too unreliable to be used in routine clinical practice. Although our conclusions are based on the analysis of a single coronary segment and therefore should be extrapolated with caution to other vascular segments, the fact that the mid-right coronary segment represents the "best scenario" for quantitative analysis makes us believe that even worse correlations would be expected if other segments of the coronary tree were to be included.

We also investigated whether the agreement between orthogonal measurements changes significantly during percutaneous intervention. In fact, we found that the agreement between single orthogonal cross-sectional area measurements obtained with either of the two techniques considered deteriorates significantly after balloon dilatation. Since tearing of the intima and atherosclerotic plaque, dehiscence of plaque from the tunica media, and variable degrees of medial and adventitial disruption are known to be common after balloon dilatation,[25] observations similar to ours have been attributed to the effect of these histopathologic changes on angiographic accuracy.[3, 4, 6, 26] However, given the characteristics of these studies, such a relationship could not been clearly

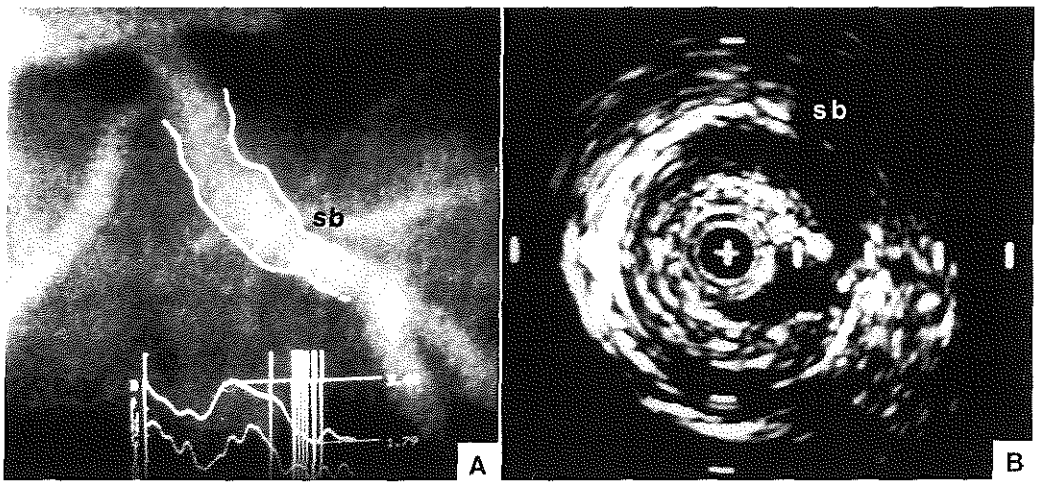

Fig. 4. Quantitative analysis of a stenosis in the circumflex coronary artery **(A)** performed immediately after balloon dilatation. Although no angiographic dissection was evident and edge detection analysis suggested a major improvement in luminal area, intravascular ultrasound **(B)** revealed that the detected edges corresponded to a nearly complete plaque dehiscence from the surrounding media and that luminal gain was clearly overestimated by angiography. During ultrasound imaging a side branch *(sb)* located at the dilatation site was chosen as a landmark.

established; experimental phantoms have a fixed luminal morphology and are free of wall disruption, and most previous clinical works have excluded or have not recorded the presence of coronary dissection.

To provide further insights, we limited the collection of angiographic data to a coronary segment with ideal characteristics for quantitative analysis. In doing so, a *true* "in vivo vascular phantom" was obtained in which the occurrence and type of vessel dissection were also documented. As shown in Fig. 3, one of our conclusions is that the increased variability between orthogonal measurements observed after balloon angioplasty may not be ascribed solely to the presence of angiographically evident dissection. This suggests that lesser or occult changes in vessel morphology must account for the loss of accuracy of quantitative angiography at this stage. Two major types of changes may account for this phenomenon. The first is the presence of intraluminal flaps and irregularities not actually identified angiographically but present after balloon dilatation, as reported in angioscopic,[27, 28] ultrasound,[29] and pathologic studies.[30] When opacified during angiography, these irregularities can be wrongly identified as the true luminal borders by edge detection algorithms, leading to a false estimation of luminal diameter. The second is the change to noncircular lumen geometry consequent to balloon dilatation.[25] Pathologic studies have shown that slit-like or very irregular lumens are rarely seen in native vessels with noncomplicated atherosclerotic plaques,[31] a fact that may explain the excellent agreement between orthogonal measurements obtained with both edge detection and videodensitometry in an in vitro study using human coronary stenosis,[23] as well as the better agreement between orthogonal edge detection measurements found at baseline in the present study (Figs. 1 and 2). These two potential sources of error are illustrated in Fig. 4, where the result of balloon dilatation in a circumflex stenosis is assessed using edge detection quantitative angiography and intravascular ultrasound.

It has been shown above that, although the overall variability in orthogonal cross-sectional area measurements was very high, videodensitometry was less influenced by balloon dilatation than was edge detection. This observation may be related to videodensitometry's theoretical independence from lumen morphology and to its relative insensitivity to imprecise border positioning.[22] In addition, although videodensitometry's application may be currently hampered by technical factors (for example, unsatisfactory background subtraction), it may in the future

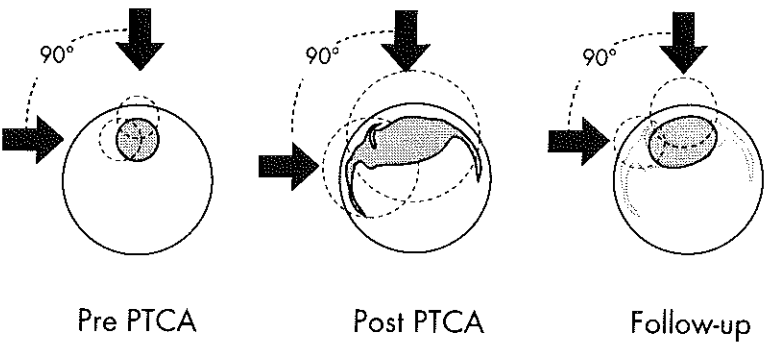

Fig. 5. Proposed anatomopathologic basis for the loss of agreement between orthogonal measurements during the different stages of balloon angioplasty. Following balloon dilatation the luminal cross-sectional area is overestimated by the use of geometric measurements *(dotted circles)* as a result of the identification of disrupted edges as true luminal borders and because of the noncircular luminal geometry. Healing of luminal disruption leads to a more regular luminal morphology and to a better agreement between orthogonal measurements at follow-up (see text for details).

constitute a valid alternative to averaging of multiple views. On the contrary, the identification of disrupted luminal edges and the assumption of an unlikely circular lumen morphology by edge detection algorithms easily lead to discrepancies in measurements obtained from a different angiographic view or with videodensitometric analysis, as illustrated in Fig. 5. In this regard, a previous work[26] has shown that coronary stenting reduces the variability between videodensitometric and edge detection measurements. This is presumably a result of the scaffolding effect of the stent on intraluminal irregularities and the achievement of a more circular luminal cross section, as documented by intravascular ultrasound studies performed immediately after stent implantation.[32] In our work the improvement in agreement between orthogonal area measurements at follow-up may be explained by the development of a more regular luminal cross-section by filling of intraluminal flaps and by smoothing of luminal irregularities during the reparative vessel response that follows balloon dilatation[25] (Fig. 5).

Study limitations. Since this study was limited to the mid-right coronary artery segment, some of the results obtained are not necessarily applicable to other coronary locations. Errors can be introduced during the calibration of the system when catheters are used as scaling devices.[33] To minimize some of the possible sources of error, all catheter tips were filmed unfilled, saved after the procedure, and micrometered at the time of quantitative analysis.[12] However, inaccuracies induced by out-of-plane position of the catheter may have occurred. Although correction for a pincushion effect in the individual intensifiers was performed, other described sources of distortion cannot be ruled out,[34] but their effect on measurements of the size range of coronary arteries is expected to be negligible. The effect of some of the physical variables potentially affecting videodensitometric analysis may be higher in the mid-right coronary than in other coronary segments. Beam hardening and veiling glare are more intense in regions of rapid transition from dark to bright areas,[35] as often happens when the mid-right coronary artery is visualized in the left anterior oblique view. Although it has been proposed by other authors,[35, 36] no correction for these factors was introduced in our analysis.

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CHAPTER 5

USEFULNESS OF REPEAT CORONARY ANGIOGRAPHY 24 HOURS AFTER SUCCESSFUL BALLOON ANGIOPLASTY, TO EVALUATE EARLY LUMINAL DETERIORATION AND FACILITATE QUANTITATIVE ANALYSIS.

Foley DP, Deckers J, van den Bos AA, Heyndrickx GR, Laarman GJ, Suryapranata H, Zijlstra F, Buller HR, Serruys PW.

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Usefulness of Repeat Coronary Angiography 24 Hours After Successful Balloon Angioplasty to Evaluate Early Luminal Deterioration and Facilitate Quantitative Analysis

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Because of the unavoidable occurrence of vessel disruption after successful coronary balloon angioplasty, the reliability of quantitative angiographic analysis in that setting has been questioned. For this reason and the suggested occurrence of delayed elastic recoil, repeat angiography at 24 hours has been advocated in clinical interventional trials. In this study, these issues are confronted by performing comprehensive quantitative analysis (Cardiovascular Angiographic Analysis System) of coronary angiograms, acquired in multiple identical projections immediately after and 24 hours after angioplasty, in 102 patients with 110 successfully dilated lesions. Vasomotion was controlled by intracoronary nitrate before angiography and all patients were fully anticoagulated (activated partial thromboplastin time 85 to 120 seconds) for >24 hours. Paired Student's *t* tests applied to angiographic measurements revealed that there was no significant deterioration in minimal luminal diameter or cross-sectional area from immediately after angioplasty to 24 hours later. It can thus be inferred that there is no phenomenon of delayed elastic recoil, at least during this time period. Measurement accuracy and precision of the Cardiovascular Angiographic Analysis System from the postangioplasty angiogram are highly acceptable, at <0.01 and ± 0.20 mm, respectively. Therefore, it is concluded that routine repeat 24-hour angiography is not indicated after successful angioplasty. A highly significant increase (p <0.001) in reference diameter (+0.11 ± 0.18 mm) was responsible for the apparent increase in percent diameter stenosis (2.4 ± 7%), a finding that demonstrates the potential for error by selective application of percent diameter stenosis measurements alone. Preferential use of absolute luminal measurements is thus strongly recommended for clinical trials with angiographic monitoring.

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Computer-assisted quantitative analysis systems have become the gold standard for measuring coronary angiographic luminal dimensions, as demonstrated in clinical studies of interventional devices and pharmacologic agents aimed at "restenosis prevention".[1–5] However, one of the main criticisms of quantitative angiography has been the potential measurement inaccuracy and imprecision immediately after apparently successful balloon angioplasty.[6] Disruptions of vessel luminal contour almost always occur,[7–9] although only seen angiographically as "dissection" in one third of cases.[10] It could thus be hypothesized that angiography 24 hours after intervention might provide a better substrate for the measurement of luminal dimensions in clinical studies.[11] Moreover, because up to 50% of achievable luminal increase may be lost immediately after balloon deflation, due to elastic recoil,[12] it could be suggested that repeat early angiography should be performed to assess the probability of further delayed elastic recoil. Such practice could lead to prolonged hospitalization and additional risk of morbidity, an increase in the work load of the medical staff of catheterization laboratories, and ultimately, increased health care costs. Furthermore, routine angiography at 24 hours could reduce the likelihood of informed consent for percutaneous interventions, especially in clinical trials. This study investigates the need for repeat angiography 24 hours after successful balloon angioplasty and provides an opportunity to examine the postangioplasty measurement variability of the Cardiovascular Angiographic Analysis System, hitherto unpublished.

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TABLE I Flow Chart from Randomization in the Safety Trial to Suitability for This Quantitative Angiographic Ancillary Study

	Number of Patients
Patient enrolled in randomized study	118
Patients excluded after enrollment	
No angioplasty performed	
Failure to cross lesion	4
Previously unrecognized left main lesion	1
Took heparin during previous 24 hours	3
Randomized to receive heparin or hirudin	110
Failure to successfully dilate all target lesions	2
Major adverse cardiac events within 24 hours	
Death	0
Myocardial infarction	1
Emergency bypass graft surgery	3
Myocardial infarction + emergency surgery	1
Repeat angioplasty	0
Complete (thrombotic) occlusion at 24 hours without major adverse event	1
Successful angioplasty + satisfactory quantitative analysis postangioplasty + 24 hrs	102

TABLE II Clinical Data and Target Lesion Distribution in 102 Patients

Age (years)	58 (35–74)
Men (%)	83 (78)
Previous MI (%)	39 (37)
Diabetes mellitus (%)	5 (5)
Hypertension (%)	32 (30)
Current smokers (%)	25 (24)
Angiographic coronary disease pattern	
1-vessel disease (%)	87 (82)
2-vessel disease (%)	17 (16)
3-vessel disease (%)	2 (2)
CCS functional classification	
I or II (%)	59 (56)
III or IV (%)	47 (44)
Medication	
Long-acting nitrates (%)	51 (48)
β blockers (%)	80 (75)
Calcium antagonist (%)	72 (68)
Acetylsalicylic acid (%)	88 (83)
Angiographic lesion location of dilated segments	
Left anterior descending	40%
Circumflex	30%
Right coronary artery	29%
Left main stem	1%

CCS = Canadian Cardiovascular Society; MI = myocardial infarction.

METHODS

Patients: The study population comprised 102 patients who underwent successful balloon angioplasty of 110 lesions and had quantitative coronary angiography performed before, immediately after, and 24 hours after angioplasty as part of a safety and efficacy trial of a new anticoagulant preparation, details of which are published elsewhere.[13] The study was performed in full accordance with the principles of the "Declaration of Helsinki," as well as specific local laws and regulations of each participating center. Before randomization, each patient gave written informed consent according to the requirements of the local institution.

Table I displays the source of the 102 patients assessed in this study. The aim of this study was to focus on luminal dimensional changes occurring during 24 hours, and assess the reliability of the angiogram immediately after angioplasty for quantitative analysis. Therefore, only patients with successfully dilated lesions and quantitative angiographic analysis both immediately after, and 24 hours after angioplasty were included in the study. Successful angioplasty was defined according to the conventionally applied method in clinical practice and trials[4,5] — a diameter stenosis <50% after angioplasty, as visually assessed by the interventionalist. Clinical outcome of the remaining 16 patients in the safety and efficacy trial, who were not included in this study, has been described elsewhere.[13] The patient population is, in general, demographically representative of modern clinical experience with coronary balloon angioplasty[4,5] in patients with stable angina (Table II). All patients had symptomatic obstructive coronary artery disease of at least 1 vessel, which was deemed suitable for treatment by angioplasty. The angioplasty procedure itself was performed according to the routine practice of the individual interventionalist.

Anticoagulation: Patients were randomly allocated to receive intravenous heparin or recombinant hirudin at doses sufficient to maintain activated partial thromboplastin time (monitored before, after, and 6, 12 and 24 hours after angioplasty) at 85 to 120 seconds for 24 hours. Dosage adjustments were made accordingly if levels were outside this target therapeutic range. Assays of prothrombin fragments F_1 and F_2, fibrinopeptide A, thrombin-antithrombin III complexes, anti-factor IIa and Xa activity, D-dimer, tissue-type plasminogen activator and plasminogen activator inhibitor antigen were performed. The collectively analyzed findings illustrated that, in general, thrombin generation was effectively inhibited by both anticoagulants throughout the 24-hour study period.[13] Thus, it would appear that the anticoagulant dosage regimens were adequate in each patient group.

Coronary angiographic procedures to facilitate quantitative analysis: Angiograms were carefully recorded according to the requirements of the computer-assisted Cardiovascular Angiographic Analysis System: (1) avoidance of projections in which the spine or other structures, or closely parallel or overlapping side-branches, obscure the vessel segment of interest; (2) filming of the lesion and segment of interest as close to the field center as possible, and in ≥2, preferably orthogonal, projections for the right coronary artery, and ≥3 projections (separated by ≥30°) for the left coronary artery, ideally at the end of a full inspiration; (3) vasomotion controlled by intracoronary nitrate (isosorbide dinitrate 1 to 3 mg or glycerol trinitrate 0.1 to 0.3 mg) before angiography, and before, immediately after, and 24 hours after balloon angioplasty; (4) to ensure exact comparability of angiographic measurements, angiography was performed in exactly similar projections (which are precisely recorded at each catheterization session) using a fixed-table approach before, immediately after, and 24 hours after angioplasty; (5) coronary arteries were optimally opacified using nonionic contrast which had been prewarmed to 37°C for ≥3 complete cardiac cycles; (6) guidewire and balloon catheter were removed before the final postangioplasty

TABLE III Quantitative Angiographic Measurements Before, Immediately After and 24 Hours After Angiography Given as Means of the Multiple Matched Projections ± SD

	Before	Immediately After	24 Hours After	Mean Diff. 24 Hours After (accuracy)	SD of Mean Diff. 24 Hours After (precision)	p Value of Mean Diff. (paired *t* test)
Minimal luminal diameter (mm)	1.03 ± 0.40	1.72 ± 0.36	1.72 ± 0.39	0.007	±0.20	0.74
Minimal luminal cross-sectional area (mm^2)	0.92 ± 0.85	2.57 ± 1.51	2.64 ± 1.53	0.07	±0.85	0.42
% area stenosis (%)	84.9 ± 10.3	57.9 ± 12.8	59.8 ± 14.1	1.9	±14.1	0.17
Lesion length (mm)	5.91 ± 1.95	5.71 ± 1.78	5.75 ± 1.79	0.05	±1.3	0.72
Lesion symmetry (ratio)	0.57 ± 0.20	0.50 ± 0.20	0.49 ± 0.18	−0.02	±0.20	0.37
Interpolated reference diameter (mm)*	2.67 ± 0.64	2.72 ± 0.58	2.83 ± 0.59	0.11	±0.18	<0.0001
% diameter stenosis (%)	60.6 ± 12.9	36.3 ± 7.9	38.7 ± 8.7	2.4	±7.0	0.0005
Reference area (mm^2)	5.95 ± 3.02	6.10 ± 2.73	6.61 ± 2.93	0.51	±0.84	<0.0001
Plaque area (mm^2)	6.40 ± 3.39	4.30 ± 2.35	4.92 ± 2.82	0.62	±1.48	<0.0001

*The interpolated reference diameter is the computer reconstruction of the original "disease-free" vessel dimensions over the analyzed segment. The actual diameter measurement taken as the reference diameter, and thus as the "vessel size," is the interpolated diametric measurement at the site of the most severe narrowing (minimal luminal diameter), thus providing an objective and user-independent estimation of the actual "normal" diameter at that site, in the absence of any disease.[15–17]
Diff. = difference.

TABLE IV Quantitative Angiographic Measurements from a Total of 308 Individual Projections, Identically Reproduced (matched) After Angioplasty and at 24 Hours

	After	24 Hours After	Mean Diff. 24 Hours After	p Value of Mean Diff.
Subsegmental lesion location (subsegment 1–6)*	2.44 ± 1.1	2.43 ± 1.2	−0.01 ± 0.73	0.75
Minimal luminal diameter (mm)	1.70 ± 0.40	1.71 ± 0.41	0.0008 ± 0.27	0.60
Minimal luminal cross-sectional area (mm^2)	2.45 ± 1.63	2.50 ± 1.63	0.05 ± 1.3	0.50
% area stenosis (%)	59.0 ± 18.4	61.3 ± 19.6	2.2 ± 21.2	0.07
Lesion length (mm)	5.72 ± 2.35	5.81 ± 2.42	0.09 ± 2.07	0.45
Lesion symmetry (ratio)	0.50 ± 0.27	0.49 ± 0.26	0.01 ± 0.31	0.70
Interpolated reference diameter (mm)	2.70 ± 0.60	2.82 ± 0.59	0.12 ± 0.29	<0.0001
Reference area (mm^2)	6.01 ± 2.81	6.55 ± 2.95	0.54 ± 1.35	<0.0001
% diameter stenosis (%)	36.5 ± 10.4	39.0 ± 11.0	2.5 ± 10.0	<0.0001
Plaque area (mm^2)	4.29 ± 2.92	4.91 ± 3.55	0.62 ± 2.49	<0.0001

*The Cardiovascular Angiographic Analysis System approach automatically subdivides the arterial segment to be analyzed (defined from side branch to side branch) into 6 subsegments of equal length; a minimal, mean and maximal diameter are determined (as well as a range of additional parameters) for each subsegment. The subsegmental location of the minimal luminal diameter within the arterial segment can thus be identified and compared over sequential analyses.
Values are expressed as mean ± SD.
Diff. = difference.

angiographic recordings; and (7) to enable accurate calibration, the contrast-empty angiographic catheter[14] (at least 7Fr) was filmed before each contrast injection and after the procedure, and the distal 20 cm of each catheter used was enclosed with the angiogram for micrometric measurement at the core laboratory.

Quantitative and qualitative angiographic analysis: In the core laboratory, quantitative angiographic analysis was performed by independent analysts without any knowledge of clinical details, using the Cardiovascular Angiographic Analysis System, which has been previously described in detail elsewhere.[15–17] To facilitate the provision of objective, reliable and reproducible measurements, end-diastolic cine-frames were selected for analysis from non- or minimally foreshortened pro-jections by 2 experienced observers. To confirm that each lesion was quantitatively analyzed in the same projections on the pre-, and post- and 24-hour angiograms, a Polaroid® print was made of each analysis. Absolute luminal measurements were obtained using the known diameter of the angiographic catheter.[14] Corrections were automatically made for so-called pincushion distortion, in nonisocentrically filmed catheter or target lesion positions. Comprehensive lesion measurements were provided, including minimal luminal diameter (MLD), interpolated reference diameter, lesion length, plaque area and percent diameter stenosis derived as: [(1 − MLD)/interpolated reference diameter] × 100%). In addition, videodensitometric measurements of minimal luminal cross-sectional area (MLCA), reference area and area stenosis were produced. In this study, the averaged values separately presented for each measurement parameter are means of the multiple projections filmed for each lesion and of the individual projections.

Statistical analysis: Since the focus of the study is on potential changes in lesion severity during the 24 hours after successful angioplasty, a lesion-specific approach was applied to evaluation of the results. Quantitatively measured and derived values are given as mean ± SD. Paired Student's *t* tests are used to compare angiographic measurements immediately after and 24 hours after angioplasty. Accuracy and precision of measurements obtained from the immediate postangioplasty angiogram are defined according to the method suggested by Bland and Altman,[18] i.e., accuracy is the mean difference between the measurement immediately after and 24 hours after angioplasty, and the precision (or measurement variability) is the standard deviation of this mean difference using the 24-hour measurement as the standard against which to compare the measurements obtained immediately after angioplasty. Linear regression analysis and Pearson's product moment correlation

coefficient are used to further evaluate the relation between these measurements.

RESULTS

Angiographically visible dissection was present in 31% of lesions immediately after successful angioplasty. Of these, 15% were type A, 9% type B and 7% type C dissections.

Table III shows that no significant change was observed in MLD or in MLCA immediately after or 24 hours after angioplasty. Because of the significant increase in reference diameter, a significant increase was also observed in percent diameter stenosis: from 36% immediately after to 39% 24 hours after angioplasty ($p = 0.0005$). Despite the significant increase in reference area, percent area stenosis did not change significantly during the 24-hour period, although a trend toward increase was observed. The increase in reference diameter was also responsible for the observed significant increase in plaque area, because the edge-detection algorithm calculates plaque area automatically from the reference diameter function and the actual detected arterial contours. There was no significant change in lesion length or symmetry immediately after to 24 hours after angioplasty.

The postangioplasty accuracy and precision of the MLD measurement was found to be <0.01 and ± 0.20 mm, respectively (Table III).

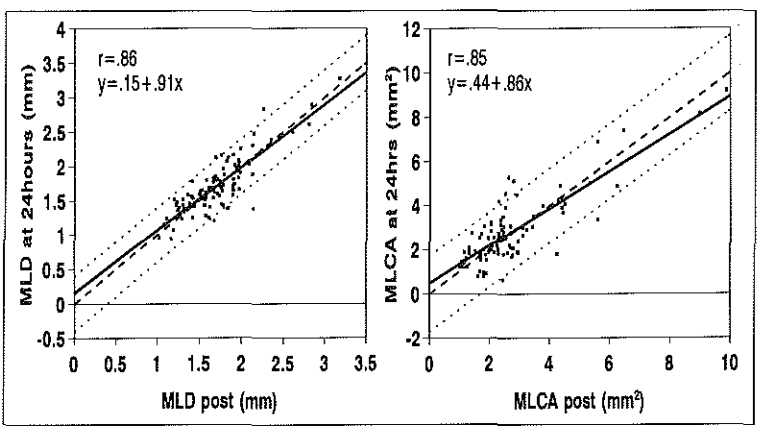

FIGURE 1. Linear regression analysis (y = a + bx) of minimal luminal diameter (MLD) and minimal luminal cross-sectional area (MLCA) after angioplasty and at 24 hours. r is Pearson's correlation coefficient. The identity line is the *dashed line* and the *parallel dotted lines* above and below are ± twice the measurement variability (i.e., 95% confidence limits for detecting a real change in MLD or MLCA from postangioplasty to 24 hours). The actual regression line is represented by the *bold line*. Excellent correlation between MLD and MLCA measurements from the postangioplasty and 24-hour angiograms is demonstrated. Only one clear "outlier" can be considered to have undergone significant deterioration in MLD (2 in MLCA) during the 24 hours.

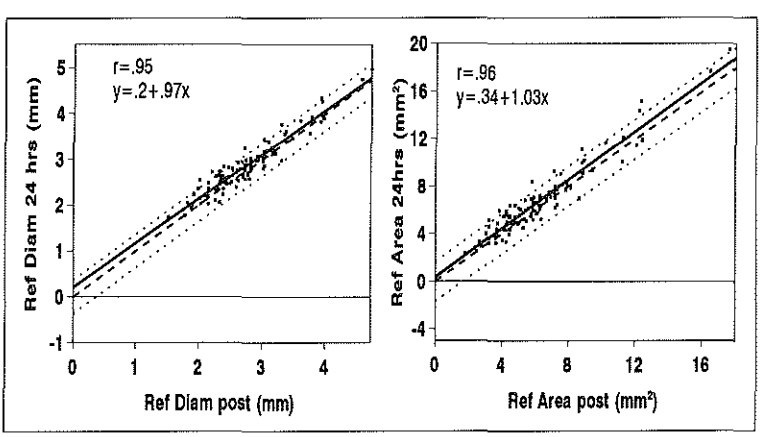

FIGURE 2. Linear regression analysis of reference diameter (Ref Diam) and area after angioplasty and at 24 hours. The format is the same as in Figure 1. Again excellent correlation is observed between measurements from the postangioplasty and 24-hour angiograms. However a systematic increase in dimensions is apparent from postangioplasty to 24 hours from the almost parallel course of the regression line above the identity line for both reference diameter and area.

Considering quantitative measurements obtained from each individual projection immediately after and 24 hours after angioplasty separate measurements, there were a total of 308 matched pairs of projections of the 110 lesions analyzed (Table IV), giving an average of 2.8 views per lesion. The subsegmental location of the MLD of the lesion did not vary during this time. Similar to the mean overall findings, there was no significant difference in MLD, MLCA, lesion length or symmetry immediately after angioplasty to 24 hours after angiography. A significant increase in reference diameter, reference area and percent diameter stenosis was observed, as well as a trend toward an increase in area stenosis, confirming the mean overall results.

The correlation between quantitative angiographic measurements immediately after and 24 hours after angioplasty was excellent for absolute luminal measurements of MLD and cross-sectional area (Figure 1), reference diameter and reference area (Figure 2). However, the correlation was not as good for the relative measurements of percent diameter and area stenoses (Figure 3).

Although 4 lesions had detectable deterioration (a statistically significant decrease from the time immediately after to 24 hours after angioplasty) in MLD (3 in the cross-sectional area), only 1 lesion had a clear deterioration in MLD (Figure 1, left) and 2 in MLCA (Figure 1, right) (from postangioplasty to 24 hours). No successfully dilated lesion was considered to require redilatation during or after the 24 hours.

DISCUSSION

In this study we have addressed the issues of reliability of the angiogram immediately after angioplasty for quantitative analysis and the occurrence of delayed elastic recoil in the first 24 hours after angioplasty by performing repeat angiography immediately after and 24 hours after angioplasty. To maximize objectivity in the evaluation of the occurrence of a real phenomenon, we attempted to perform the study under "ideal" angiographic conditions. Thus, the angiographic table height is kept constant at all stages and exactly the same angiographic projections are repeated for each individual patient at 24 hours as done immediately after angioplasty. In addition, to avoid the potentially confounding influence of vasomotion and thrombosis, intracoronary nitrate was administered before angiography, and all patients underwent complete anticoagulation for the 24-hour period.

Whether the mean of the multiple matched projections was considered or each projection was considered as a separate measurement, no change in MLD (measured by an edge detection approach) or in MLCA (measured by videodensitometry) was detected from immediately after to 24 hours after balloon angioplasty, which leads to the following interpretative statements.

1. There is no need for routine 24-hour angiography: After successful balloon angioplasty, immediate angiography is just as reliable a substrate for quantitative analysis as angiography at 24 hours. Thus, the presence of angiographically visible but nonocclusive dissection in 31% of lesions (similar to previous reports[10,11]) clearly does not unduly interfere with the quantitative analysis. A recent study, examining reliability of post-angioplasty angiography, stratified patients according to whether or not angiographic complications after angioplasty occurred, and found a significant difference in MLD (measured by a hand-tracing technique from magnified angiographic images) between post- and 24-hour angioplasty in the complicated versus uncomplicated groups.[11] Although apparently similar, that study and this present study are in fact difficult to compare overall since our study was intended to answer the question of whether routine repeat angiography is necessary at 24 hours in patients with successful balloon angioplasty, and the previous study examined the effect of angiographic complications on reliability of quantitative an-

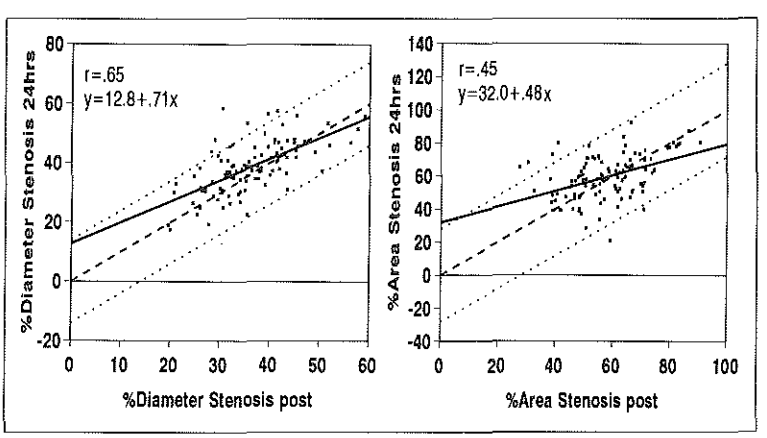

FIGURE 3. Linear regression analysis of percent diameter and area stenosis after angioplasty and at 24 hours. The format is the same as in Figure 1. Note the much greater degree of scatter of individual data points for these relative measurements compared with the absolute measurements shown in Figures 1 and 2. In addition, from the percent diameter stenosis display, it would appear that 6 lesions underwent significant early deterioration in lesion severity ("early restenosis"). This discrepancy with the absolute minimal luminal diameter measurements is due to the increase in reference diameter (Figure 2, left), as described in the text.

giography. Patients in whom balloon angioplasty was not satisfactorily successful, for whatever reason, need to be managed differently (perhaps including repeat angiography), and is not an issue in this report. In lesions without important angiographic complications, Preisack et al[11] also found no significant change in absolute minimal luminal dimensions during 24 hours, in general agreement with our findings and a previous report from Laarman et al.[19]

Thus, it must be concluded that the additional risk of patient morbidity (± mortality) prolonged hospitalization, as well as health care worker and specialist time, labor and cost involved in carrying out routine repeat 24-hour angiography would yield no extra information or benefit and is clearly not warranted.

2. Postangioplasty measurement variability is highly acceptable: The postballoon angioplasty lesion measurement accuracy of the Cardiovascular Angiographic Analysis System is <0.01 mm and the variability is ± 0.2 mm, which in our estimation is eminently acceptable. Twice this lesion measurement variability (± 0.4 mm) identifies (with 95% confidence) lesions in which a real, detectable ("significant") luminal decrease (or increase) occurs over time. Three times the variability (± 0.6 mm) will provide 99% confidence for the detection of a real change in luminal dimensions. Thus, in this study, 4 lesions showed a detectable deterioration during 24 hours (Figure 1, left). Although we do not advocate the application of a categorical approach to evaluating long-term angiographic outcome of interventions,[2] it may occasionally be desirable to stratify patients or lesions according to the degree of luminal change developing over time. To this end, the application of lesion measurement variability of the particular measurement system involved is recommended as the stratification method. Measurement variability may vary from system to system, and is a vital piece of information necessary for the purpose of objective comparison of the results of intervention trials using different angiographic measurement systems.

The measurement variability reported here is considerably different from that previously reported in patients undergoing diagnostic coronary angiography a mean of 90 days apart, without therapeutic intervention (0.72 mm).[16] The reasons for this difference need to be highlighted: In the original study published in 1985, mean vessel size was 3.7 mm, compared with 2.7 mm in this study (which is representative of current experience[4,5]). The former study was performed under a self-proclaimed "worst-case scenario," i.e., unmatched angiographic projections, no particular care taken in recording angiograms suitable for quantitative analysis, no vasomotor control, and so forth, whereas the current study was performed under ideal angiographic conditions, as outlined previously. Because such procedures are routinely performed in all important angiographic studies,[4,5] the lesion measurement variability previously reported is no longer relevant. It is worth noting, however, that the medium term measurement variability (obtained using vasomotion control and matched projections) previously reported was 0.20 mm,[16] exactly the same as found in this study. Recent experimental investigations of the accuracy and precision of off-line and on-line quantitative angiographic analysis (using digital and cineangiographic recording of swine "phantom" coronary stenoses of known dimensions) revealed a measurement accuracy of –0.07 mm and a precision of ± 0.2 mm (measured dimension of the phantom stenoses versus actual phantom dimension).[20] These findings are collectively indicative of the high level of accuracy and precision of the MLD measurement by the Cardiovascular Angiographic Analysis System, even in the aftermath of balloon angioplasty.

3. There is no delayed elastic recoil after successful angioplasty: Previous reports[12,21] that elastic recoil is an instantaneous phenomenon occurring immediately after balloon deflation and that no additional recoil occurs during the next 24 hours are confirmed. Nobuyoshi et al[22] previously reported a 16% incidence of "early restenosis" based on the measurement variability of their quantitative angiographic measurement system, in accordance with a significant decrease in MLD during 24 hours after successful angioplasty. In our patient group, only 4 lesions (3.6%) had a significant luminal decrease from postangioplasty to 24 hours. The reasons for this disagreement may lie in the methodologic and quantitative angiographic approaches. For example, intracoronary nitrate may not have been consistently administered before angiography by Nobuyoshi et al, who also used only a videodensitometric approach to estimate diameter, a method better suited to cross-sectional area measurements.[17,23] In addition, it is worth noting the apparent increase in MLD between 1 day and 1 month (almost to the level of the postangioplasty result), and the lack of correlation between the change within 24 hours and the long-term change at 6 months, which could not be explained. Either the reliability of their 24-hour measurements must be questioned, or the possibility of early mural thrombus formation with later resolution (since their patients were not anticoagulated for 24 hours) must also be considered as a possible explanation for the early luminal deterioration and subsequent improvement. According to biochemical and angiographic evidence, with adequate anticoagulation control in this study (having excluded patients with complicated angioplasty or major adverse cardiac events), there appeared to be no significant thrombus formation during the first 24 hours after successful balloon angioplasty.

4. Percent diameter stenosis is an unreliable measurement: The significant increase in interpolated reference diameter from postangioplasty to 24 hours is responsible for the observed increase in measured percent diameter stenosis. This finding reiterates conclusions of previous studies[24,25] regarding potential for misinformation by preferential use of percent diameter stenosis for description of the severity of luminal obstructions. Figures 1 to 3 further illustrate the imprecision of percent versus absolute measurement parameters.

The increase in reference vessel dimensions may be due to greater effectiveness of intracoronary nitrate at 24 hours on the relatively disease-free vessel segment. The vasoconstrictive stimulus of the dilatation procedure and the release of vasoactive substances from the damaged

endothelium and platelets may prevent immediate realization of dimensional increase in the relatively undiseased vessel adjacent to the target lesion.

Study limitations: Patients with unstable angina receiving intravenous heparin were excluded. It could be suggested that unstable lesions might "behave" differently during the 24 hours after successful angioplasty, since it is known that unstable angina predisposes to periprocedural and in-hospital major adverse cardiac events.[26] This limitation would need to be addressed by further study in "unstable" patients.

Perhaps the ideal test of accuracy and precision of quantitative angiography, according to current technology, would involve comparison with intravascular ultrasound findings.[7,8,27] However, it must be recognized that intravascular ultrasound is itself fraught by considerable limitations. It cannot be usefully applied to the evaluation of severe stenoses or to extremely tortuous or small vessels, which makes complete preinterventional assessment impossible in a large proportion of lesions treated in daily practice[8] (average MLD in recent "restenosis prevention trials" was approximately 1 mm[4,5]). Furthermore, "good" quality images may not be obtainable in certain clinical situations, such as the presence of intimal disruptions after angioplasty.[28] Until the vessel wall and lumen areas are more objectively and reproducibly quantifiable by intravascular ultrasound, quantitative angiography must still be considered as the "gold standard."

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CHAPTER 6

USEFULNESS OF QUANTITATIVE AND QUALITATIVE ANGIOGRAPHIC LESION MORPHOLOGY AND CLINICAL CHARACTERISTICS IN PREDICTING MAJOR ADVERSE CARDIAC EVENTS DURING AND AFTER NATIVE CORONARY BALLOON ANGIOPLASTY.

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AM J CARDIOL 1993;72:14-20.

Usefulness of Quantitative and Qualitative Angiographic Lesion Morphology, and Clinical Characteristics in Predicting Major Adverse Cardiac Events During and After Native Coronary Balloon Angioplasty

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Major, adverse cardiac events (death, myocardial infarction, bypass surgery and reintervention) occur in 4 to 7% of all patients undergoing coronary balloon angioplasty. Prospectively collected clinical data, and angiographic quantitative and qualitative lesion morphologic assessment and procedural factors were examined to determine whether the occurrence of these events could be predicted. Of 1,442 patients undergoing balloon angioplasty for native primary coronary disease in 2 European multicenter trials, 69 had major, adverse cardiac procedural or in-hospital complications after ≥1 balloon inflation and were randomly matched with patients who completed an uncomplicated in-hospital course after successful angioplasty. No quantitative angiographic variable was associated with major adverse cardiac events in univariate and multivariate analyses. Univariate analysis showed that major adverse cardiac events were associated with the following preprocedural variables: (1) unstable angina (odds ratio [OR] 3.11; p <0.0001), (2) type C lesion (OR 2.53; p <0.004), (3) lesion location at a bend >45° (OR 2.34; p <0.004), and (4) stenosis located in the middle segment of the artery dilated (OR 1.88; p <0.03); and with the following postprocedural variable: angiographically visible dissection (OR 5.39; p <0.0001). Multivariate logistic analysis was performed to identify variables independently correlated with the occurrence of major adverse cardiac events. The preprocedural multivariate model entered unstable angina (OR 3.77; p <0.0003), lesions located at a bend >45° (OR 2.87; p <0.0005), and stenosis located in the middle portion of the artery dilated (OR 1.95; p <0.04). If all variables were included, then angiographically visible dissection (OR 6.58; p <0.0001), unstable angina (OR 3.46; p <0.002) and lesions located at a bend >45° (OR 2.54; p <0.006) were independent predictors of major adverse cardiac events.

(Am J Cardiol 1993;72:14–20)

In the initial "National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry" publication, which described the immediate results of patients treated by balloon angioplasty, major adverse cardiac events (i.e., death, myocardial infarction, coronary artery bypass grafting and repeat dilatation) were reported in 13.6% of patients.[1] Because of improvement in operator experience, as well as radiographic equipment and balloon catheter design over the succeeding 5 years, this percentage decreased to 4 to 7%, despite extension of the indications for coronary balloon angioplasty to include patients aged >70 years, and those with multivessel disease or poor left ventricular function, prior bypass surgery, and more severe and complex lesions.[2–6] Many clinical factors such as multivessel disease, female gender, unstable angina and multiple lesions, as well as qualitative angiographic lesion morphology, including eccentricity, presence of calcium, lesion length, stenosis at a bend, stenosis at a branch point, presence of thrombus, and complex lesions, have been suggested to be predictors of a major procedural or in-hospital cardiac event.[3–9] Previous studies used visual interpretation of the coronary angiogram, which is now known to be limited by considerable inter- and intraobserver variability.[10–12] Thus, quantitative coronary angiographic systems are now the "gold standard" for objective geometric assessment of coronary narrowings, and for assessing the short- and long-term results of interventions.[13,14] In addition to the actual degree of lumen narrowing, these quantitative coronary

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systems can also provide detailed lesion morphologic characteristics such as lesion length, atherosclerotic plaque area, lesion eccentricity and vessel curvature.[13] The present study investigated whether comprehensive evaluation of lesion morphology by quantitative coronary analysis, in addition to conventional qualitative assessment, and inclusion of baseline, clinical characteristics and procedural details, could identify patients at particularly high risk for major procedural or in-hospital adverse cardiac events. The identification of risk factors for the occurrence of these complications may be of considerable clinical value in deciding which patients or lesions would be suitable for an alternative treatment to balloon angioplasty.

METHODS

In all, 1,442 patients were enrolled in 2 randomized, double-blind, placebo-controlled, restenosis prevention trials (CARPORT [n = 707] and MERCATOR [n = 735]) between December 1987 and June 1990. Neither trial (described in detail previously) found any clinical or angiographic benefit from the agent under investigation.[15,16] For the purpose of this ancillary study, the patient cohort comprised those who had major procedural or in-hospital complications (as previously defined) after ≥1 balloon inflation, regardless of the final result of balloon angioplasty (group I; n = 69). Each patient in group I was randomly matched with 3 control patients by the date of angioplasty (to the nearest week in the same hospital) (group II; n = 207) to assess the predictability of major adverse cardiac events. In cases of multilesion dilatation, the most severe lesion was selected and used for comparison. Each available cineangiogram was separately reviewed by 2 experienced interventionalists who were unaware of clinical or procedural information, or the outcome of intervention.

Percutaneous transluminal coronary angioplasty procedure and angiographic analysis: At the beginning of the angioplasty procedure, all patients received a bolus of 10,000 IU of intravenous heparin; for prolonged procedures, an additional infusion of 5,000 IU/hour was commenced after 2 hours and continued until the end of the procedure. Aspirin was routinely administered to all patients in the MERCATOR trial and to those randomized to placebo in the CARPORT trial.[15,16] Use of a calcium antagonist was permitted for 24 to 48 hours after coronary balloon angioplasty. The choices of guiding catheter, guide wire, balloon type, inflation duration and pressure were made by the operator. Primary angioplasty success was defined at the time the guide catheter was removed as diameter stenosis <50% by visual estimation, without the occurrence of a major adverse cardiac event.

At least 2 angiographic projections (orthogonal if possible) were recorded in such a way that they were suitable for quantitative analysis by the Coronary Angiography Analysis System, which was validated and described in detail previously.[13] An example of an analysis is shown in Figure 1.

The absolute stenosis and reference diameters were measured by the computer using the known contrast-empty, guiding catheter diameter as a scaling device. For that purpose, the catheter tips were retained for accurate measurement with a micrometer. To achieve maximal coronary vasodilation, either nitroglycerin (0.1 to 0.3 mg) or isosorbide dinitrate (1 to 3 mg) was administered (intracoronary) to each affected coronary artery before angiography. All contour positions of the catheter and arterial segment were corrected for "pincushion distortion" introduced by the image intensifiers. Because the algorithm cannot measure total occlusions or lesions with Thrombolysis in Myocardial Infarction grade 1 perfusion, a value of 0 mm was substituted for the minimal lumen diameter and 100% for percent diameter stenosis in such cases.

Variables used in the analysis: BASELINE CLINICAL CHARACTERISTICS: The following patient-related variables were recorded in the patient files: age, gender, duration of angina, cholesterol level, previous myocardial infarction, current smoking, diabetes mellitus, extent of atherosclerotic disease (single or multivessel), Canadian Cardiovascular Society angina classification, and unstable angina (defined as pain at rest needing treatment with intravenous nitrates).[17]

QUALITATIVE ANGIOGRAPHIC CHARACTERISTICS: The following qualitative lesion parameters were assessed: (1) vessel dilated (right, left anterior descending or left circumflex); and (2) location of the stenosis in the vessel dilated, according to the numeric scheme proposed by Austen et al.[18] The following subdivisions were used for location of the stenosis: proximal corresponding with segments 1, 6 and 11; middle corresponding with segments 2, 7, 13 and 15; distal corresponding with seg-

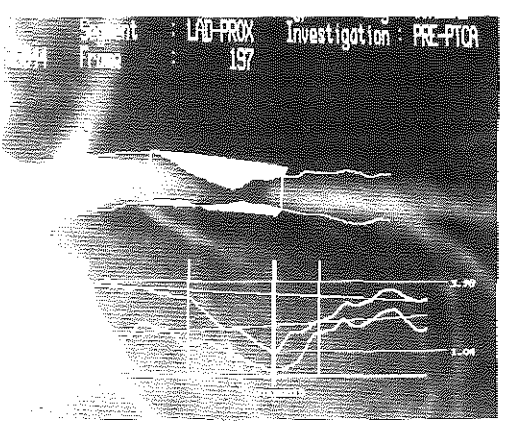

FIGURE 1. Single-frame angiogram of proximal left anterior descending (LAD) artery stenosis before dilatation in right anterior oblique (30°) projection. Quantitative coronary analysis was performed using Cardiovascular Angiography Analysis System. Arterial boundaries automatically detected by system are shown on angiogram, and diameter function curve derived from these contours by interpolating is shown in *middle part of figure (upper curve)*. *Lower horizontal line* (1.04 mm) is minimal lumen diameter. *Outside vertical lines on graph,* and *2 vertical lines* on angiogram are lesion boundaries (lesion length 8.6 mm). *Innermost vertical line* is position of minimal luminal diameter, and point where this line intersects diameter function curve *(upper horizontal line)* is considered reference diameter (3.25 mm; value not shown). Lesion length is automatically determined by curvature analysis of detected vessel contours.

ments 8 to 10, 12 and 14; (3) type of lesion, defined by a modified Ambrose classification, as follows: concentric, eccentric (a stenosis asymmetrically positioned in the vessel in any nonforeshortened angiographic projection), tandem (2 discrete lesions in the same coronary segment separated by an apparently normal segment), multiple irregularities (≥2 serial diffuse irregularities in the same coronary segment), and totally occluded vessel[19]; (4) a bend >45° was considered present if in any nonforeshortened projection, the balloon in position to dilate was located in a portion of the vessel with a ≥45° angulation at end-diastole[20]; (5) presence of a side branch in the lesion to be dilated; (6) presence of a side branch, separate from the actual lesion but within the dilated segment; (7) presence of intracoronary thrombus (a noncalcified filling defect within the lumen, surrounded by contrast material observed in multiple projections or the persistence of contrast material within the lumen, or a visible embolization of intraluminal material "downstream")[21]; (8) presence of calcification (defined as fixed radiopaque densities in the area of the stenosis to be dilated); and (9) type of lesion (A, B or C) according to the American College of Cardiology/American Heart Association Task Force.[22]

QUANTITATIVELY ANGIOGRAPHIC CHARACTERISTICS: The following quantitative measurements were obtained: minimal lumen and interpolated reference diameters, diameter stenosis, lesion length and eccentricity, atherosclerotic plaque area and vessel curvature (Figure 2).

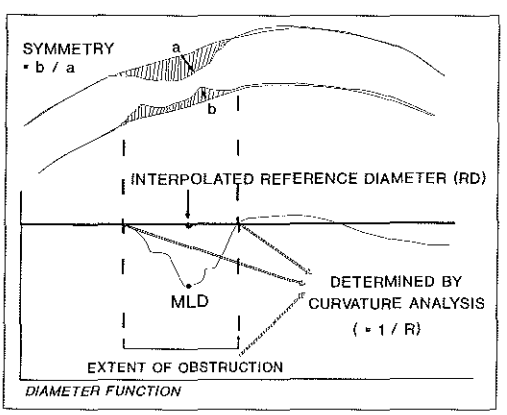

FIGURE 2. Area between actual and reconstructed contours at obstruction site is measure of amount of atherosclerotic plaque. Length of obstruction is determined from diameter function on basis of automatically detected curvature analysis without interference by analyst. Symmetry is defined as coefficient of left- and right-hand distance between reconstructed interpolated reference diameter and actual vessel contours at site of obstruction. In this equation, largest distance between actual and reconstructed contours becomes denominator, so that symmetrical lesion has value of 1, and a severely eccentric lesion has value of 0. To assess extent of coronary bending, curvature value at obstruction site is computed as average value of all individual curvature values along centerline of coronary segment, with curvature defined by rate of change of angle through which tangent to curve turns in moving along curve, and which for circle is equal to reciprocal of radius. Curvature value and symmetry index are determined in projection in least foreshortened view (in which analyzed segment was longest between 2 defined landmarks and is expressed as continuous integer value, ranging from 0 for straight segment to 90 for segment with 90° bend). MLD = minimal lumen diameter.

PROCEDURAL FACTORS: Balloon-artery ratio was used to assess the suitability of the balloon size for the vessel segment, and was defined as the ratio between the measured mean balloon size and the (interpolated) reference diameter of the dilated segment. Angiographically visible dissections were defined according to modified National Heart, Lung, and Blood Institute criteria.[22]

Reproducibility of morphologic assessment: Interobserver variability of the 2 reviewers for qualitative lesion assessment was examined in an arbitrarily selected number of lesions. The coronary angioplasty films of 138 patients with 151 lesions (consecutive films reaching the core laboratory) were independently assessed for the diverse lesion morphologic characteristics by each observer on 2 separate occasions, 3 months apart, with blinding for earlier assessment. Interobserver discordance was as follows: lesion eccentricity 21%; branch point location 29%; branch point location in dilated segment 19%; bend point location 14%; presence of thrombus 2%; presence of calcification 10%; presence of dissection 11%; and lesion type according to the American College of Cardiology/American Heart Association Task Force classification 25%.

Statistical analysis: Analyses were performed to test the hypothesis that clinical, qualitative and quantitative lesion morphologic and procedural characteristics are important determinants of major adverse cardiac events. The risk of major cardiac adverse events for each variable was expressed as an odds ratio: (probability of an event variable present/probability of no event variable present)/(probability of an event variable absent/probability of no event variable absent).

Continuous variables were dichotomized by cut points derived by dividing the data into 2 groups, each containing approximately 50% of the population. This method of subdivision has the advantage of being consistent for all variables and thus avoids any bias in selection of subgroups, which may be performed to emphasize a particular point. An odds ratio (OR) of 1 for a particular variable suggests that its presence poses no additional risk for a major event. An OR > or <1 suggests additional or reduced risk, respectively. The 95% confidence intervals (CI) were calculated to describe the statistical certainty. If the CI included 1, no significant increased or reduced risk was deemed to be conferred by the variable. Multivariate analysis by multiple logistic regression was performed to identify variables independently correlated with the occurrence of a major cardiac, procedural or in-hospital adverse event, using only those variables significant at the $p < 0.1$ level in the univariate analysis. All statistical analyses were performed with a commercial statistical package (BMDP Statistical Software Package 1990).

RESULTS

Of 1,442 patients recruited, balloon angioplasty was not performed in 9 patients, because the lesion severity had changed or because of equipment failure. A further 43 patients had (sub)totally occluded lesions that could

TABLE I Clinical Variables and the Risk for a Major Procedural or In-Hospital Adverse Cardiac Event

Variable	Patient Positive for Variable (event/total)	Patient Negative for Variable (event/total)	Odds Ratio (95% CI)
Myocardial infarction (history)	23/107	46/169	0.73 (0.41 to 1.30)
Currently smoking	10/45	59/231	0.83 (0.39 to 1.79)
Multivessel coronary narrowing	29/117	39/146	0.89 (0.51 to 1.51)
Diabetes mellitus	6/25	63/251	0.94 (0.36 to 2.46)
Age (<58 years)	35/136	34/140	1.08 (0.63 to 1.86)
Duration of angina (>142 days)	35/137	31/135	1.15 (0.66 to 2.01)
Total cholesterol (<6.2 mmol/L; <240 mg/dl)	34/129	27/132	1.39 (0.78 to 2.48)
Canadian Cardiovascular Society class III or IV	47/169	21/100	1.45 (0.81 to 2.61)
Men	59/221	10/55	1.64 (0.78 to 3.46)
Unstable angina	29/69	39/206	3.11 (1.72 to 5.61)

CI = confidence interval.

TABLE II Lesion and Procedural Variables, and the Risk for a Major Procedural or In-Hospital Adverse Cardiac Event

Variable	Patient Positive for Variable (event/total)	Patient Negative for Variable (event/total)	Odds Ratio (95% CI)
Coronary artery dilated			
Right	15/67	54/209	0.83 (0.43 to 1.59)
Left circumflex	17/72	52/204	0.90 (0.48 to 1.69)
Left anterior descending	37/137	32/139	1.24 (0.72 to 2.14)
Multiple site dilated	12/45	57/231	1.11 (0.54 to 2.29)
Total occlusion	8/24	61/252	1.57 (0.64 to 3.84)
Middle portion of vessel dilated	36/112	33/164	1.88 (1.08 to 3.26)
Lesion morphology quantitatively derived before angioplasty			
Symmetry index (<0.34)*	30/121	32/131	1.00 (0.56 to 1.77)
Minimal lumen diameter (>0.98 mm)	35/139	34/137	1.02 (0.59 to 1.76)
Diameter stenosis (<62%)	35/136	34/140	1.08 (0.63 to 1.86)
Length lesion (>5.8 mm)*	32/127	29/125	1.12 (0.63 to 1.99)
Vessel size (>2.53 mm)	37/140	30/134	1.25 (0.72 to 2.17)
Atherosclerotic plaque (>6.1 mm^2)*	35/127	26/125	1.45 (0.81 to 2.59)
Curvature index (>19)*	37/128	24/124	1.69 (0.94 to 3.05)
Lesion morphology; qualitative assessment			
Side branch in area of balloon	46/186	20/80	0.99 (0.54 to 1.81)
Calcified lesion	9/33	57/233	1.16 (0.51 to 2.63)
Side branch in stenosis	38/144	28/122	1.20 (0.69 to 2.11)
Eccentric located stenosis	36/130	30/136	1.31 (0.75 to 2.28)
Bend >45°	31/86	35/180	2.34 (1.31 to 4.15)
Type C lesion	19/46	47/220	2.53 (1.32 to 4.86)
Procedural variables			
Balloon–artery ratio (>1.02)	17/110	16/105	1.02 (0.48 to 2.14)
Thrombus after dilatation	4/7	62/259	4.31 (0.94 to 19.80)
Intimal tear or dissection	47/111	19/155	5.39 (2.90 to 10.00)

*Although 276 lesions were analyzed in total, some could not be analyzed for certain variables.
CI = confidence interval.

be neither reached nor crossed with the guide wire or balloon catheter. Thus, of 1,390 patients in whom balloon dilatation was actually performed, 69 had a major adverse cardiac event. Myocardial infarction occurred during or shortly after the procedure in 15 patients (1%) and during the hospital stay in an additional 22 (1.5%). Emergency coronary bypass graft surgery was necessary immediately after unsuccessful coronary balloon angioplasty in 18 patients (1.3%), and the indication for surgery occurred after leaving the catheterization laboratory in a further 9 (1%). In 5 patients, a redilatation was performed during the hospital stay. No patient died during the procedure or hospital stay.

Clinical characteristics as predictors of major adverse cardiac events (Table I): Patients with unstable angina had more coronary events than did those without unstable angina (OR 3.11; p <0.0001; 95% CI 1.72 to 5.61). Age, gender, duration of angina, serum cholesterol, history of myocardial infarction, diabetes mellitus, multivessel disease and Canadian Cardiovascular Society angina class did not influence the occurrence of a major adverse cardiac event.

Angiographic lesion characteristics as predictors of major adverse cardiac events (Table II): Location of the target lesion in the middle segment of the coronary artery dilated (OR 1.88; p <0.03; 95% CI 1.08 to

3.26), lesions located at a bend >45° (OR 2.34; p <0.004; 95% CI 1.31 to 4.15), and type C lesions (OR 2.53; p <0.004; 95% CI 1.32 to 4.86) were significantly associated with the occurrence of major adverse cardiac events; no other lesion morphologic characteristic (whether assessed qualitatively or by quantitative analysis) predicted subsequent development of these events.

Procedural predictors of major adverse cardiac events: The presence of any type of angiographically visible dissection after the procedure was strongly associated with the subsequent occurrence of a major adverse cardiac event (OR 5.39; p <0.0001; 95% CI 2.9 to 10.0). Neither thrombus after dilatation nor balloon-artery ratio was found to be predictive of major adverse cardiac events (Table II).

Logistic regression analysis: In considering only baseline preprocedural factors, the model entered unstable angina (OR 3.77; p <0.0003; 95% CI 1.89 to 7.48), lesions located at a bend >45° (OR 2.87; p <0.0005; 95% CI 1.47 to 5.59), and stenosis located in the middle portion of the artery dilated (OR 1.95; p <0.04; 95% CI 1.01 to 2.74). When postprocedural variables were added, then unstable angina (OR 3.46; p <0.002; 95% CI 1.67 to 7.17), lesions located at a bend >45° (OR 2.54; p <0.006; 95% CI 1.26 to 5.13), and angiographically visible dissection (OR 6.58; p <0.0001; 95% CI 3.17 to 13.7) were independent predictors of major adverse cardiac events.

DISCUSSION

Despite the improvements in equipment and technique that have made it possible to dilate >90 to 95% of coronary obstructions, the occurrence of procedural and in-hospital cardiac adverse events due to acute or subacute vessel closure continues to be largely unpredictable. The reported frequency of so-called major cardiac adverse events depends on the time window applied — after the patient left the catheterization laboratory 1 to 2%, or during and after the procedure 4 to 7%. In the present study, major adverse cardiac events were observed in 33 of 1,390 patients (2.4%) after ≥1 balloon inflation in the catheterization room and in a further 36 (2.6%) during the hospitalization period.

Risk factors of major procedural and in-hospital adverse cardiac events: In 1988, Ellis et al[3] reported the results of 4,772 procedures performed between April 1, 1982 and March 31, 1986, and found (using multivariate analysis) 7 independent preprocedural factors related to abrupt vessel closure: stenosis length ≥2 lumen diameters, female gender, stenosis at a bend point ≥45°, stenosis at a branch point, stenosis-associated thrombus (filling defect or staining), other stenoses in the same vessel, and multivessel disease. They concluded that although an estimation of risk can be obtained before performing coronary balloon angioplasty, the most powerful predictors of closure can only be assessed during the procedure (postangioplasty percent diameter stenosis, intimal tear or dissection, and prolonged postangioplasty use of heparin). The 1985–1986 National, Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry study analyzed 1,801 patients, and revealed that baseline factors inherently associated with increased occlusion rates included 3-vessel disease, high-risk status for surgery, and acute coronary insufficiency, and lesion characteristics included severe stenosis before coronary angioplasty, diffuse disease or multiple discrete lesions, thrombus and collateral flow from the lesion. De Feyter et al[5] reported an acute coronary artery occlusion rate of 7.3% (total population 1,423), with unstable angina, multivessel disease and complex lesions as predictors for closure during or after the procedure.

In all the aforementioned studies that involved large groups of patients, lesion characteristics were visually assessed. No data are available on the predictability of major cardiac complications from quantitative coronary analysis, which has now emerged as the gold standard for assessment of long-term angiographic outcome of percutaneous transluminal coronary interventions.[15,16] In addition to the "simple" quantitative parameters of minimal lumen (obstruction) diameter, reference diameter (or vessel size) and percent diameter stenosis, quantitative analysis computes length of the obstruction, area of atherosclerotic plaque, symmetry index of the stenosis, and curvature of the vessel. In the present study, quantitative coronary analysis was combined with assessment of qualitative lesion morphology and clinical characteristics to determine whether this thorough, integrated approach could improve the prediction of major adverse cardiac events.

The present results are in agreement with those of the earlier published studies showing that unstable angina, lesions located at a bend >45°, and angiographically visible dissection after angioplasty were independent predictors of major procedural or in-hospital cardiac events. Lesion morphology as assessed by quantitative coronary analysis was not useful for the prediction of major adverse cardiac events.

The well-described association of unstable angina with the occurrence of major adverse cardiac events was confirmed in this study. Patients presenting with the clinical syndrome of unstable angina continue to provide the clinician with the difficult task of selecting a suitable management strategy that usually needs to be applied on an urgent basis. The increasing use of intracoronary angioscopy may be helpful in substratifying these patients and therefore guiding therapeutic strategies that may improve short- and long-term outcome.[23]

The location of the target lesion in a bend >45° was previously identified by Ellis et al[3] as a risk factor for acute vessel closure. Their explanation was that the balloon must necessarily tear an atherosclerotic fixed and rigid bend lesion, as it straightens and stretches the lesion. In addition, the maximal stress is several times greater when there is a geometric discontinuity in the object to which the stress is applied.

The association of midsegment balloon dilatation with a greater risk of major adverse cardiac events is not readily explicable and could simply be a chance finding.

The most powerful predictor for major adverse cardiac events is the occurrence of an angiographically visible dissection after angioplasty, which is not surprising

because all patients with procedural events had a dissection with flow limitation on their postdilatation angiogram, in agreement with previous reports.[3,9]

Other investigators have found that thrombus on the predilatation angiogram was predictive for a major adverse cardiac event.[3–5] However, thrombus was seldom observed on the predilatation angiogram in the present study, although unstable angina, in which the presence of intracoronary thrombus is frequently observed,[23,24] was a risk factor for a major adverse cardiac event. In this study, patients with unstable angina were aggressively treated with intravenous heparin that may have effectively dealt with intracoronary thrombus in some cases. Therefore, thrombus was not a remarkable angiographic feature in the study.

In contrast with Black et al,[9] the balloon-artery ratio was not a factor for predicting major adverse cardiac events in the present study, although there was a difference in definition. Because of such previously published findings, many investigators may have carefully ensured appropriate matching of balloon with artery size.

From the literature, one would expect that dilation of type C lesions would be a risk factor for a major adverse cardiac event, because it is associated with a <60% acute success rate according to the American College of Cardiology/American Heart Association Task Force.[22] However, a recent study of 1,000 lesions by Myler et al[25] reported an angioplasty success rate of 90% for type C lesions, which was only slightly less than that for type A and B. In the present study, type C lesions were predictive of major adverse cardiac events in univariate but not multivariate analysis. The relatively high discordance between observers suggests that the use of this subjective evaluation should be cautiously interpreted.[26]

Study limitations: The study cohort of this retrospective analysis comprised patients recruited for 2 multicenter, restenosis, pharmacologic prevention trials in Europe. Although in both trials, consecutive patients of the participating clinics were recruited, only 25% of those undergoing angioplasty were recruited, because ≥1 specific exclusion criterion was found.[15,16]

In the CARPORT trial, patients treated with the new thromboxane A2-receptor blockade did not receive aspirin before or during the angioplasty procedure, but all others did; this may have influenced the incidence of major adverse cardiac events.[27]

Although the Cardiovascular Angiography Analysis System has been validated and extensively described in the literature, validation studies of quantitatively derived, lesion morphologic characteristics such as lesion length and eccentricity, and vessel curvature have not been performed.[13]

Coronary angiography, as a 2-dimensional silhouette of the vessel lumen, is inherently limited for the assessment of atherosclerotic plaque morphology, as has been increasingly demonstrated by intravascular ultrasound techniques.[28] Furthermore, the use of objective quantitative analysis does not provide insight to the prediction of major adverse cardiac events from angiographic measurements and lesion morphology. Newer and more sophisticated quantitative analysis systems may be more helpful in this regard[29]; however, the combined use of intracoronary angioscopy and ultrasound is more likely to shed new light on the continued unpredictability of major adverse cardiac events after coronary interventions.

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CHAPTER 7

THE INFLUENCE OF CORONARY VESSEL SIZE ON LUMINAL RENARROWING AND LATE ANGIOGRAPHIC OUTCOME AFTER SUCCESSFUL BALLOON ANGIOPLASTY.

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CIRCULATION 1994;90:1239-51.

Influence of Coronary Vessel Size on Renarrowing Process and Late Angiographic Outcome After Successful Balloon Angioplasty

David P. Foley, MB BCh, MRCPI; Rein Melkert, MD; Patrick W. Serruys, MD, PhD, FACC, on behalf of the CARPORT, MERCATOR, MARCATOR, and PARK Investigators

Background Although coronary angioplasty is increasingly applied in the treatment of multivessel disease and a broadening range of vessel size, the influence of vessel size itself on the late results of intervention is unresolved. An influence of vessel size on late outcome would carry implications for the application and evaluation of interventional devices, which are selectively used in larger or smaller vessels. The purpose of the present study was to investigate the influence of vessel size on both the restenosis process and late angiographic outcome in a large homogeneous patient group after successful percutaneous transluminal coronary angioplasty (PTCA).

Methods and Results The study population comprised 3072 patients with 3736 successfully dilated native primary coronary artery lesions and satisfactory quantitative angiographic analysis in multiple identical projections before and after PTCA and at a 6-month follow-up. Late luminal loss, minimal luminal diameter (MLD) at follow-up, and net luminal gain, as well as percent diameter stenosis at follow-up, net gain in percent diameter stenosis, restenosis rates (according to three definitions), and net gain index, were all compared among nine equally sized groups (noniles) according to vessel size. A direct influence of vessel size on continuous measures of late result was also evaluated by linear regression. These evaluations provided conflicting information with no consistent influence of vessel size emerging. To elucidate the independent influence of vessel size on the restenosis process (late loss) and late angiographic outcome (MLD at follow-up), multiple linear regression analysis was performed taking into account luminal gain, preprocedural MLD, and lesion location. In this manner, vessel size was found to be exert a significantly positive influence on MLD at follow-up ($P<.0001$) and an equally negative effect on loss. Correcting for vessel size by using percent stenosis measurements led to an anticipated neutralization of this influence. Lesion location in the left anterior descending coronary artery was found to be independently associated with greater loss and smaller MLD at follow-up ($P<.0001$).

Conclusions Increasing coronary vessel size was found to be independently predictive of decreasing late luminal loss and increasing follow-up MLD after successful balloon angioplasty. Apparently superior or inferior late angiographic results of new interventional devices may thus be explained in part by preferential use in larger or smaller vessels, respectively. Devices that can safely optimize the short-term result of intervention may realize their ultimate long-term value in larger coronary vessels. (***Circulation*. 1994;90:1239-1251.**)

Key Words • quantitative angiography • angioplasty • restenosis

Although it is becoming generally appreciated that safe maximization of the short-term result of transluminal coronary intervention is the optimal practical approach to augment late outcome,[1-11] increasing intervention in multivessel disease and in a broadening range of vessel size raises the issue of whether the size of the vessel itself influences late results. Lower restenosis rates have been reported in larger vessels following balloon angioplasty and other devices in some studies[2,3] but not in others.[1,12-15] Larger vessel size has been reported to predict greater minimal luminal diameter (MLD) at follow-up, as a measure of late outcome, in patients treated by directional atherectomy or stent implantation.[3,9] On the other hand, luminal loss, as a measure of the restenosis process, has not been found to vary with vessel size.[3,7,9,15-17] Thus, the influence of vessel size on the restenosis process and late angiographic outcome after successful angioplasty is unresolved. A significant influence of vessel size on late results would carry implications for selection of patients and lesions for intervention as well as for the use of new devices for intervention. For example, the reported superiority of stent implantation and directional atherectomy over conventional balloon angioplasty[4-6] might be related to their general application to larger vessels. Similarly, the use of excimer laser angioplasty and rotational atherectomy in smaller vessels might explain in part the somewhat discouraging late results associated with these devices.[18,19]

The purpose of the present study was to comprehensively investigate the influence of vessel size on both the restenosis process (luminal loss) and the angiographic outcome (follow-up luminal diameter)[9,20] after successful balloon angioplasty in a large homogeneous patient population with serial quantitative angiography before and after angioplasty and at a 6-month follow-up.

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Methods

The study population comprised 3072 patients with 3736 native coronary arterial lesions successfully treated by balloon angioplasty (percutaneous transluminal coronary angioplasty [PTCA]) (postprocedural diameter stenosis <50%) during four major multicenter pharmacological restenosis prevention trials. Details of the trials have been presented or published.[21-24] In each of these trials, the agent under investigation was found to have no significant effect on either clinical or angiographic outcome by either univariate and multivariate analysis, so, for the purposes of the present study, all the patients were pooled and considered as one group. Angiographic follow-up with comprehensive automated quantitative analysis performed by independent blinded analysts in an off-line core laboratory was performed on a total of 93.4% of the study population. With the aim of evaluating the biological process of restenosis from the quantitative angiographic perspective, homogeneity of the population was a legitimate prime concern. Because there is an inevitable contribution of thrombosis to coronary occlusion after angioplasty and occluded lesions at baseline may behave differently during and after angioplasty,[25,26] 264 lesions that were occluded at baseline and an additional 167 that became occluded during follow-up were excluded for the study, as well as three left main lesions.

Quantitative Angiographic Methodology

Standardization of Image Acquisition by Investigators

Coronary angiography, before and after angioplasty and at follow-up after 26±2 weeks, was recorded for quantitative analysis using the Cardiovascular Angiographic Analysis System (CAAS) (PIE Medical) at the angiographic core laboratory. All investigators were given specific guidelines by the core laboratory to standardize angiographic acquisition and ensure reproducibility of quantitative analysis, as previously described.[27,28] The most important features of standardization of image acquisition are, first, use of multiple projections for each lesion, identically repeated before and after angioplasty and at follow-up angiography ("multiple matched projections"); second, use of 0.1 to 0.3 mg nitroglycerin IC or 1 to 3 mg isosorbide dinitrate IC before each set of angiographic recordings to control vasomotor tone; and, third, recording of the contrast-free angiographic catheter tip[27,29] immediately before each contrast injection and enclosure of the cleaned tip (distal 10 cm) of each catheter with the cinefilm to facilitate later calibration during analysis at the core laboratory.

Quantitative Analysis

The procedural and technical details of quantitative analysis using CAAS have been well described elsewhere.[28,30-32] The important standardized features of the specific core laboratory approach used are as follows: selection of cineframes for analysis by independent panel assessment based on frames selected by the investigator and taking into account the requirement of absence of overlapping side branches and clarity of luminal contours in nonforeshortened projections at end diastole. For each analysis, the micrometrically measured catheter tip was used for calibration against the automatically detected contours of its angiographically recorded contrast-free image. The arterial segments to be analyzed were identified between major proximal and distal side branches. The only other user interaction required in the analysis of the panel selected cineframe was the arbitrary selection of center points within the identified arterial segment, which are subsequently automatically readjusted after contour detection. The reference diameter of the target lesion is automatically derived by the algorithm based on a first-degree polynomial through diametric measurements made at every scan line proximal and distal to the lesion itself, followed by a translation to the 80th percentile level, allowing for tapering of the vessel distal to side branches.[33] The measurement taken as the reference diameter for the lesion, or interpolated reference diameter, is the value of the polynomial (the "diameter function curve") at the site of the MLD. The advantages of this approach are that it is essentially user independent and thus highly reproducible and that the measurement taken is based on multiple measurements (every pixel) proximal and distal to the lesion. The limitation is observed in ostial lesions where no proximal segment exists and in diffusely diseased or severely ectatic segments. However, in clinical trials of balloon angioplasty, the majority of lesions tend to be nonostial and discrete.[21-24] Before automatic calculation of absolute measurements (in millimeters), all contour positions of the catheter and segment were corrected for pincushion distortion introduced by the image intensifiers. To ensure serial analysis was consistently performed in identical projections, photographs were saved of each analysis. Before the algorithm cannot measure total occlusions or lesions with Thrombolysis in Myocardial Infarction (TIMI) flow grade I, a value of 0 mm is imputed for MLD and 100% for percent diameter stenosis. Finally, all measurements were the mean values of the multiple matched projections.

Specific Angiographic Parameters of Interest

MLD of the analyzed segment is measured in millimeters. Gain and loss, respectively, represent the improvement in MLD achieved at intervention (MLD after PTCA minus MLD before PTCA) and the change at follow-up (MLD after PTCA minus MLD at follow-up). Net gain is the net angiographic improvement from before angioplasty to follow-up (MLD at follow-up minus MLD after PTCA). Loss index, as defined by Kuntz et al,[34] represents late loss expressed as a fraction of acute gain (loss/gain). The "vessel size" is represented by the interpolated reference diameter before intervention, so chosen because it is the closest and most objective angiographic approximation available of the disease-free or "normal" vessel diameter[10,20,35] and avoids the variability in the reference diameter as a consequence of intervention and of the restenosis process.[10,20,35-38]

Binary definitions for the occurrence of restenosis were applied: (1) diameter stenosis ≥50% at follow-up (traditional "clinical" definition of restenosis); (2) loss during follow-up >50% of the gain at PTCA (National Heart, Lung, and Blood Institute definition 4); (3) loss during follow-up >0.40 mm (twice the post-PTCA lesion measurement variability of the CAAS system[37]).

Statistical Analysis

Statistical analyses were carried out using a commercially available statistical software package (SAS, SAS Institute Inc) using a lesion-based approach, as has been previously justified.[16,17,39] The 3302 lesions were divided into nine approximately equal-sized groups ("noniles") according to vessel size. The incidence of binary restenosis, according to the definitions given above, was compared among noniles by χ^2 test. The influence of vessel size on luminal loss and MLD at follow-up, as well as percent diameter stenosis and loss index, was evaluated by ANOVA of mean values per nonile and in simple linear regression analysis.

Multiple linear regression analysis was used to take account of the known influences of preprocedural MLD (lesion severity) and acute gain (the input of the physician)[3,6,9,16,17,20,34,40] and the unresolved influence of the epicardial lesion location[9,14,17,41,42] in evaluating the influence of vessel size on luminal loss and MLD at follow-up. Since addition of either the luminal gain or postprocedural MLD variable to a model already including preprocedural MLD makes the same statistical contribution to the model, a choice was made to use the gain variable, since this term better conveys the dynamic effect of intervention.

TABLE 1. Demographic Data of Total Population

No. of patients	3072
Lesions, n	3736
Male, %	80
Mean age, y	56.4±9.6
Diabetes, %	7
Anginal status (Canadian Cardiovascular Society Class), %	
I	13
II	31
III	38
IV	18
Unstable angina, %	27
Total coronary occlusion before angioplasty, %	7.1
Total occlusion at follow-up, %	4.5
Lesion distribution of 3302 lesions, n (%)	
Left anterior descending coronary artery	1428 (43)
Circumflex artery	819 (25)
Right coronary artery	1055 (32)

The influence of vessel size on percent diameter stenosis at follow-up was also evaluated, since this is the conventional clinically applied measure of coronary stenosis severity, corrected for vessel size. In the multivariate model, preprocedural MLD and gain were replaced by measures of percent diameter stenosis beforepre and gain in percent diameter stenosis.

Results

Baseline demographic characteristics (Table 1) confirm that the patient group is representative of current clinical practice with balloon angioplasty. The 3302 lesions were well distributed throughout the coronary tree: 43% in the left anterior descending coronary artery (LAD), 25% in the circumflex artery, and 32% in the right coronary artery.

Univariate Analysis

A mean of 2.12 sets of identically matched angiographic projections per lesion (ranging from a 1.7 for the diagonal branches of the LAD and the distal right coronary and circumflex to 2.5 for the proximal circumflex) had satisfactory quantitative analysis before and after PTCA and at follow-up. Preprocedural percent diameter stenosis appears comparatively mild since total occlusions were excluded (see Tables 2 and 3).

Restenosis Rate

The influence of vessel size on the restenosis rate (Fig 1A) depended on the definition used. The frequency of diameter stenosis ≥50% at follow-up varied significantly throughout the noniles (P=.002), as did the frequency of loss >0.40 mm (P<.0001), with a general increase with vessel size. However, there was no variation in the frequency of loss >50% of the initial gain (P=.41).

Percent Diameter Stenosis at Follow-up

Percent diameter stenosis at follow-up displayed a minor but significant (P<.001), increase with vessel size (Fig 1B). Although percent stenosis before and after PTCA showed a similar general pattern, there was no variation in the loss (increase) in percent stenosis during follow-up (P=.11). Since the acute gain (decrease) in percent stenosis significantly increased with vessel size (P<.0001), the net gain in percent stenosis at follow-up was also observed to increase with vessel size.

Luminal Loss and MLD at Follow-up

Luminal loss showed a significant variation throughout the nonile divisions (Table 2; P=.006), with a general but inconsistent pattern of increase with vessel size (Fig 1C). Although loss increased with vessel size (loss=0.13±0.04 · vessel size; P=.005), the association was weak (Fig 2A). Because of the significantly increasing acute luminal gain achieved in larger vessels (Fig 1C; gain=0.21±0.13 · vessel size; P<.0001), however, a significant increase in net luminal gain (Table 2) and in MLD at follow-up (Fig 2B; MLD at follow-up= 0.48±0.40 · vessel size; P<.0001) was also observed with increasing vessel size.

Loss Index

No significant variation in loss index (Fig 1D) was observed throughout the noniles, apparently due to the wide variability in this parameter in this population (P=.71).

These analyses did not clarify the influence of vessel size on late angiographic results of angioplasty, although the balance of findings suggested a beneficial effect of larger vessel size. To further elucidate the relation between vessel size and the restenosis process and late angiographic outcome, multiple linear regression analysis was carried out, taking into account the influences of gain and MLD before PTCA on loss and MLD at follow-up (Fig 2C through 2F), as well as the influence of lesion location.

Multiple Linear Regression Analysis

In multiple linear regression analysis, vessel size was found to demonstrate an independent negative influence on luminal loss and an identical positive influence on MLD at follow-up (P<.0001; Table 3, Figs 3 and 4). To further illuminate these findings, three-dimensional graphs have been constructed in which the influence of vessel size is represented using nonile divisions as already defined. The negative influence of vessel size on loss is appreciated from Fig 3 by the parallel downward shift of the regression plane with increasing vessel size (the contrasting univariate finding of increasing loss with vessel size is due to the effect of increasing MLD before PTCA and gain in larger vessels [Fig 3, especially Fig 3A]). Analogously, the equal and opposite influence of vessel size on MLD at follow-up is demonstrated in Fig 4 by the parallel upward shift in the regression planes. With a 1-mm increase in vessel size (while the other parameters remain constant), there would be an estimated decrease in loss of 0.14 mm and an identical increase in MLD at follow-up. Accordingly, it must be concluded that late results of successful balloon angioplasty are better in larger vessels. Correcting for vessel size, using percent diameter stenosis measurements, effectively neutralized this significant influence on outcome (P=.68; Table 4).

TABLE 2. Quantitative Angiographic Measurements Before and After Angioplasty and at Follow-up and Restenosis Rates Compared Within Nine Equally Sized Groups (Noniles) According to Vessel Size

	Overall	Nonile 1	Nonile 2	Nonile 3	Nonile 4	Nonile 5	Nonile 6
No. of lesions	3302	366	368	367	361	377	360
RefD pre, mm	2.63±0.55	1.78±0.17	2.11±0.07	2.30±0.05	2.44±0.04	2.59±0.05	2.75±0.04
RefD post, mm	2.70±0.58	2.01±0.31	2.26±0.25	2.40±0.21	2.53±0.24	2.64±0.24	2.77±0.23
RefD fup, mm	2.70±0.55	1.99±0.37	2.26±0.30	2.40±0.30	2.53±0.35	2.64±0.34	2.78±0.33
MLD pre, mm	1.08±0.29	0.85±0.17	0.95±0.21	1.00±0.21	1.02±0.22	1.08±0.23	1.09±0.26
MLD post, mm	1.75±0.37	1.36±0.27	1.51±0.27	1.60±0.23	1.68±0.27	1.73±0.27	1.80±0.27
MLD fup, mm	1.53±0.47	1.20±0.33	1.32±0.34	1.38±0.38	1.46±0.38	1.51±0.39	1.53±0.44
% DS pre	58.2±9.87	51.5±9.9	55.0±9.6	56.4±9.2	58.1±9.1	58.3±8.8	60.1±9.5
% DS post	34.5±9.41	31.2±10.7	33.2±9.7	33.0±9.7	33.5±8.7	34.1±9.2	34.7±9.0
% DS fup	42.8±14.0	39.2±13.3	41.4±13.7	42.2±14.5	42.1±12.9	42.5±13.6	44.9±14.9
Gain, mm	0.67±0.35	0.51±0.28	0.56±0.29	0.60±0.27	0.66±0.33	0.66±0.31	0.71±0.34
Loss, mm	0.22±0.42	0.16±0.34	0.19±0.38	0.22±0.37	0.22±0.41	0.22±0.39	0.28±0.45
Net gain,mm	0.45±0.44	0.35±0.33	0.37±0.35	0.38±0.39	0.44±0.42	0.43±0.41	0.43±0.45
Loss index	0.27±1.99	0.31±1.47	0.25±1.99	0.26±3.21	0.30±2.37	0.34±1.85	0.43±1.16
Loss>gain/2	39.0%	39.1%	39.7%	42.0%	38.0%	38.2%	43.1%
% DS≥50%	31.6%	23.2%	28.5%	30.0%	29.0%	32.6%	37.3%
Loss>0.4 mm	31.7%	22.7%	26.3%	30.8%	31.0%	32.9%	37.5%

RefD indicates reference diameter; MLD, minimal luminal diameter; pre, before; post, after; fup, follow-up; and % DS, percent diameter stenosis.

Gain, loss, net gain, loss index, and restenosis criteria are defined in the text. *P* value refers to ANOVA of mean values or to χ^2 test, where appropriate. %DS pre appear moderate, as total occlusions are excluded.

Influence of Gain and MLD Before PTCA on Loss and MLD at Follow-up

Luminal gain and MLD before PTCA exerted significant positive independent influences ($P<.0001$) on loss and MLD at follow-up (Table 3), which do not vary with increasing vessel size confirmed by the consistent slope of the regression planes, from right to left or front to back, throughout the noniles. The negative univariate influence of MLD before PTCA on loss (Fig 2C) was in contrast with this significant positive influence (Fig 3) and is due to the influence of luminal gain (Fig 5). According to the models and figures, the steeper right-to-left slope in the loss figure (Fig 3), compared with MLD at follow-up (Fig 4), means that with increasing gain, the expected incremental increase in loss is greater than the incremental increase in MLD at follow-up. Specifically, from Table 3, for a 1-mm increase in gain, the estimated increase in loss would be 0.62 mm compared with a 0.38-mm increase in MLD at follow-up. From the clinical perspective, maximization of the luminal increase would be worthwhile, according to this finding. Increasing MLD before PTCA provides a greater increase in MLD at follow-up than in loss, since the front-to-back slope of each regression plane is steeper in the MLD on follow-up graphs. Thus, a 1-mm increase in MLD before PTCA would provide an estimated 0.69-mm increase in MLD at follow-up and a 0.31-mm increase in loss (Table 3). Also, greater percent stenosis before PTCA and gain in percent stenosis were associated with greater percent stenosis at follow-up (Table 4). Accordingly, angioplasty in progressively milder lesions is associated with improving outcome.

Influence of Lesion Location on Late Results

Lesion location in the LAD (compared with right or circumflex artery) was associated with greater loss and smaller MLD at follow-up as well as with greater percent stenosis at follow-up ($P<.0001$).

Discussion

Univariate Analysis: Conflicting Findings

The influence of vessel size on the restenosis process and the angiographic outcome was not elucidated using univariate analysis. The restenosis rate per nonile depended on the definition used, which is not surprising, in view of extensive previous work highlighting the limitations of a categorical approach to evaluation of the long-term outcome of intervention.[10,11,20,31,35-38] Although greater percent diameter stenosis at follow-up was observed in larger vessels, final net improvement in percent stenosis was actually considerably greater in larger vessels (Table 2, Fig 1B). Similarly, although luminal loss was observed to increase with vessel size, a striking increase in final net gain in MLD was also observed. These increasing net improvements in larger vessels appeared to be due to the significantly greater acute results achieved (Table 2, Figs 1 and 2) and translated into significantly greater MLD at follow-up in larger vessels (Table 2, Figs 1 and 2). Loss index (loss/gain, as a proposed measure of the "proliferative potential of an instrumented vessel[42]"), was not influenced by vessel size. This was mainly due to its wide variability, explicable by the frequent finding of negligible luminal gain by CAAS after visually assessed successful angioplasty (Fig 2E and 2F). After successful stent implantation or atherectomy, there is virtually

TABLE 2. Continued

Nonile 7	Nonile 8	Nonile 9	*P*
372	363	368	
2.92±0.06	3.15±0.08	3.64±0.31	<.0001
2.94±0.25	3.13±0.27	3.59±0.39	<.0001
2.95±0.33	3.14±0.37	3.56±0.50	<.0001
1.17±0.26	1.22±0.27	1.34±0.37	<.0001
1.90±0.26	1.99±0.32	2.18±0.36	<.0001
1.64±0.45	1.74±0.44	1.95±0.52	<.0001
59.8±9.1	61.1±8.7	63.2±9.8	<.0001
35.0±8.6	36.2±9.1	38.9±9.7	<.0001
44.1±14.9	44.3±13.1	44.9±13.8	<.0001
0.73±0.34	0.77±0.38	0.84±0.43	<.0001
0.26±0.46	0.25±0.47	0.23±0.50	.006
0.47±0.47	0.51±0.47	0.61±0.51	.02
0.21±2.05	0.23±1.54	0.12±1.47	.71
39.0%	38.3%	34.0%	.41
33.3%	35.3%	34.5%	.002
34.1%	35.3%	34.8%	<.0001

always a substantial acute gain,[3,5-8,34,43-46] so regardless of the degree of subsequent change, large negative or positive values for loss index are rare. Collectively, although there is a general, but not systematic, trend toward better late results in larger vessels, these findings do not provide a clear message, with the conclusions of one approach conflicting with those of another.

Multiple Regression Analysis: Influence of Vessel Size on Late Results

In multiple regression analysis, vessel size was demonstrated to have a significant independent positive influence on MLD at follow-up (Table 3, Fig 3) and an equally negative effect on luminal loss (Table 3, Fig 4), in contrast to the increase in median loss with vessel size seen in univariate analysis (Figs 2A and 3). This is a consequence of the greater gain and MLD before PTCA in larger vessels, as illustrated in Fig 3. It must be recognized, therefore, that for all its attractive simplicity, univariate analysis does not provide a true evaluation of the apparently multifactorial phenomenon of restenosis, due to an inability to take account of important confounding factors. The findings may be explained through the conventional hypothesis that vessel injury is directly related to the degree of neointimal response.[47-49] It is logical that achieving a given luminal gain, in a lesion of given MLD before PTCA, would result in diminishing wall injury in progressively larger

TABLE 3. Multiple Linear Regression to Determine Independent Influence of Vessel Size on Luminal Loss; MLD at Follow-up, Taking Account of MLD Before Angioplasty, Luminal Gain, and Lesion Location in Left Anterior Descending Coronary Artery; and True Corollary Nature of Loss and MLD at Follow-up by Simple Stepwise Mathematical Derivation of Exact Model for Loss Starting With Model for MLD at Follow-up

	(A) Luminal Loss During Follow-up			(B) MLD at Follow-up		
	Estimated Coefficient	SEE	*P*	Estimated Coefficient	SEE	*P*
Intercept	−.11	.04	.002	.11	.04	.002
Vessel Size	−.14	.02	<.0001	.14	.02	<.0001
MLD pre	.31	.03	<.0001	.69	.03	<.0001
Gain	.62	.02	<.0001	.38	.02	<.0001
LAD	.07	.01	<.0001	−.07	.01	<.0001
	$P<.0001$; $R^2=.17$.			$P<.0001$; $R^2=.32$.		

(C) Mathematical Derivation of Loss Model From MLD at Follow-up Model

The model for loss may be mathematically derived from the model for MLD at follow-up as follows:

$$\text{MLD fup} = 0.11 + 0.14 \cdot \text{VS} + 0.69 \cdot \text{MLD pre} + 0.38 \cdot \text{gain} - 0.07 \cdot \text{LAD}$$

Loss = MLD post − MLD fup; but: MLD post = (MLD pre + gain); so:

Loss = (MLD pre + gain) − (MLD fup); therefore:

$$\text{Loss} = (\text{MLD pre} + \text{gain}) - (0.11 + 0.14 \cdot \text{VS} + 0.69 \cdot \text{MLD pre} + 0.38 \cdot \text{gain} - 0.07 \cdot \text{LAD})$$

Removing the brackets, this equation may be rewritten as:

$$\text{Loss} = \text{MLD pre} + \text{gain} - 0.11 - 0.14 \cdot \text{VS} - 0.69 \cdot \text{MLD pre} - 0.38 \cdot \text{gain} + 0.07 \cdot \text{LAD}$$

This equation may then be rearranged as follows:

$$\text{Loss} = (\text{MLD pre} - 0.69 \cdot \text{MLD pre}) + (\text{gain} - 0.38 \cdot \text{gain}) - 0.11 - 0.14 \cdot \text{VS} + 0.07 \cdot \text{LAD}$$

or according to the original format:

$$\text{Loss} = -0.11 - 0.14 \cdot \text{VS} + (\text{MLD pre} - 0.69 \cdot \text{MLD pre}) + (\text{gain} - 0.38 \cdot \text{gain}) + 0.07 \cdot \text{LAD}$$

$$\text{Loss} = -0.11 - 0.14 \cdot \text{VS} + 0.31\text{MLD pre} + 0.62\ \text{gain} + 0.07 \cdot \text{LAD}$$

MLD indicates minimal luminal diameter; pre, before angioplasty; vs, vessel size; fup, follow-up; post, after angioplasty; and LAD, left anterior descending coronary artery.

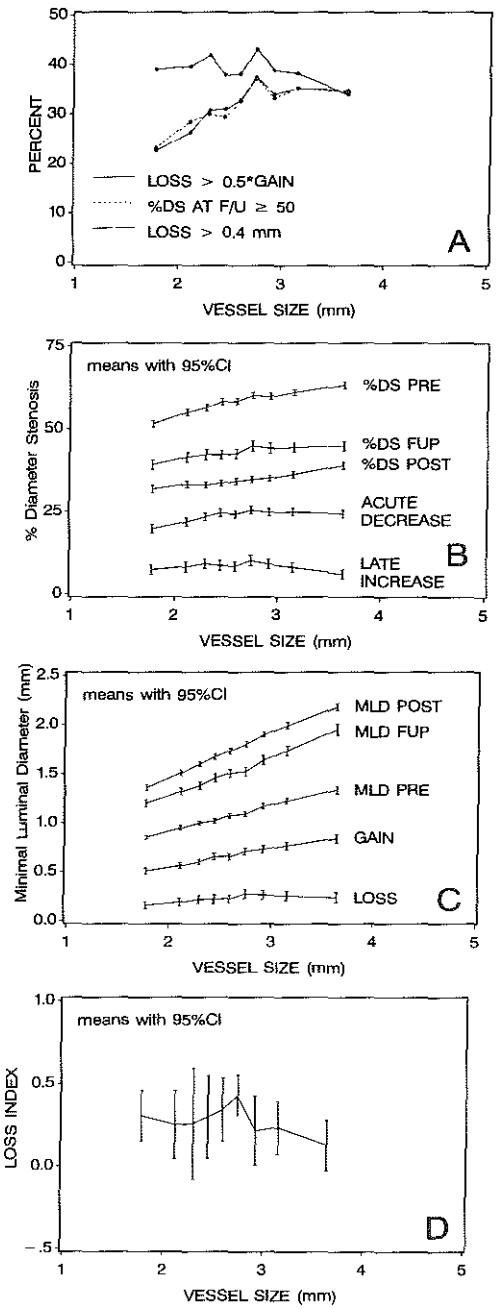


FIG 1. A through D, Plots of influence of vessel size, divided in noniles, on (A) restenosis rates (incidence in percent), according to three binary definitions. Loss >0.5*gain indicates loss during follow-up of more than half the gain at percutaneous transluminal coronary angioplasty (PTCA); %DS at F/U ≥50, percent diameter stenosis at follow-up of more than 50%; and loss > 0.4 mm, loss during follow-up of more than 0.4 mm, which is twice the postangioplasty lesion measurement variability of the CAAS system. B, %DS at follow-up, as well as %DS before and after PTCA and acute decrease in %DS immediately after PTCA and late increase in %DS during follow-up. C, Luminal loss and MLD at follow-up, as well as MLD before and after PTCA and acute gain. D, Loss index. In B through D, mean values and 95% confidence intervals (CIs) of each parameter are provided for each nonile. Actual differences between the noniles are provided in Table 2. MLD indicates minimal luminal diameter; %DS, percent diameter stenosis; FUP, follow-up; PRE, before; and POST, after.

vessels. Less injury would result in less neointimal formation, measured as less angiographic loss, leaving a greater MLD at follow-up. We can use the multivariate models to illustrate this: In a lesion with a pre-PTCA MLD of 0.5 mm, achieving an acute gain of 1.5 mm would result in a loss of 0.72 mm in a small vessel (1.83 mm) and 0.48 mm in a large vessel (3.56 mm). The estimated MLD at follow-up in the small vessel would be 1.28 mm compared with 1.52 mm in the large vessel. The gain of 1.5 mm would cause actual overenlargement of the small vessel and thus considerably greater wall injury than in the larger vessel (in which a 1.5-mm gain would provide a comparatively modest acute result), so that less loss would be provoked and a greater MLD at follow-up is provided in the large vessel. Of course, this does not present a good reason to accept marginal interventional results in larger vessels, since if a gain of 2.5 mm (instead of 1.5 mm) had been achieved in the large vessel, an MLD at follow-up of 1.90 mm could be anticipated, even if greater loss would be provoked (1.10 mm). In agreement with reports based on stent implantation and directional atherectomy,[3-9] maximization of the acute result must be generally recommended as the goal of intervention. Neutralization of the independent influence of vessel size by using percent stenosis would be expected, since percentage measurements inherently precorrect for the influence of vessel size and since the proportional vessel injury would be similar across all vessel sizes when percent stenosis before PTCA and gain in percent stenosis are constant. Accordingly, the observed advantage of larger vessels seems to be a simple mechanical privilege rather than a cryptic biological phenomenon that protects larger vessels.

Use of a Dual Approach and Value of a Selective Model

A number of recent studies have used comprehensive multivariate analysis to predict luminal loss, MLD or percent diameter stenosis at follow-up, or occurrence of binary "restenosis,[1-7,9-16]" using clinical, procedural, angiographic, and histological variables. Despite its thoroughness, the potential flaw of such an approach is that some of the angiographic variables used provide overlapping information (eg, preprocedural MLD, gain, and postprocedural MLD). Also, inclusion of relative (percent stenosis or relative luminal changes) and absolute parameters may also be criticized for inconsistency of approach. This may partly explain why different factors have been found to predict luminal loss, MLD at follow-up, percent diameter stenosis at follow-up, and binary restenosis in different studies.[1-3,6,7,9,12-17] For this reason, even when the evaluation of late results of intervention was restricted to a "dual approach," greater luminal loss after directional atherectomy was found to be determined by greater luminal increase and greater

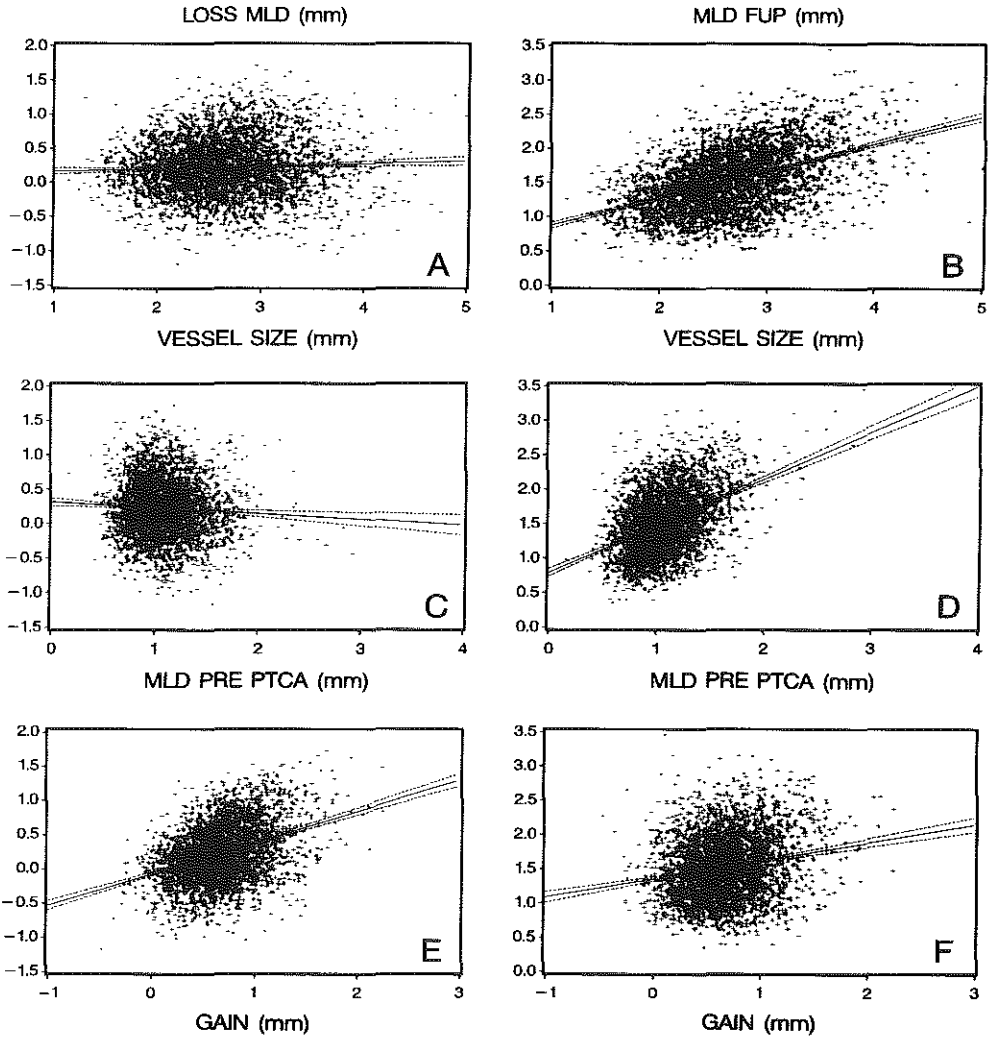
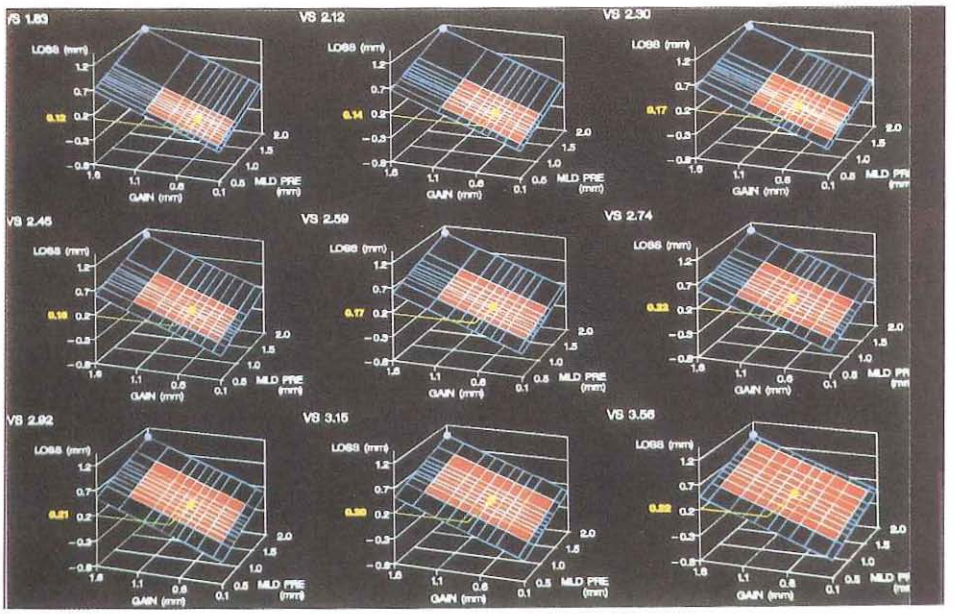


FIG 2. A through F, Scatterplots of linear regression analysis, with 95% confidence intervals, of loss and MLD at follow-up with each of vessel size (A and B), gain (C and D), and MLD before (E and F). MLD indicates minimal luminal diameter; FUP, follow-up; PRE, before; and PTCA, percutaneous transluminal coronary angioplasty. Note that the *x*- and *y*-axis scales vary according to the parameters displayed.

MLD before PTCA, whereas greater MLD at follow-up was determined by larger vessel size, postprocedural lumen, and non-LAD location.[9] In the present study, in addition to the use of a dual approach, a selective multivariate model was used to isolate the principal angiographic factors (ie, preprocedural MLD, luminal increase, and lesion location) and investigate their dynamic interrelationships and their respective effects on the influence on vessel size and late results of balloon angioplasty. Although the need to use a "dual approach[9]" has been recognized[10,11] and may be clinically obvious, the truly converse nature of luminal loss and MLD at follow-up, as correlates of the restenosis process and the late angiographic outcome, respectively, has not been previously demonstrated and was only facilitated in this study by application of the selective model. This has been illustrated in Table 3C by simple mathematical derivation of the findings for loss through the findings for the MLD at follow-up. Much of the debate regarding determination of "restenosis" after transluminal coronary interventions has been due to preferential consideration by investigators of one or other of these opposite "end points[10,11,16,17,20]" or of binary restenosis.[1,2,4,7,12-15,35,40] The opposite points of focus have been descriptively termed the "doughnut" and the "hole," respectively,[10,11,49] and studies aimed at investigation of the late clinical and/or angiographic outcome will require to focus on the MLD at follow-up (the hole), whereas those



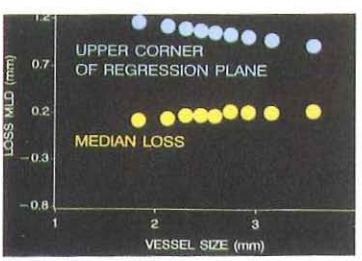


FIG 3. A and B, Three-dimensional schematic and scatterplot that depict the influence of vessel size (VS; interpolated reference diameter before angioplasty) on luminal loss, considering the influence of gain and minimal luminal diameter (MLD) before angioplasty (PRE) (Table 3A). Vessel size is represented using the noniles, as described in the text. Loss is on the (vertical) *y* axis, and gain is on the *x* axis (increasing from right to left) for illustrative purposes, and MLD before angioplasty is on the *z* axis (increasing from front to back). For consistency, the limits of each axis are equal for each nonile. The actual range of gain and MLD before angioplasty for the lesions within each nonile is represented by the outlined rectangle within each "regression plane." Purely for illustrative purposes, the lesions have been assembled in nine rows containing equal numbers of lesions, both from front to back and from side to side. The yellow dot in the center of the red rectangle represents the median loss for the nonile, displayed numerically on the *y* axis. Although the regression plane shifts progressively downward with increasing vessel size, indicating decreasing estimated loss for any given gain and MLD before angioplasty (emphasized by a pale blue dot at the upper left corner of each regression plane), the median loss is observed to actually increase. This finding is highlighted in Fig 3B by including only the median loss and the upper border of the regression planes and can be explained by the confounding effect of MLD before angioplasty and gain, whereby there is a preponderance of lesions with small MLD before angioplasty and small gain in small vessels and greater MLD before angioplasty and greater gain in larger vessels (conveyed in the graphs by progressive movement of the rectangle from right to left and front to back).

evaluating the restenosis process will need to evaluate the loss (the doughnut) and a thorough study must ultimately adopt a dual approach.[9-11]

Clinical Implications of the Findings: An Added Meaning to "Bigger Is Better"

Previous studies have reported lower categorically defined restenosis rates in larger vessels after balloon angioplasty,[2] directional atherectomy, and stent implantation,[3] whereas others have found no relation between vessel size and incidence of restenosis.[12-15,40] Moreover, while greater MLD at follow-up after directional atherectomy or stent implantation[3,9] was predicted by larger vessel size, luminal loss was not influenced by the vessel size in these or other studies.[9,16] This study would thus appear to be the first to demonstrate the independent equal and opposite effects of vessel size on the restenosis process and angiographic outcome. The obvious clinical interpretation of this finding is that intervention in larger vessels is inherently likely to be associated with a more favorable long-term outcome. According to this scheme, it would be appropriate to conclude that not only does a "bigger" gain independently yield a "better" outcome,[11] as is also confirmed in this study (Table 3B, Fig 4) but also that, indeed, a "better" long-term outcome may be anticipated, after intervention in a "bigger" vessel. This finding may partly explain the reportedly superior long-term results of directional atherectomy and stent implantation in observational studies, compared with results of conventional balloon angioplasty,[4-6] since these devices are generally restricted to more proximal segments in larger

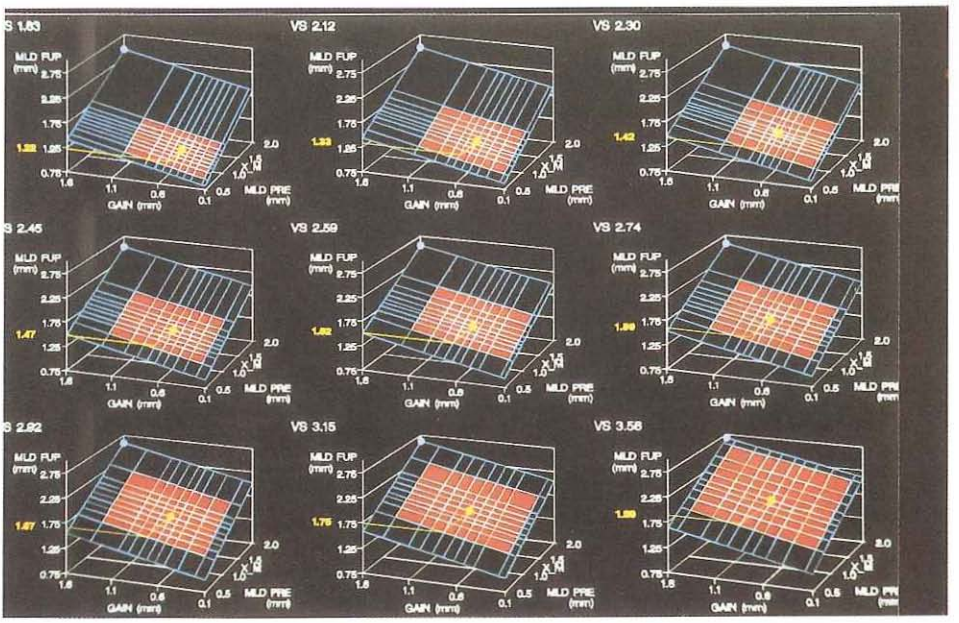


FIG 4. Schematic with approach similar to that of Fig 3A to represent the model for minimal luminal diameter (MLD) at follow-up (FUP) (*y* axis). The equal but opposite effect of vessel size on MLD at follow-up compared with luminal loss is displayed here by the progressively upward shift of the regression planes with increasing vessel size, to the same degree as the downward shift observed in Fig 3. The median MLD at follow-up also consistently increases with increasing vessel size. PRE indicates MLD before balloon angioplasty; VS, vessel size (interpolated reference diameter before angioplasty).

coronary vessels. Moreover, the finding augurs well for continued use of these devices in larger vessels, as not only is it possible to take advantage of their mechanical superiority over balloon angioplasty in larger vessels[3-11,20,34,43-46] but the independent beneficial effect of intervention in a larger vessel per se may also be realized. Likewise, the negative influence of smaller vessels on late outcome does not herald a bright future for devices more practically suited to smaller vessels, namely, rotablator and excimer laser. Although excimer laser is increasingly associated with improved short-term clinical success in unfavorable coronary lesions,[50] significantly greater loss and smaller MLD at follow-up have been reported in a matched comparison with balloon angioplasty.[51] Late results after successful high-speed rotational atherectomy are no more encouraging,[19] so application of these devices may be inherently doomed to comparatively poor long-term results, partly due to their preferential use in smaller vessels.

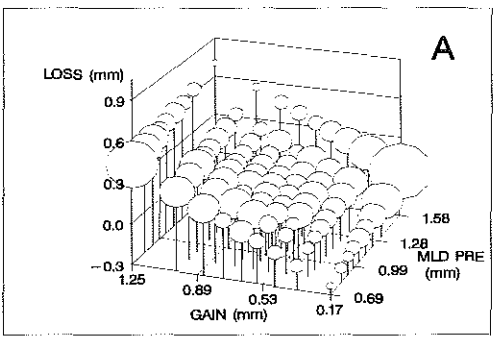
TABLE 4. Multiple Linear Regression to Evaluate Influence of Vessel Size on Percent Diameter Stenosis at Follow-up, Using Same Approach as in Table 3 but Percent Diameter Stenosis Before and After Angioplasty in Place of Minimal Luminal Diameter Before Angioplasty and Gain

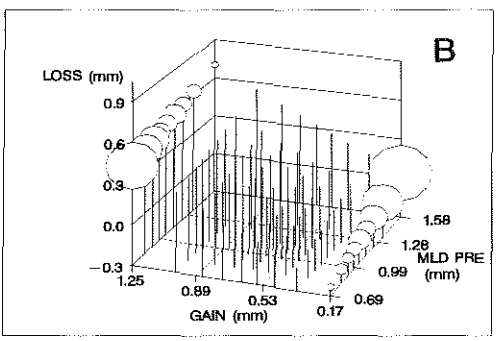
	Estimated Coefficient	SEE	*P*
Intercept	13.7	1.57	<.0001
Vessel size	.19	.45	.68
% DS pre	.64	.03	<.0001
Gain in % DS	.33	.02	<.0001
LAD	1.51	.47	.001

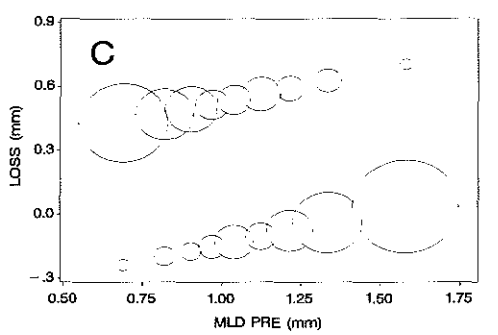
DS indicates diameter stenosis; pre, before angioplasty; and LAD, left anterior descending coronary artery.
$P<.0001$; $R^2=.12$.

Implications for Comparative Studies

In randomized trials, such as CAVEAT (Coronary Angioplasty Versus Excisional Atherectomy Trial)[8] and CCAT (Canadian Coronary Atherectomy Trial),[44] all patient characteristics are considered equally distributed, enabling direct comparisons of outcome. Thus, in these trials, no significant difference in late angiographic results was reported, despite the greater initial luminal increase noted in the atherectomy-treated groups. In the BENEstent (Belgium Netherlands stent) and STRESS (STent RESstenosis Study) randomized trials of Palmaz-Schatz stent implantation and balloon angioplasty, a significant long-term advantage of stent implantation over conventional balloon angioplasty has been reported.[45,46] Comparison of late results of different interventions in observational studies could be considered misleading, unless either the groups are suitably matched for vessel size[5,43,51] or differences in vessel size are taken into account.[10] Separate observational studies in coronary lesions specifically matched for vessel size, as a "surrogate" for a randomized trial comparing atherectomy[43] and stent implantation[5] with balloon angioplasty, in retrospect had actually predicted







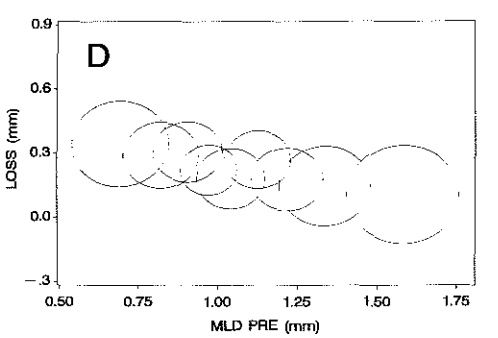


FIG 5. A through D, Confounding effect of gain on the relation between minimal luminal diameter (MLD) before angioplasty (PRE) and loss is shown by representing the entire lesion population with loss on the *y* axis, gain on the *x* axis, and MLD before angioplasty on the *z* axis. Purely for illustrative purposes, the lesions have been assembled in nine rows (containing equal numbers of lesions) from front to back and from side to side. The actual number of lesions at each of the thus created 81 possible positions in this graph is represented by the diameter of the sphere. The corresponding loss at each position is represented by the vertical height at the center of the sphere. To demonstrate the influence of gain on the relation between MLD before angioplasty and luminal loss, the rows from front to back on the extreme left and right have then been isolated from the remaining lesions, which have been obscured for this purpose (Fig 4B). The graph has then been rotated clockwise until these two rows are visualized two-dimensionally from left to right with MLD before angioplasty now occupying the horizontal axis (Fig 4C). It is appreciated that the top row in C depicts lesions with greater gain, and the bottom row depicts lesions with lesser gain. Both rows display the consistent positive multivariate relationship between MLD before angioplasty and loss. When the two rows are merged, because of the preponderance of lesions with a small MLD before angioplasty in which a large gain is achieved and of those with a large MLD before angioplasty in which a small gain was achieved, the positive relation between MLD before angioplasty and loss is actually reversed, depicting the univariate relation, as observed in Fig 2C.

the outcome of the four randomized trials mentioned. Such matching studies may thus provide useful information in comparing outcomes of different interventions, since the important and confounding influence of vessel size on late results is balanced.

Influence of Lesion Location on Late Results

Greater luminal loss, smaller MLD at follow-up, and greater percent stenosis at follow-up are associated with lesion location in the LAD, independent of luminal increase and lesion severity before PTCA. Previous studies in patients treated by balloon angioplasty have reported increased restenosis rates in LAD lesions[2,13]; others found no association between lesion location and restenosis rates, luminal loss, or relative luminal loss[16,41]; and one study reported less relative loss in right coronary artery lesions.[17] Location in the right coronary artery was also found to predict less late loss, larger MLD at follow-up, and lower incidence of restenosis in patients treated by directional atherectomy or stent implantation.[3]

Subsequently, in a larger study,[42] the same authors found LAD location to be the strongest independent predictor of binary restenosis and percent stenosis at follow-up. Other investigators have found LAD location to predict smaller MLD at follow-up, but not luminal loss, after directional atherectomy.[9] In randomized studies, the CAVEAT trial reported improved long-term angiographic outcome in LAD lesions treated by atherectomy compared with balloon angioplasty,[8] whereas in the CCAT trial, which compared directional atherectomy and balloon angioplasty for proximal LAD lesions only, no advantage of DCA was found.[44] In this study of 3302 lesions, the association of LAD lesion location with less favorable long-term results is inescapable. However, a plausible explanation for this has not yet been advanced. Greater frequency of intimal hyperplasia was found in tissue retrieved by directional atherectomy from primary lesions of the LAD compared with RCA and circumflex,[52] which might convey an increased propensity to renarrowing after initially successful angioplasty in LAD lesions. Such findings

deserve prospective histological confirmation in larger studies, and further reports from CAVEAT[8] may be helpful. Also, since chronic recoil, measured by serial intracoronary ultrasound, has been advanced as a major component of late restenosis,[53] its distribution throughout the coronary vessels is of major interest, if the phenomenon can indeed be verified and reliably quantified.

Reference Diameter Changes: Implications for Percent Stenosis Measurements

Reference diameter changes from postangioplasty to 24 hours have been found to erroneously indicate deterioration in lesion severity during this time, whereas MLD and area remained unchanged.[37] Similarly, apparently normal coronary segments adjacent to a target lesion may be involved in the restenosis process (since these are invariably subjected to the trauma of balloon dilatation) and provide misleading percent stenosis measurements at follow-up.[35,36,38] In this study, a significant increase in interpolated reference diameter was observed from before to after angioplasty, which was maintained at follow-up and the variability of this parameter also increased from before to after PTCA to follow-up (Table 2). When reference diameter is measured by arbitrary selection of normal-appearing segments adjacent to the stenotic lesion, variability of percent diameter stenosis measurement increases even further.[10,20,31,35-38] Although traditional percent diameter stenosis continues to appropriately form the cornerstone of clinical practice, its reliability in clinical studies of the biological process of restenosis must therefore be questioned. Absolute luminal measurements, which are much more precisely obtained by quantitative angiographic analysis,[28,30,32,36,37] must be preferentially recommended. According to the findings in this study, the effect of the vessel size must be taken into account when evaluating late results of intervention, especially in comparative studies. To this end, a constant, objective, and reproducible measure of vessel size is recommended, namely, the interpolated reference diameter before intervention. With increasing availability of reliable on-line quantitative analysis,[54,55] the clinical utility of such measurements must not be underestimated, since extrapolation of experience using automated analysis has been shown to be eminently applicable to the clinical interpretation of coronary angiograms.[56,57]

Study Limitations

Various clinical and biological factors may theoretically modify the influence of vessel size on late angiographic outcome and deserve evaluation in future studies. However, it is worth noting that although some clinical factors have been found to be independently correlated with luminal renarrowing (eg, diabetes and duration of angina before angioplasty[16]), a recent study found no clinical, procedural, or histological factors to influence the relations between quantitative angiographic parameters.[9] The predictive value of the multivariate models in this study could be considered poor (although 32% of the variance of MLD at follow-up was explained by the model), this is a limitation of applying simple geometric principles to a compound, multifactorial phenomenon. Nevertheless, the intention of the study and, particularly, the multiple regression analysis was not to "predict" restenosis but rather to evaluate the independent influence of vessel size on the late results of angioplasty.

Summary and Conclusions

Vessel size is an important determinant of the extent of the renarrowing process and MLD at follow-up after successful angioplasty. An extra dimension may be added to the "bigger is better" maxim, namely, that "bigger vessels have a better outcome." Predisposition of stent implantation and directional atherectomy to larger coronary vessels may partly explain their reported superior late results compared with "plain old" balloon angioplasty, and the rather poor results of excimer laser angioplasty and rotational atherectomy may be partly due to their use in smaller vessels. By extension, the results portend well for continued application of devices that can safely and consistently achieve large increases in luminal dimensions at intervention, whose ultimate benefit may be most effectively realized in larger vessels.

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CHAPTER 8

A COMPARISON OF ANGIOGRAPHIC RESTENOSIS PROPENSITY OF EXCIMER LASER CORONARY ANGIOPLASTY AND BALLOON ANGIOPLASTY IN LONGER CORONARY LESIONS.

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ABSTRACT

Background: Excimer laser coronary angioplasty has become widely used for coronary angioplasty, on the basis of atheroma ablation and particularly because of clinical success in lesion subsets considered unfavourable for conventional balloon angioplasty. The AMROE (Amsterdam-Miami-ROtterdam-Eindhoven) trial was the first randomized clinical trial designed to compare acute and long term clinical and angiographic results of ELCA with balloon angioplasty, for treatment of longer coronary lesions in patients with stable angina.

Purpose: The purpose of this ancillary study was to compare angiographic restenosis propensity of ELCA with BA among patients who had initially successful intervention and serial quantitative coronary angiographic follow up in the AMROE trial.

Results: Procedural success (diameter stenosis < 50%, without a major adverse cardiac event) was achieved in 126 (80%) of 151 patients randomly assigned to excimer laser, and in 132 (79%) of 157 patients randomized to BA. Among patients eligible for angiographic follow up, 120 with 124 lesions in the ELCA treated group (93%) and 123 with 126 lesions in the balloon angioplasty treated group (91%), had quantitative angiographic follow up and were eligible for this study. Despite achievement of a significantly greater acute lumen diameter in the ELCA group (1.69mm versus 1.59mm, p=.05), greater late loss subsequently developed (0.52mm versus 0.34mm, p=.04) and the follow up luminal diameter was not significantly different (1.17mm versus 1.25mm, p=.30). In addition, a significantly greater loss index was observed for the ELCA treated lesions (0.74 versus 0.36, p=.02) as well as trends towards higher incidence of clinical restenosis (53% versus 41%, p=.058). In multiple linear regression analysis to predict loss and MLD at follow up, a trend towards an independent influence of the device used for intervention was observed favouring balloon angioplasty (p=.08). Further analyses to comparatively evaluate angiographic restenosis propensity of ELCA and BA in certain lesion subsets revealed a consistently greater loss index associated with ELCA for treatment of smaller vessels ((<2.5mm), 0.98 versus 0.45, p=.06), longer lesions ((>9mm), 0.71 versus 0.38, p=.05) and among the more optimally treated lesions ((post procedural MLD > 1.67mm), 0.51 versus 0.20, p=.05).

Conclusions: These findings indicate that excimer laser coronary angioplasty is associated with a greater restenosis propensity than conventional balloon angioplasty. This may be due to more extensive or intense vessel wall injury caused during intervention by laser than conventional balloon alone. New developments in laser technique and particularly in catheter technology, which promise to reduce the tissue ablation : injury ratio, will be required to justify continued use of this powerful interventional tool.

INTRODUCTION

Excimer laser coronary angioplasty was introduced as an alternative device for percutaneous coronary revascularization, with the working hypothesis that ablation of atheromatous tissue would allow successful recanalization of diseased coronary arteries [1-3]. Observational studies and registry based reports have shown that ELCA can achieve acute procedural success which is comparable or superior to other percutaneous devices in difficult lesion sub-sets, such as longer lesions, ostial lesions and especially in smaller vessels and total coronary occlusion [5-9]. The absence of a randomized clinical trial comparing ELCA with conventional angioplasty, with regard to long term as well as acute, clinical and angiographic outcome, stimulated the inauguration of the AMROE (Amsterdam-Miami-ROtterdam-Eindhoven) trial in 1991. This trial, in which patients requiring treatment of longer coronary lesions (≥ 10mm), were randomly assigned to conventional BA or ELCA, has now been completed. Essentially, no significant difference was detected between the treatment groups, in acute or 6 month angiographic or clinical outcome [10].

Because of a prior report of less favourable late angiographic results after ELCA compared with balloon angioplasty, in a matched patient comparison [11], the study described in this report was designed to comprehensively investigate whether device specific differences in restenosis propensity can be detected between these treatment modalities, among the patients randomized in the AMROE trial. To facilitate this, multivariate analysis was applied to investigate the angiographic determinants of luminal loss and minimal luminal diameter at follow up, to evaluate the possibility of a device specific effect on late angiographic outcome. In addition, sub-group analyses were performed, to ascertain whether differences in outcome were evident between the treatment groups, according to lesion length, vessel size, total coronary occlusion or the magnitude of the acute result.

PATIENTS AND METHODS

Patient population

Between September 1991 and November 1993, a total of 308 patients (330 lesions) were randomized in the Amsterdam-Rotterdam comparative evaluation of excimer laser angioplasty and balloon angioplasty for treatment of longer coronary lesions (patient demographics are provided in table 1). Of these, 151 patients with

158 lesions were randomly assigned to excimer laser and 157 with 167 lesions to balloon angioplasty (angiographic lesion characteristics are given in table 2). Procedural success (diameter stenosis < 50% at the end of the procedure, without the occurrence of a major adverse cardiac event [12]) was achieved in 126 of 158 (80%) lesions treated by ELCA and 132 of the 167 (79%) lesions treated by balloon angioplasty. Among patients eligible for angiographic follow up, a total of 120 with 124 lesions in the ELCA treated group (93%) and 123 with 126 lesions in the balloon angioplasty treated group (91%), had quantitative angiographic follow up and were eligible for this study.

Table 1: Demographic characteristics of the patients included in the AMROE trial.

		ELCA	**BA**
Patients		151	157
Lesions		158	167
Age		58.1	59.4
Gender (M:F)		115:36	114:43
Diabetes (%)		15	20
History of Smoking		74	68
Currently smoking		33	36
Hypertension		57	50
Hypercholesterolemia		58	59
Prior myocardial infarction		70	68
Prior CABG		10	13
Prior PTCA		16	25
Anginal status:	CCS I	11	8
	CCS II	44	49
	CCS III	82	86
	CCS IV	14	14
Non-exertional angina		77	81
Angiographic 1 vessel disease		83	79
Angiographic 2 vessel disease		51	63
Angiographic 3 vessel disease		17	15
Target lesion location:	LAD	61	64
	RCA	56	61
	Cx	41	42
Lesion type :	A	1	-
(ACC/AHA)	B1	-	2
	B2	83	71
	C	74	94
Estimated length :	<10mm	1	3
	10-20mm	122	109
	>20mm	33	44
	unknown	2	11

The randomization process, inclusion and exclusion criteria and procedural protocols of the laser and balloon angioplasty procedures have been described in detail in the main trial report. In summary, patients with stable angina and a native primary coronary lesion longer than 10mm by visual assessment, suitable for treatment by excimer laser angioplasty or balloon angioplasty, were eligible. The laser systems in use were the Dymer 200+ (Advanced Interventional Systems Inc., Irvine, Ca.), with a pulse duration of 210 nanoseconds and a repetition rate of 20Hz, delivered by 1.3mm, 1.6mm or 2.0mm catheters, at a fluence of 45-65 mJ/mm^2, used in 80% of the patients and the CVX-300 system (Spectranetics, Colorado Springs, Colo.), which emits a pulse duration of 135ns at a repetition rate of 25Hz, delivered by 1.4mm, 1.7mm or 2.0mm catheters, with a similar fluence. Adjunctive balloon angioplasty was performed when clinically necessary to improve the acute angiographic result. Conventional balloon angioplasty was performed according to the standard clinical practice of the operator.

Quantitative Angiography:

All patients had serial coronary angiography in multiple projections, identically repeated pre and post procedure and for all follow-up angiograms. Routine follow up angiography was scheduled for 26±2 weeks after intervention. Angiographic acquisition was standardized, according to previously published guidelines [13-15], to suit automated analysis at the core laboratory using the Cardiovascular Angiographic Analysis System,

the methodology and technical aspects of which have been extensively described in detail in previous reports [14]. Similarly, the core laboratory approach to screening and analysis of angiograms followed a standardized protocol, which has also been previously described [13-15].

Analytical approach

To investigate whether excimer laser or balloon therapy in this trial were more or less successful, in terms of propensity to late angiographic restenosis in : (i) larger or smaller vessels, (ii) longer or shorter lesions and (iii) after more or less optimal acute results had been achieved, both groups were divided at the median value for each of these parameters (vessel size, lesion length and post procedural minimal luminal diameter, respectively). Comparisons were then made, with respect to angiographic dimensions before and after treatment and at follow up, as well as in acute luminal gain, late luminal loss, loss index (loss/gain) and in binary restenosis rates, according to a number of widely known criteria. In addition, to determine whether epicardial lesion location influenced results, angiographic parameters were compared between treatment groups for the 3 epicardial vessels. To investigate a general device specific effect on late angiographic results, multiple linear regression analysis was performed, first taking the entire group of 250 lesion as a single group and then in the sub-group analyses. In the models for luminal loss and minimal luminal diameter at follow up, the "dummy" device variable was included, as well as the known determining influence of vessel diameter, epicardial location, baseline lesion severity (minimal luminal diameter pre), acute luminal increase (acute gain) and lesion length [13].

Statistics

Statistical analyses were performed using the commercial SAS (SAS Institute Inc, Cary, North Carolina) package. Mean, standard deviation, minimum, maximum and median values are provided for all parameters, where appropriate. Inter-group comparisons of continuous variables are performed using the student's t test and of categorical variables using the chi-square test. Univariate and multivariate analysis were also performed to evaluate determinants of luminal loss and minimal luminal diameter at follow up and to investigate an independent device specific effect on these parameters.

RESULTS

General comparison of angiographic findings between ELCA and PTCA groups

Table 2 provides direct comparisons of baseline, post-procedural and follow up angiographic parameters between the ELCA and BA groups. To determine the influence of lesions which were totally occluded at baseline or became occluded at follow up, comparisons were made between the respective populations, including or excluding these lesions and no detectable effect was detected, so the remainder of this evaluation will focus on the entire lesion groups.

Table 2: Overall quantitative angiographic characteristics of the lesions with successful intervention and QCA pre, post and at follow up.

	ELCA (n=124)	**BA** (n=126)	
Vessel size (mm)	2.51±0.47	2.47±0.59	.60
Lesion length (mm)	9.41±3.55	8.91±3.66	.33
MLD pre (mm)	0.77±0.44	0.77±0.47	.96
MLD post (mm)	1.69±0.41	1.59±0.34	.05
MLD fup (mm)	1.17±0.71	1.25±0.68	.34
% DS pre	68.5±18.3	68.9±18.6	.86
% DS post	37.6±10.3	38.0±8.9	.76
% DS fup	56.1±23.2	52.6±23.4	.24
Acute Gain (mm)	0.91±0.53	0.82±0.50	.15
Late Loss (mm)	0.52±0.70	0.34±0.62	.04
Net Gain (mm)	0.40±0.69	0.48±0.66	.34
Loss Index	0.74±1.57	0.36±1.26	.03
DS ≥ 50%	53.2%	41.3%	.06
Loss ≥ 0.4mm	48.4%	35.7%	.04
Loss ≥ gain/2	49.2%	38.1%	.07
Total occlusion pre	20.2%	20.6%	.93
Total occlusion fup	16.9%	14.3%	.56

Virtually identical baseline lesion characteristics are evident in the two groups. A significantly greater acute lumen diameter was achieved in the ELCA group (1.69mm versus 1.59mm, p=.05), but as a consequence of the greater late loss (0.52mm versus 0.34mm, p=.04), this initial advantage was attenuated and the follow up luminal diameter was not significantly different, although a slight trend in favour of the balloon treated group was evident (1.25mm versus 1.17mm, p=.30). A significantly greater loss index is observed for the ELCA treated lesions (0.74 versus 0.36, p=.02). In addition, trends are observed towards higher incidence of a stenosis ≥ 50% (53% versus 41%, p=.058) and greater frequency of a loss ≥ half the initial gain (49% versus 38%, p=.077) and of a loss ≥ 0.4mm (48% versus 36%, p=.04), in the ELCA compared to the balloon group. Simple linear regression analysis revealed a somewhat greater incremental increase in luminal loss with increasing luminal gain, in the laser group (lineslope 0.52 versus 0.40, p = .08, figure 1).

In multiple linear regression analysis to predict loss and MLD at follow up, a trend towards an independent influence of the device used for intervention was observed favouring balloon angioplasty (p=.08). The following models were obtained:

Loss = 0.35 - 0.28 Vessel size + 0.26 MLD pre + 0.71 gain - 0.11 device

MLD at follow up = - 0.35 + 0.28 Vessel size + 0.74 MLD pre + 0.29 gain + 0.11 device

(where balloon = 1 and ELCA = 0)

Comparison of ELCA and PTCA in smaller and larger vessels

To investigate whether ELCA or BA achieved better late angiographic in large or small vessels, the population was divided at the median vessel size of 2.49mm. Table 4 provides comparisons of baseline and acute and late angiographic results between treatment groups. In smaller vessels, although baseline vessel size was significantly greater in the ELCA group and a marginally greater post procedural lumen was achieved by ELCA, there was a trend towards greater late loss after ELCA (0.46mm versus 0.28mm, p=0.07), and late luminal diameter was similar (1.02mm versus 1.11mm, p=0.30). However a considerably greater loss index was observed in the ELCA group (0.98 versus 0.45, p=.06).

In larger vessels, again ELCA achieved a marginally greater post-procedural lumen (1.89mm vs 1.80mm; p=.11), a somewhat greater loss was also observed in the ELCA group (0.57mm compared with 0.41mm, p=0.15) and a trend towards a larger follow up lumen was evident in the BA group (1.40mm vs 1.31mm; p=.16). This non-significant angiographic benefit of BA was also manifest as a lesser loss index (0.27 versus 0.51, p=.16) and translated into a statistically lower recurrence of a stenosis greater than 50% at follow up angiography (34% versus 55%, p=.02).

Comparison of ELCA and PTCA after "sub-optimal" and "optimal" acute results

Division of the treatment groups according to the post-procedural result gave a threshold minimal luminal diameter post of 1.67mm (table 5). For the group thus termed "sub-optimal", vessel size was greater in the ELCA group (2.30mm versus 2.17mm,p=.05). No differences in post-procedural or follow up results were observed and although the loss index was considerably greater in the ELCA group (0.98 versus 0.52), due to wide variability, this difference was not significant (p=0.14).

Among "optimally treated" lesions, the vessel diameter did not differ between the groups. The acute luminal gain was significantly greater in the ELCA group, giving a significantly greater post-procedural result (1.99mm versus 1.86mm, p=.006). However, during follow up, significantly greater late loss accrued in the ELCA group (0.65mm versus 0.36mm, p=.02) so that the net gain was similar between the groups and the minimal luminal diameter at follow up actually showed a favourable trend for the BA treated group (1.50mm versus 1.34mm, p=0.10). Accordingly the loss index was greater in the ELCA treated group (0.51 versus 0.20, p=.05) and in addition, the incidence of binary restenosis was significantly greater among ELCA treated lesions (55% versus 33%, p=.015).

Comparison of ELCA and PTCA according to lesion length

Comparisons of outcome according to lesion length are shown in table 6. In the treatment of shorter coronary lesions (less than 8.98mm, with a mean of 6.48mm), no significant differences in outcome were detected between the groups, although similar trends as previously noted, including a larger acute gain in the ELCA group (0.91mm versus 0.81mm), followed by a somewhat greater late loss (0.47mm versus 0.36mm) and a greater loss index (0.78 versus 0.33, p=0.14). For longer lesions (greater than 8.98mm, with a mean of 12.25mm), ELCA again provided a somewhat greater acute luminal result (MLD post = 1.71mm versus 1.60mm, p=0.10), but was attended by a significantly greater late luminal loss (0.56mm versus 0.32mm, p=.05), so that BA provided a larger, albeit not statistically significant, net gain (0.51mm versus 0.36mm, p=.16) and a greater lumen at follow up (1.29mm versus 1.15mm, p=0.17). Again, the loss index was significantly greater in the ELCA group (0.71 versus 0.38, p=.05). The binary restenosis rate in the ELCA group was significantly greater (52% versus 32%, p=.02). In multiple linear regression analysis in this subgroup of longer lesions, ELCA was retained as an independent determinant of greater late loss and a smaller luminal diameter at follow up (p=0.08).

Table 3. Acute and late results of ELCA and PTCA groups by vessel size, divided into "smaller" and "larger" vessels, at the median for the entire group (2.49mm)

	Smaller vessels (1.39 - 2.49mm)			Larger Vessels (2.49 - 5.34mm)		
	ELCA	**BA**		**ELCA**	**BA**	
Vessel size (mm)	2.13±0.24	2.03±0.26	.03	2.88±0.31	2.90±0.50	.81
Lesion length (mm)	9.12±3.35	8.99±3.83	.89	10.03±4.04	8.94±3.44	.29
MLD pre (mm)	0.74±0.40	0.68±0.39	.40	0.80±0.48	0.87±0.52	.46
MLD post (mm)	1.48±0.38	1.39±0.22	.08	1.89±0.33	1.80±0.31	.13
MLD fup (mm)	1.02±0.66	1.11±0.60	.46	1.31±0.74	1.40±0.73	.54
% DS pre	64.9±19.1	66.6±18.8	.62	72.0±16.9	70.9±18.4	.75
% DS post	38.1±12.5	37.6±9.2	.77	37.0±7.6	38.2±8.7	.41
% DS fup	56.5±24.5	52.2±24.3	.34	55.6±21.6	53.1±22.8	.52
Acute Gain (mm)	0.74±0.50	0.70±0.40	.63	1.09±0.52	0.93±0.55	.11
Late Loss (mm)	0.46±0.69	0.28±0.60	.12	0.57±0.72	0.41±0.64	.17
Net Gain (mm)	0.28±0.68	0.43±0.67	.24	0.51±0.69	0.53±0.66	.90
Loss Index	0.98±2.10	0.45±1.19	.08	0.51±0.66	0.27±1.33	.21
DS ≥ 50%	33.9%	34.4%	.95	54.8%	34.4%	.02
Loss ≥ 0.4mm	45.2%	32.8%	.16	51.6%	39.1%	.16
Loss ≥ gain/2	48.1%	41%	.41	50.0%	35.9%	.11
Total occlusion pre	17.7%	21.3%	.61	22.6%	20.3%	.76
Total occlusion fup	21%	14.8%	.37	12.9%	14.1%	.85

Table 4. Acute and late results of ELCA and PTCA by lesion length, divided into "shorter" and "longer" lesions, at the median lesion length for the entire group (8.93mm).

	Shorter lesions (3.10 - 8.93mm)			Longer lesions (8.98 - 21.59mm)		
	ELCA	**BA**		**ELCA**	**BA**	
Vessel size (mm)	2.40±0.43	2.41±0.45	.84	2.62±0.48	2.54±0.70	.46
Lesion length (mm)	6.48±1.42	6.08±1.21	.18	12.25±3.11	11.60±3.08	.24
MLD pre (mm)	0.75±0.44	0.77±0.49	.78	0.79±0.45	0.78±0.45	.87
MLD post (mm)	1.66±0.41	1.59±0.31	.27	1.71±0.40	1.61±0.38	.14
MLD fup (mm)	1.19±0.73	1.22±0.63	.77	1.15±0.69	1.29±0.74	.29
% DS pre	68.5±18.7	68.0±19.0	.89	68.5±18.1	69.6±18.4	.73
% DS post	36.3±9.8	36.1±7.9	.90	38.8±10.7	39.7±9.6	.65
% DS fup	54.2±24.2	51.7±22.2	.54	57.9±22.3	53.6±24.7	.32
Acute Gain (mm)	0.91±0.50	0.82±0.52	.30	0.92±0.57	0.83±0.47	.33
Late Loss (mm)	0.47±0.71	0.37±0.56	.35	0.56±0.70	0.32±0.69	.05
Net Gain (mm)	0.44±0.70	0.45±0.64	.92	0.36±0.69	0.51±0.69	.16
Loss Index	0.78±2.06	0.34±1.49	.17	0.71±0.84	0.38±1.06	.05
DS ≥ 50%	37.1%	37.1%	1.0	51.6%	31.7%	.02
Loss ≥ 0.4mm	45.2%	26.0%	.71	51.6%	30.2%	.01
Loss ≥ gain/2	45.2%	38.7%	.47	53.2%	38.1%	.08
Total occlusion pre	21.0%	14%	.83	19.4%	19.1%	.96
Total occlusion fup	17.7%	8.0%	.46	16.1%	15.9%	.97

Comparison of ELCA and PTCA according to epicardial lesion location

Comparison of angiographic outcome according to epicardial lesion location is provided in table 7. Among the 45 ELCA and 56 BA treated lesions located in the LAD, no significant differences in baseline features, acute angiographic results or late angiographic outcome were observed.

Among the 45 ELCA and 38 BA treated lesions in the RCA, ELCA achieved a significantly greater acute luminal gain (1.06mm versus 0.71mm,p=.003), yielding a greater MLD post than BA (1.84mm versus 1.65mm, p=.03). However, due to a non-significantly greater luminal loss in the ELCA treated lesions (0.57mm versus 0.37m, p=0.18), follow up luminal diameter was similar between the two groups (1.27mm in each group). Although loss index was once again larger in the ELCA group (0.54 versus 0.36), this difference was not statistically significant (p=0.30).

Among the 34 ELCA and 31 BA treated lesions located in the circumflex, vessel diameter was similar but, there was a trend towards a larger MLD pre in the ELCA group (0.80mm versus 0.62mm, p=0.11) and also a trend towards a smaller acute gain in the ELCA group (0.76mm versus 0.95mm, p=0.10), so that theacute post-procedural luminal diameter was similar (1.56mm versus 1.57mm). However, during follow up, late loss was significantly greater in the ELCA group (0.52mm versus 0.22mm, p=0.05), so that the net gain was significantly greater in the BA group (0.73mm versus 0.24mm, p=.003) and the follow up luminal diameter was significantly larger (1.35mm versus 1.04mm, p=.05) and the diameter stenosis significantly less (45.4% versus 56.2%, p=.06) in the BA group. The loss index was concomitantly significantly larger in the ELCA group (0.77 versus 0.08, p=.008). Accordingly, in multiple linear regression analysis applied to circumflex lesions, the device used was associated with a significant independent influence on the late loss and lumen diameter at follow up, in favour of balloon angioplasty (p=.01). Concomitantly, binary restenosis rates were significantly higher in the laser treated circumflex lesions (50% versus 23%, p=.02).

DISCUSSION

In this comparison of angiographic results obtained by excimer laser coronary angioplasty and conventional balloon angioplasty in the randomized AMROE trial (among the lesions which were initially successfully treated and had quantitative angiographic follow-up), it may be concluded that ELCA was associated with less favourable late angiographic results, due to a greater restenosis propensity, as delineated by the increased angiographic loss index and by the greater loss response to increasing luminal gain.

Increased restenosis propensity of ELCA compared with PTCA

General overall comparison revealed that ELCA with adjunctive balloon angioplasty provided a greater acute lumen, which according to the "bigger is better" hypothesis and the generalized model of restenosis [16,17], should also provide a greater late lumen. This was not the case however, and greater late luminal loss after ELCA led to similar late luminal diameter (although a marginally larger lumen was actually evident in the BA treated group). The calculated loss index, which was introduced as a measure of angiographic restenosis propensity [18] and previously reported not to vary among patients treated by balloon angioplasty, stent implantation, directional atherectomy or excimer laser angioplasty [16,17,19], was found to be significantly higher in the ELCA treated lesions, suggesting that ELCA therapy, at least in this randomized trial, inherently provokes a greater degree of luminal renarrowing than balloon angioplasty. The sub-group analyses substantiate this finding, whereby consistently greater loss index is found for ELCA compared with PTCA in virtually all sub-group comparisons, especially for lesions located in the circumflex and right coronary arteries, in shorter lesions, in smaller vessels and after achievement of more optimal results.

Since the acute results of both therapies were similar and actually tended to be somewhat superior in the ELCA treated group, such an increased restenosis propensity of excimer laser angioplasty may be considered to be a manifestation of the injury/hyperplasia phenomenon [20,21], whereby the injury imparted to the vessel wall by excimer laser in the achievement of an apparently similar interventional result may provoke a greater renarrowing response than does balloon angioplasty. Compared with plaque stretching, compression and variable degrees of mechanical vessel wall dissection by conventional angioplasty [22-24], generation of high pressure acoustic shockwaves of up to hundreds of atmospheres [4] and of fast imploding and expanding vapour bubbles at energy levels higher than 17mJ/mm^2 [25] by ELCA, are known to cause extensive intimal dissection, medial necrosis and internal elastic lamina abrasion [25,27]. In addition, photodissociation at the laser tip produces insoluble gas formation which has no escape route and ultraviolet radiation itself has been suggested to be somewhat mutagenic [26]. Accordingly, perhaps it is not that surprising to find an increased angiographic restenosis propensity after ELCA compared with BA, especially when it is recognized that ELCA is also followed by balloon dilatation injury, in virtually all cases.

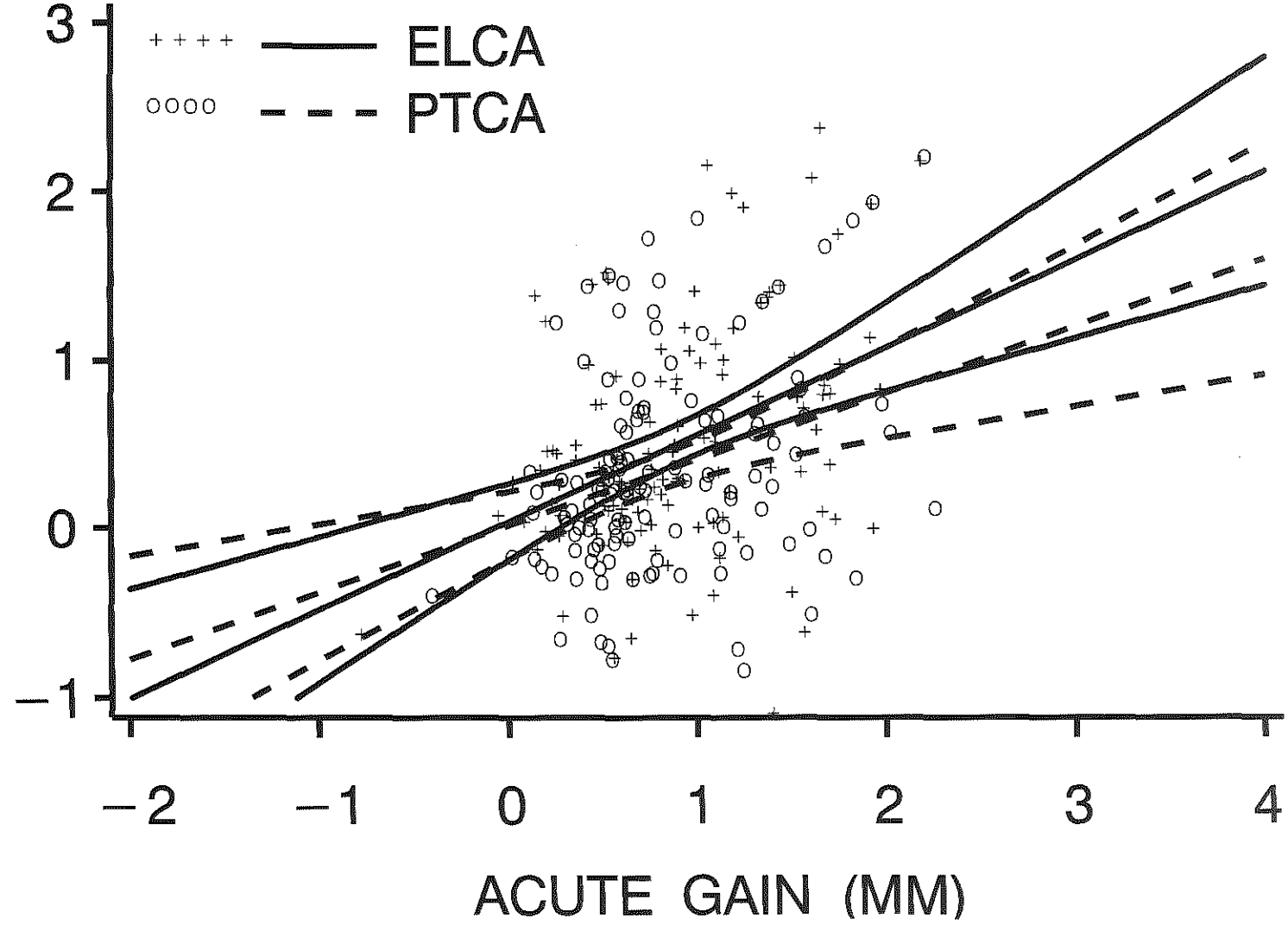
Table 5. Acute and late results of ELCA and PTCA according to the acute luminal diameter, divided into "less optimal" and "more optimal", at the median (1.67mm).

	"Less optimal" acute MLD (0.91 - 1.67mm)			"More optimal" acute MLD (1.67 - 2.93mm)		
	ELCA	**BA**		**ELCA**	**BA**	
Vessel size (mm)	2.30±0.40	2.17±0.38	.06	2.71±0.44	2.78±0.61	.48
Lesion length (mm)	9.28±3.04	8.74±3.78	.38	9.62±4.18	9.14±3.83	.50
MLD pre (mm)	0.73±0.46	0.64±0.43	.27	0.81±0.42	0.91±0.47	.22
MLD post (mm)	1.38±0.28	1.33±0.18	.22	1.99±0.26	1.86±0.25	.006
MLD fup (mm)	1.00±0.62	1.01±0.59	.96	1.34±0.76	1.50±0.69	.10
% DS pre	67.5±20.5	70.5±19.1	.41	69.5±15.8	67.2±18.3	.46
% DS post	41.5±11.6	40.7±9.2	.65	33.7±6.8	35.2±7.8	.24
% DS fup	57.7±23.4	56.3±25.1	.76	54.4±22.7	49.1±21.4	.18
Acute Gain (mm)	0.65±0.47	0.69±0.45	.65	1.18±0.46	0.95±0.51	.01
Late Loss (mm)	0.38±0.61	0.33±0.61	.60	0.65±0.77	0.36±0.64	.02
Net Gain (mm)	0.27±0.67	0.36±0.65	.42	0.53±0.70	0.59±0.66	.59
Loss Index	0.98±2.11	0.52±1.21	.14	0.51±0.64	0.20±1.30	.09
DS ≥ 50%	51.6%	50.0%	.86	54.8%	33.3%	.01
Loss ≥ 0.4mm	41.2%	33.9%	.35	54.8%	38.1%	.06
Loss ≥ gain/2	46.8%	41.9%	.59	51.6%	34.9%	.06
Total occlusion pre	24.2%	25.8%	.84	16.1%	15.9%	.97
Total occlusion fup	19.4%	19.4%	1.0	14.5%	9.5%	.39

Table 6. Comparison of quantitative angiographic acute and late results between the ELCA and PTCA groups according to epicardial lesion location.

	Left anterior descending location			Right coronary artery location			Circumflex location		
	ELCA	**BA**		**ELCA**	**BA**		**ELCA**	**BA**	
	(n=45)	(n=56)		(n=45)	(n=38)		(n=34)	(n=31)	
Vessel size (mm)	2.47±0.49	2.41±0.48	.52	2.65±0.45	2.60±0.78	.74	2.37±0.43	2.45±0.49	.51
Lesion length (mm)	8.81±3.95	8.90±4.06	.18	9.98±3.95	8.98±3.27	.38	9.29±3.23	8.88±3.75	.43
MLD pre (mm)	0.74±0.46	0.76±0.46	.83	0.79±0.45	0.93±0.45	.14	0.80±0.42	0.62±0.46	.11
MLD post (mm)	1.63±0.37	1.58±0.31	.49	1.84±0.46	1.65±0.36	.03	1.56±0.32	1.57±0.37	.88
MLD fup (mm)	1.17±0.59	1.19±0.65	.84	1.27±0.86	1.27±0.76	.99	1.04±0.63	1.35±0.68	.05
% DS pre	69.2±20.4	68.4±17.8	.85	69.6±17.1	65.4±18.8	.29	66.0±17.1	73.7±19.5	.10
% DS post	38.0±10.1	37.3±9.0	.69	37.1±12.4	39.7±9.7	.78	37.7±7.8	36.9±7.6	.69
% DS fup	54.9±20.4	53.9±22.3	.81	57.2±25.1	56.9±25.4	.94	56.2±24.8	45.4±22.1	.06
Acute Gain (mm)	0.89±0.52	0.82±0.46	.50	1.06±0.57	0.71±0.43	.003	0.76±0.46	0.95±0.61	.15
Late Loss (mm)	0.46±0.64	0.39±0.57	.56	0.57±0.85	0.37±0.66	.24	0.52±0.57	0.22±0.67	.05
Net Gain (mm)	0.43±0.70	0.43±0.61	.97	0.49±0.73	0.34±0.71	.36	0.24±0.63	0.73±0.66	.003
Loss Index	0.94±2.24	0.52±0.80	.19	0.54±0.74	0.36±1.96	.61	0.77±1.27	0.08±0.72	.008
DS ≥ 50%	55.6%	48.2%	.46	53.3%	47.4%	.59	50.0%	22.6%	.02
Loss ≥ 0.4mm	46.7%	37.5%	.35	46.7%	39.5%	.51	52.9%	29.0%	.05
Loss ≥ gain/2	48.9%	41.1%	.43	46.7%	44.7%	.86	52.9%	25.8%	.03
Total occlusion pre	24.4%	19.6%	.56	20.0%	13.2%	.41	14.7%	32.3%	.09
Total occlusion fup	11.1%	14.3%	.64	20.0%	18.4%	.86	20.6%	9.7%	.22

Figure 1: Linear regression analysis comparing the relationship between luminal increase at intervention and loss during follow up between PTCA and ELCA. Somewhat greater luminal loss can be anticipated after ELCA than PTCA at increasing luminal gain.



Comparison with other studies - evidence for device specific effects on restenosis after intervention

Supportive findings have been reported by a recent observational study comparing excimer laser angioplasty and balloon angioplasty in patients matched for baseline clinical and angiographic characteristics [11]. When these results are interpreted together with the findings of other observational studies in matched [28-30] and unmatched comparisons [31,32], a hypothesis of device specific influences on late angiographic results of intervention may be supported [33,34]. The opposing findings of the previously mentioned studies represent the alternative viewpoint of what may actually be considered something of a conundrum in interventional cardiology, namely whether or not the device chosen for intervention may exert a specific influence on the propensity for luminal renarrowing and restenosis after coronary interventions [35]. That the magnitude of the acute luminal result exacts an integral determining influence on the late interventional outcome now seems beyond doubt [13,16-19,28-39], as is confirmed also in this study, by the significant positive association between acute gain and late luminal diameter in multivariate analysis (in addition, considerably greater late lumen is evident among "optimal" compared with "sub-optimal" acute results). What remains to be resolved is whether there may be an additional individual effect of the device used for intervention. The results of this evaluationstrongly support the existence of such an effect, which might be considered responsible for the consistently less favourable late angiographic results observed for ELCA treatment in patients, who, it must be remembered, demonstrate similar baseline clinical characteristics and angiographic morphology and in whom, acute post-procedural results tended to be actually somewhat superior to those achieved by balloon angioplasty alone.

Insights provided by sub-set analyses

Given the previously proposed role of excimer laser angioplasty, for the treatment of lesions unfavourable for conventional angioplasty [5], it is noteworthy that in this study, ELCA achieved less favourable late results in the longer lesion sub-set, demonstrating particularly greater loss index compared with PTCA. Similarly, inclusion or omission of totally occluded lesions from analysis did not alter the findings of greater restenosis propensity associated with ELCA. Also, in smaller vessels, loss index was significantly greater in the ELCA treated group. In the "more optimal" acute result sub-group comparison, PTCA also achieved more favourable late angiographic results, despite the fact that the acute result had been significantly larger in the ELCA treated group.

The strikingly more favourable late angiographic outcome after PTCA compared with ELCA among circumflex lesions is a curious finding. Although the number of lesions located in the circumflex artery in each group is small (34 in the ELCA group and 31 in the PTCA group), the groups are well balanced and comparable for both baseline and post-procedural angiographic measurements. Thus the significantly greater luminal loss and smaller follow up lumen in the ELCA group can be interpreted as being due to the greater restenosis propensity of ELCA, reflected by the significantly greater loss index. A trend toward greater loss index was also observed among right coronary artery lesions treated by ELCA. It is also worth noting, that in contrast to other studies in patients treated by balloon angioplasty and other devices [13,16-18], lesion location in the LAD was not found to be an independent determinant of greater luminal renarrowing in multivariate analysis in this study.

Clinical implications

Ultimately, the findings of a greater restenosis propensity of ELCA compared with conventional balloon angioplasty raise serious doubts as to the long term effectiveness of this treatment modality, at least according to the prevailing interventional practice during the course of this trial. It must be considered that if the capacity of ELCA to ablate atherosclerotic tissue and to recanalize unfavourable coronary lesions, is to be utilized to its fullest extent, the demonstrated increased propensity to luminal renarrowing must be overcome. This may be considered as having 2 perspectives: first, the simple mechanical aspect of optimization of acute results to compensate for the increased restenosis propensity, thus use of progressively larger catheters to ablate more tissue and facilitate more optimal adjunctive balloon angioplasty, or by clinical reflection on adjunctive use of intracoronary stent implantation, which would carry additional risks and potential multiplication of costs [36,37]; second and still the major challenge in interventional cardiology, the problem of attempting to actually reduce the degree of restenosis. This latter aspect may actually be promisingly addressed in the near future, by a combination of the rather simple technique of saline infusion at the laser tip during each ablation run, coupled with slow catheter advancement (0.5mm/second) but more excitingly by a revolutionary development in laser catheter design. This will entail some diminution in individual fiber diameter to reduce the mechanical dead space, but more importantly, through employment of a silica window at the catheter tip to diverge the emitted light beams, a homogenous light distribution at the target is achieved, which has already been convincingly demonstrated in experimental studies to produce effective and virtually atraumatic tissue ablation. Further, with increase in the ablating surface and decrease in effective dead space, less energy is required for tissue ablation, whereby at $9mJ/mm^2$ a rate of 1mm per 30 seconds and at $15mJ/mm^2$, 1mm per 7.5 seconds have been

demonstrated in human atherosclerotic tissue, compared with no ablation at 30mJ/mm^2 using a conventional 1.4mm laser catheter (PW Serruys personal communication).

Limitations

Although this study has been performed in the context of randomized clinical trial, it involves post-hoc analyses, which were not prospectively included in the study design and as such the specific sub-studies described here may be considered "observational". The overall patient numbers are relatively small, compared with the patient numbers reported in some clinical ELCA registry reports [7-9] and those recruited in randomized trials of other devices [36-39]. Nevertheless, the strong points of the trial are meticulous and comprehensive prospective data collection and, in particular, the virtually complete quantitative angiographic follow-up in all patients who underwent an initially successful intervention. The 80% procedural success rate with ELCA is less than in some registry based reports, which may relate to the inclusion of 30% of lesions with functional or total occlusion and inclusion in the report of all patients randomized, whether the lesion was crossed by guidewire or not, whereas in registry reports, patients are only included if the lesion is successfully crossed by guidewire [7-9]. Of the 138 lesions randomized to ELCA which were successfully crossed by guidewire and in which an attempt was made to treat by excimer laser, 126 yielded procedural success giving a 92% success rate, which is certainly comparable to registry reports. During the course of this study, saline infusion at the catheter tip during laser activtion (to reduce shock wave and vapour bubble formation), has become incorporated into clinical practice by many practitioners, so that the basic technique practiced throughout most of this study may now be considered inappropriate. However, although carrying some implication for restenosis provocation, it was the universal clinical practice during most of the study period and must thus be considered more a general technical limitation in prevailing excimer laser technique rather than a specific limitation of this study.

Conclusions

Among the patients successfully treated by excimer laser coronary angioplasty and or balloon angioplasty in the AMROE trial, despite comparable or event somewhat superior acute angiographic results, excimer laser was found to be associated with a significantly greater angiographic restenosis propensity. This finding may be related to inherently greater vessel wall injury during the laser procedure than by balloon angioplasty alone. Fundamental improvements in laser technology appear to be required to address this issue, so that this powerful interventional tool may retain a suitable role in percutaneous coronary revascularization.

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CHAPTER 9

A CLINICAL AND ANGIOGRAPHIC COMPARISON OF MATCHED PATIENTS WITH SUCCESSFUL DIRECTIONAL ATHERECTOMY OR STENT IMPLANTATION FOR PRIMARY CORONARY ARTERY LESIONS

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Abstract

Background: Directional atherectomy and coronary stent implantation have been shown to achieve a more optimal acute result which subsequently may lead to a more favorable long-term angiographic and less target vessel revascularizations than angioplasty. However, it remains to be determined whether one of these devices may in fact provide consistently superior results than the other.

Objectives: This study was designed to compare the long-term clinical and angiographic effects of successful directional atherectomy and stent implantation and to examine whether restenosis is related to the mechanism of luminal improvement as well as the extent of luminal gain.

Methods: To allow meaningful comparisons a prospectively collected series of 117 patients successfully treated by atherectomy were individually matched with a prospectively collected series of 117 patients successfully treated by stent implantation. Matching for baseline characteristics identified patients with identical lesion location and lesion severity and acute and late angiographic and clinical outcome were compared. To evaluate the possibility of a device-effect on restenosis, patients were further matched for acute angiographic outcome, as well as baseline characteristics, providing 150 matched patients for comparison. As confirmatory analysis, multivariate models were constructed to predict late lumen diameter.

Results: Matching resulted in two comparable groups with equivalent baseline clinical and stenosis characteristics. Atherectomy led to a smaller acute gain than stenting and because late loss was similar in both groups, stenting resulted in a larger late lumen (1.96 mm vs 1.66 mm;$p < 0.0001$). When matched for acute gain and baseline characteristics, luminal loss was more pronounced after atherectomy and thus the minimal luminal diameter at follow-up differed significantly between the two groups (1.66 mm vs 1.90 mm;$p = 0.004$). This beneficial angiographic effect of stenting was accompanied by a reduced need for repeat interventions. Multivariate analysis confirmed the independent effect of device used, whereby less loss and greater follow-up lumen was predicted for stent implantation compared with atherectomy.

Conclusions: Successful stent implantation provided a more favorable long-term angiographic outcome, a reduction in restenosis rate and need for target lesion revascularization than atherectomy. This favorable effect is not only related to a larger acute gain but stenting also seems to attenuate of late lumen loss.

INTRODUCTION

The importance of optimization of acute interventional results with all treatment devices is now well recognized [1-13]. However, it remains to be determined whether the extent of the vessel wall healing process after an intracoronary intervention, and therefore, the angiographic outcome, is also influenced by the specific mechanism of an interventional device. An initial exploration of such a relationship between device-specificity and restenosis using the loss index as an angiographic correlate of the "proportional injury model [1,2]" could not detect such an independent effect even if the results were corrected for the difference in acute gain which has been shown to be the most important predictors of restenosis [1,4,5,7,9]. On the other hand, our group has hypothesized that the varying mechanisms of action of interventional devices might induce varying degrees of luminal renarrowing in patients matched for clinical and lesion characteristics [7,8]. In order to try to reconcile these two viewpoints, an automated case-match method inwhich patients are matched for baseline *and* procedural characteristics is developed to explore differences in late outcome between patients treated with new devices. An additional advantage of this matching technique is the possibility to assess the long-term results without a collinearity between acute gain and device.

Recently, directional atherectomy and coronary stenting have been evaluated against conventional balloon angioplasty for their ability to reduce restenosis [10-13]. Although both techniques achieved a greater luminal gain than balloon angioplasty, only the stent reduced the restenosis rate significantly [12,13]. While these trials showed a comparable luminal gain after atherectomy and stenting, we recognized that the difference in luminal renarrowing following atherectomy and stenting may relate to either the extent *or* the mechanism (debulking versus scaffolding) of luminal improvement. In this study we comparatively evaluated successful directional atherectomy and stent implantation in a prospectively collected series of 234 patients using the previously validated matching methodology. By matching for acute angiographic outcome, as well as baseline characteristics, we extended our observations and tested the hypothesis that each device has unique properties with respect to luminal renarrowing which are independent of clinical, angiographic or procedural characteristics.

PATIENTS AND METHODS

Atherectomy patients: From September 1989 through March 1994, 208 patients underwent 214 directional atherectomy procedures for native coronary or bypass graft lesions. Of these, 150 consecutive patients (who underwent 157 successful procedures) presently have had a 6 months follow-up angiography (angiographic

follow-up rate of 90%). For the purpose of this study, the late outcome of atherectomy was compared with that of stenting for consecutive native primary lesions. Therefore patients with restenotic lesions and patients with a subacute coronary occlusion <24 hours were excluded. Of the 150 patients, 3 were treated for a lesion in a venous bypass graft and 13 had an atherectomy for 18 restenotic lesions after a previous angioplasty. Thus, 134 patients who underwent 136 successful atherectomy procedures for native primary coronary artery disease were eligible for matching.

Stent patients: From January 1990 through March 1994, 240 patients were successfully treated by Palmaz Schatz stent implantation at the Thoraxcenter. Of these, 213 patients had a stent electively implanted for a primary coronary lesion without clinical sequelae (i.e. no sub-acute occlusion). Of these, 179 consecutive patients presently have had a 6 months follow-up angiography and were thus eligible for matching.

Prior to intervention, patients had documented myocardial ischemia which required revascularization. Patients were selected for directional atherectomy or stent implantation when they presented with a stenosis in a proximal non-tortuous coronary artery with a presumed reference diameter >2.5 mm. All patients gave informed consent and were prospectively scheduled for 6-months angiography which was completed in 90% of the patients. The study was approved by the hospital's Institutional Review Board. All clinical and angiographic data were collected prospectively.

Atherectomy and stenting procedural details: The atherectomy procedure was performed as described previously [7,8,9,12]. Briefly, the atherectomy device was directed over a guide-wire and positioned across the stenosis. The support balloon was then inflated up to 7.5 psi, the cutter was retracted and balloon inflation pressure was increased to maximally 45 psi. The driving motor was activated and the rotating cutter was slowly advanced to cut and collect the protruding atherosclerotic lesion in the collecting chamber located at the tip of the catheter. After every pass the balloon was deflated and either removed or repositioned. The following atherectomy devices were used: 6 Fr device in 34% and the 7 Fr device in 66% of the patients. Adjunctive balloon dilatation was performed in 23%. While an optimum angiographic result was sought for each lesion treated, the procedure was considered angiographically successful when the residual diameter stenosis was less than 50% after tissue retrieval. This classic definition of success should be viewed in the historical perspective, while nowadays a luminal gain of at least 0.7 mm or a post-atherectomy diameter stenosis <20% may be deemed necessary before considering the procedure as successful as recently observed in retrospective analyses [2] and as defined in the ongoing atherectomy trials (BOAT, OARS, EUROCARE).

Stenting was performed via the femoral approach and the stent was delivered by inflation of the balloon which contained the crimped stent. The following Palmaz Schatz stents were implanted: 3.0 mm (46%), 3.5 mm (39%) and 4.0 mm (18%). Additional intra-stent balloon dilatation was performed in 27 (23%) patients. Anticoagulation during and following stent implantation was given according to the protocol and contained heparin, dextran, dipyridamole, aspirin and warfarin for three months. Patients were monitored as described earlier [7,8,9,12].

Quantitative coronary angiography: Quantitative analysis of the coronary segments was performed with the computer based Coronary Angiography Analysis System (CAAS), which has been previously validated and described in detail, including the standardized angiographic acquisition and core laboratory assessment and analysis methods [8,12,17,18].

Matching process: The process of matching for clinical and angiographic characteristics has been previously described [7,8,15]. Lesions were individually matched according to location, minimal luminal diameter aand interpolated reference diameter. According to previously described principles (i) the angiographic dimensions of matched lesions are assumed to be "identical", (ii) the observed difference between the two "identical" lesions must be within the range of the reproducibility of the CAAS analysis, 0.1 mm (=1 SD) and (iii) the reference diameter of the lesions to be matched are selected within a range of ± 0.3 mm (=3 SD) [8,17,18]. Clinical factors such as gender, diabetes, hypercholesterolemia and non-exertional angina were taken into account.

The automated matching programme, carried out in blinded fashion, identified 117 patients with 117 lesions treated by atherectomy which individually matched 117 patients with 117 lesions successfully treated by stent implantation (diameter stenosis <50% on visual inspection). The remaining patients (13%) of the atherectomy cohort could not be matched because no identical stent patient was found according to the pre-specified matching criteria. The clinical and angiographic details of the two groups are given in Table 1. In the second matching programme, where post procedural minimal luminal diameter was added to the parameters for matching, 75 patients could be matched from each traetment group and constituted the study population for specific evaluation of the influence of the device itself of late results.

Clinical follow-up: All patients were prospectively seen at the outpatient clinical at regular time intervals during a 7 months follow-up period. The clinical endpoints were the following: death, myocardial infarction, coronary artery bypass grafting and repeat percutaneous intervention. Death was defined to include all death. Myocardial infarction was defined as the occurrence of a new abnormal Q-wave and an increase in creatine kinase more

than twice the upper limit of normal. Revascularization of the target lesion was defined as angioplasty or bypass surgery performed because of restenosis of the target lesion in association with angina, objective evidence of myocardial ischemia or both.

Statistics: The unit of analysis reported here is the lesion, not the patient. All values are expressed as mean values ± 1 SD). Comparisons of continuous parameters between the two groups were performed using the paired student's t-test. Selected angiographic variables were evaluated by univariate regression analysis for their correlation with absolute luminal loss and minimal luminal diameter at follow-up. Multivariate stepwise regression analysis using a commercially available statistical software package (SAS, SAS Institute Inc, Cary, North Carolina) was utilized to take account of the influence of lesion location, pre-procedural minimal luminal diameter, acute luminal gain and vessel size in evaluating their contribution to the minimal luminal diameter at follow-up and late luminal loss, as previously described [3]. Differences between categorical variables were tested with the chi-square and Fisher exact tests as appropriate. Target lesion revascularization was analyzed by means of Kaplan-Meier survival curves, with differences between the two groups compared by Wilcoxon test. Differences were considered statistically significant where the p-value was less than 0.05.

RESULTS

Outcome of the matching process (Table 1): The automated computer matching programme provided 117 paired atherectomy and stent patients with comparable clinical and angiographic characteristics (lesion location and severity). The 234 patients were predominantly male with a mean age of 57 ± 11 years. Patients were predominantly treated for stable angina according to the American Heart Association classification. By matching design no difference in lesion distribution exists between the atherectomy and stent group: left anterior descending (77% vs 77%), right coronary artery (15% vs 15%) and left circumflex artery (8% vs 8%). No differences between the groups were found for risk factors for coronary artery disease or preceding cardiovascular events such as infarction or bypass surgery. By study design, no significant differences between the atherectomy and stent group were found in baseline quantitative angiographic parameters: mean vessel size (3.09 ± 0.45 vs 3.10 ± 0.44 mm), pre-procedural minimal luminal diameter (1.12 ± 0.29 mm vs 1.12 ± 0.27 mm) and percentage diameter stenosis (64 ± 8% vs 64 ± 8%) respectively.

Table 1. Clinical and angiographic characteristics of the 117 study patients.

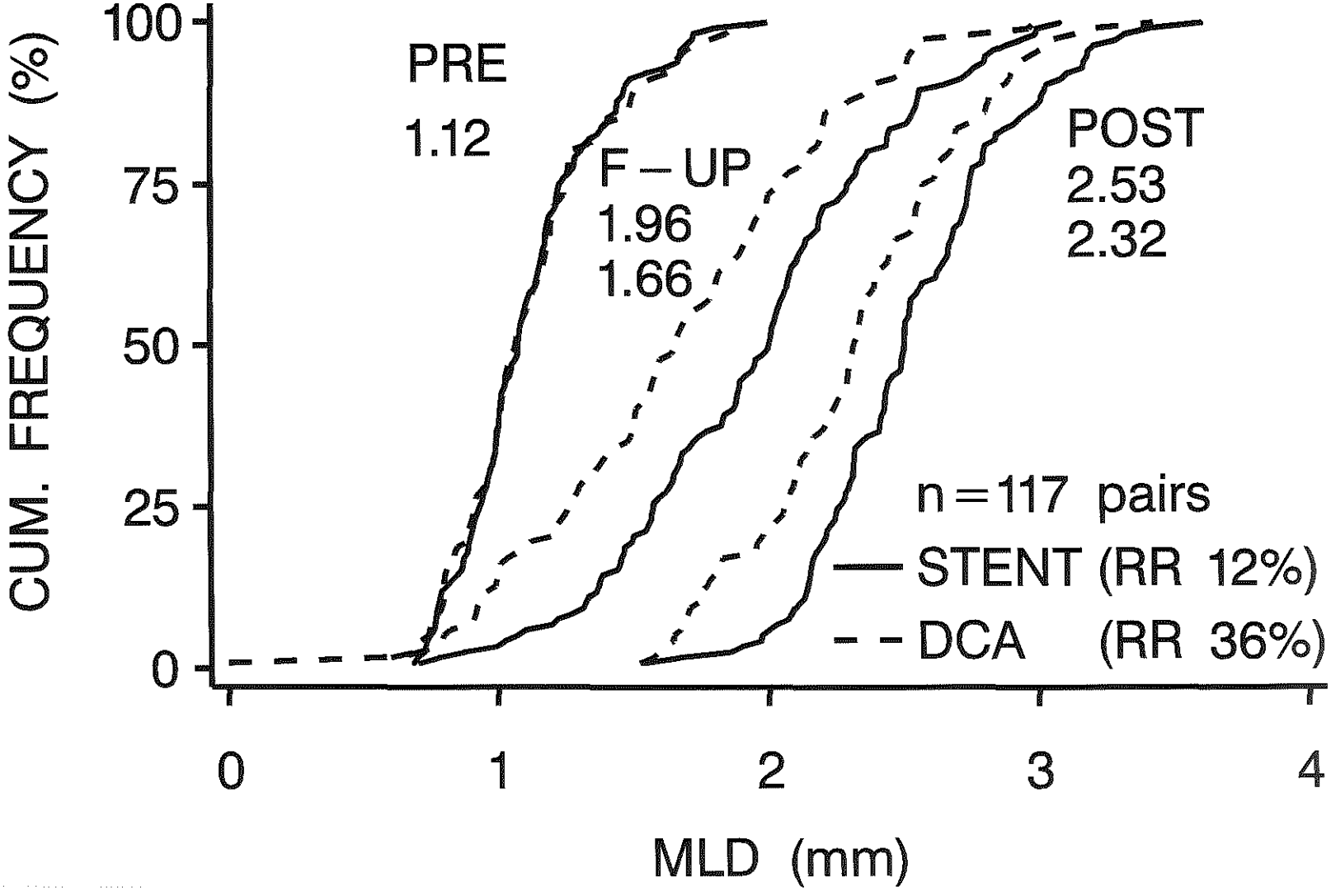
	Atherectomy	Stent	p-value
Age (yr)	58 ± 11	57 ± 10	NS
Male (%)	76	81	NS
Vessel treated (%)			
LAD	77	77	NS
LCX	8	8	NS
RCA	15	15	NS
Non-exertional angina (%)	38	48	NS
Previous infarction (%)	25	18	NS
Previous CABG (%)	0	0	NS
Diabetes (%)	6	9	NS
Hypercholesterolemia(%)	24	23	NS

LAD=left anterior descending coronary artery, LCX=left circumflex, RCA=right coronary artery, CABG=coronary artery bypass grafting, Min Luminal Diameter=minimal luminal diameter.

Immediate and late outcome after matching for baseline characteristics (table 2, 3 and figure 1):

The reference diameters were not significantly different after atherectomy or stenting (3.23 ± 0.46 mm vs 3.22 ± 0.41 mm;p=0.83). Directional atherectomy resulted in a smaller acute gain in minimal luminal diameter (1.20 ± 0.46 mm versus 1.41 ± 0.39 mm;p=0.002) with a consequently lower post-procedural minimal luminal diameter (2.32 ± 0.41 mm versus 2.53 ± 0.37 mm;p<0.001) and concomitantly higher percent diameter stenosis (28 ± 10% versus 21 ± 7%;p<0.001). Because absolute loss during follow-up did

Figure 1: Cumulative frequency curves to illustrate acute and follow-up effects in minimal luminal diameter (MLD) of directional atherectomy and stent implantation in patients matched for lesion location and severity. Stent implantation is associated with significantly greater acute and 6 month results.



not differ significantly (0.66 ± 0.58 mm vs 0.57 ± 0.53 mm;p=0.22), the initial favorable acute result following stenting was maintained during follow-up. Thus, the minimal luminal diameter at follow-up after atherectomy was significantly lower than after stenting (1.66 ± 0.55 mm versus 1.96 ± 0.52 mm; p<0.0001). Accordingly, atherectomy yielded a lower net gain (0.54 ± 0.58 vs 0.84 ± 0.53;p<0.0001) and a higher percentage diameter stenosis at follow-up (44 ± 16% vs 35 ± 13%;p<0.0001). The restenosis rate (diameter stenosis at follow-up >50%) after stenting was significantly lower (14% vs 36%;p=.0053) and late ***clinical*** follow-up which was 100% complete, was also more favorable, with a reduced need for repeat revascularization (12% versus 23%;p=0.05)(figure III). In simple linear regression analysis, the well described linear relationship was observed between acute gain and late loss in the two groups, with a steeper line slope in the atherectomy group (0.50) than in the stent group (0.30) although, apparently because of data scatter giving wide confidence intervals, this difference did not reach statistical significance.

In multivariate analysis, lesion location, vessel size, minimal luminal diameter pre-intervention, absolute gain and device type were identified as independent predictors of the absolute luminal loss and minimal luminal diameter at follow-up. The models can be described by the following equations:

(i) ***loss*** = -0.35 - 0.24 vessel size + 0.63 gain + 0.58 MLD pre + 0.16 LAD + 0.22 device.

(ii)***MLD at follow-up*** = 0.35 + 0.24 vessel size + 0.37 gain + 0.42 MLD pre - 0.16 LAD - 0.22 device.

(where atherectomy =1 and stenting =0)(LAD lesion =1, non-LAD lesion =0).

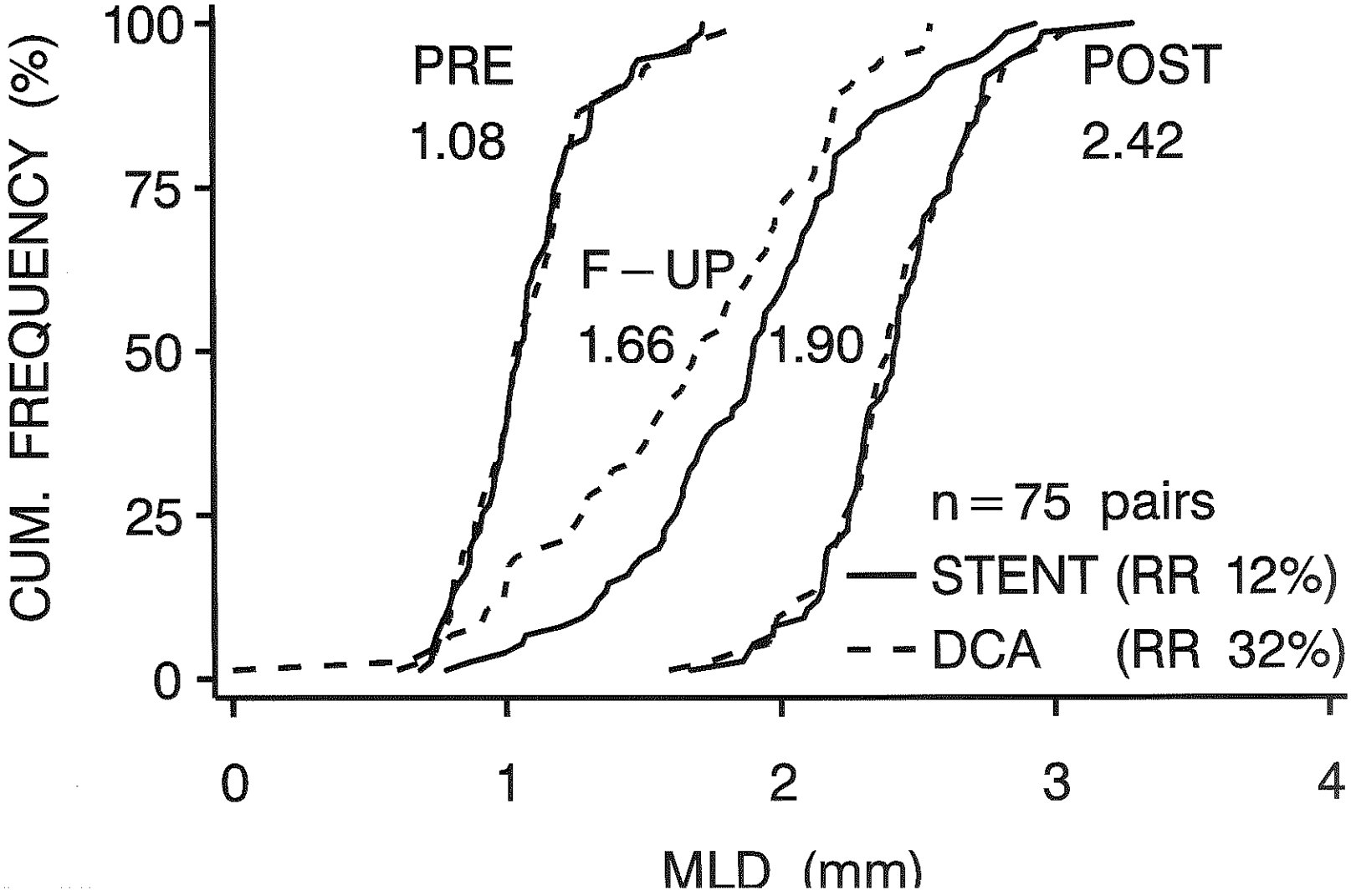
Table 2. Comparison of quantitative angiographic data of 234 matched patients who underwent atherectomy or stent implantation for similar lesion severity.

	Atherectomy (n=117)	Stent (n=117)	p-value
Reference diameter pre (mm)	3.09 ± 0.45	3.10 ± 0.44	NS
Minimal luminal diameter pre (mm)	1.12 ± 0.29	1.12 ± 0.27	NS
Minimal luminal diameter post (mm)	2.32 ± 0.41	2.53 ± 0.37	0.001
Minimal luminal diameter f-up (mm)	1.66 ± 0.55	1.96 ± 0.51	0.0001
Diameter stenosis pre (%)	64 ± 8	64 ± 8	0.0001
Diameter stenosis post (%)	28 ± 10	21 ± 7	0.0001
Diameter stenosis f-up (%)	44 ± 17	35 ± 13	0.0001
Absolute luminal loss (mm)	0.66 ± 0.58	0.57 ± 0.47	NS
Relative luminal loss	0.22 ± 0.19	0.19 ± 0.15	NS
Restenosis rate (%)	36	14	0.005
Lesion length (mm)	6.83 ± 2.54	7.23 ± 2.05	NS
Symmetry index pre	0.45 ± 0.25	0.37 ± 0.25	NS

TABLE 3. Long-term clinical outcome after successful atherectomy and stent implantation in matched patients.

	Atherectomy	Stent	
Death (%)	0	0	NS
Myocardial infarction (%)	3	3	NS
CABG (%)	3	2	NS
Repeat PTCA (%)	20	10	0.07

Figure 2: The graphic display of the immediate and late results after atherectomy and stenting in patients who were matched for acute results as well as baseline characteristics. Stent implantation is associated with superior late results, due to less luminal loss than directional atherectomy.



Immediate and late outcome after matching for procedural outcome as well as baseline characteristics (table 4, figure 2):

Matching for procedural outcome (MLD post = 2.41 ± 0.29 mm vs 2.42 ± 0.28 mm ;p=0.84), as well as baseline characteristics (vessel size = 3.06 ± 0.43 mm vs 3.05 ± 0.42 mm;p=0.93), (MLD pre = 1.09 ± 0.25 mm vs 1.08 ± 0.24 mm;p=0.98) identified 75 pairs of matched atherectomy and stent patients. Despite the similar acute gain achieved by each device (1.33 ± 0.37 mm vs 1.34 ± 0.34 mm;p=0.86), the atherectomy patients had a significantly greater late loss (0.75 ± 0.57 mm vs 0.52 ± 0.44 mm;p<0.006) so that the residual minimal luminal diameter at follow-up was significantly smaller (1.66 ± 0.53 mm vs 1.90 ± 0.46 mm;p<0.004) and percentage diameter stenosis at follow-up greater (43 ± 17% vs 36 ± 12%;p<0.004) after atherectomy than after stenting. Additionally, the restenosis rate (diameter stenosis at follow-up >50%) after stenting were significantly lower than after atherectomy (12% vs 32%;p=.00026).

The multivariate models to predict late loss and residual diameter at follow-up were found to be:

(i) *loss* = -0.74 - 0.18 vessel size + 0.68 Gain + 0.76 MLD pre + 0.13 LAD + 0.24 device.

(ii)*MLD at follow-up* = 0.74 + 0.18 vessel size + 0.32 gain + 0.24 MLD pre - 0.13 LAD - 0.24 device.

(where atherectomy =1 and stenting=0).

After matching for procedural outcome, thus, the greater loss observed after directional atherectomy is reflected by the finding in multivariate analysis of a significant independent effect of the device used, whereby less late loss and greater minimal luminal diameter at follow-up is predicted for stent implantation.

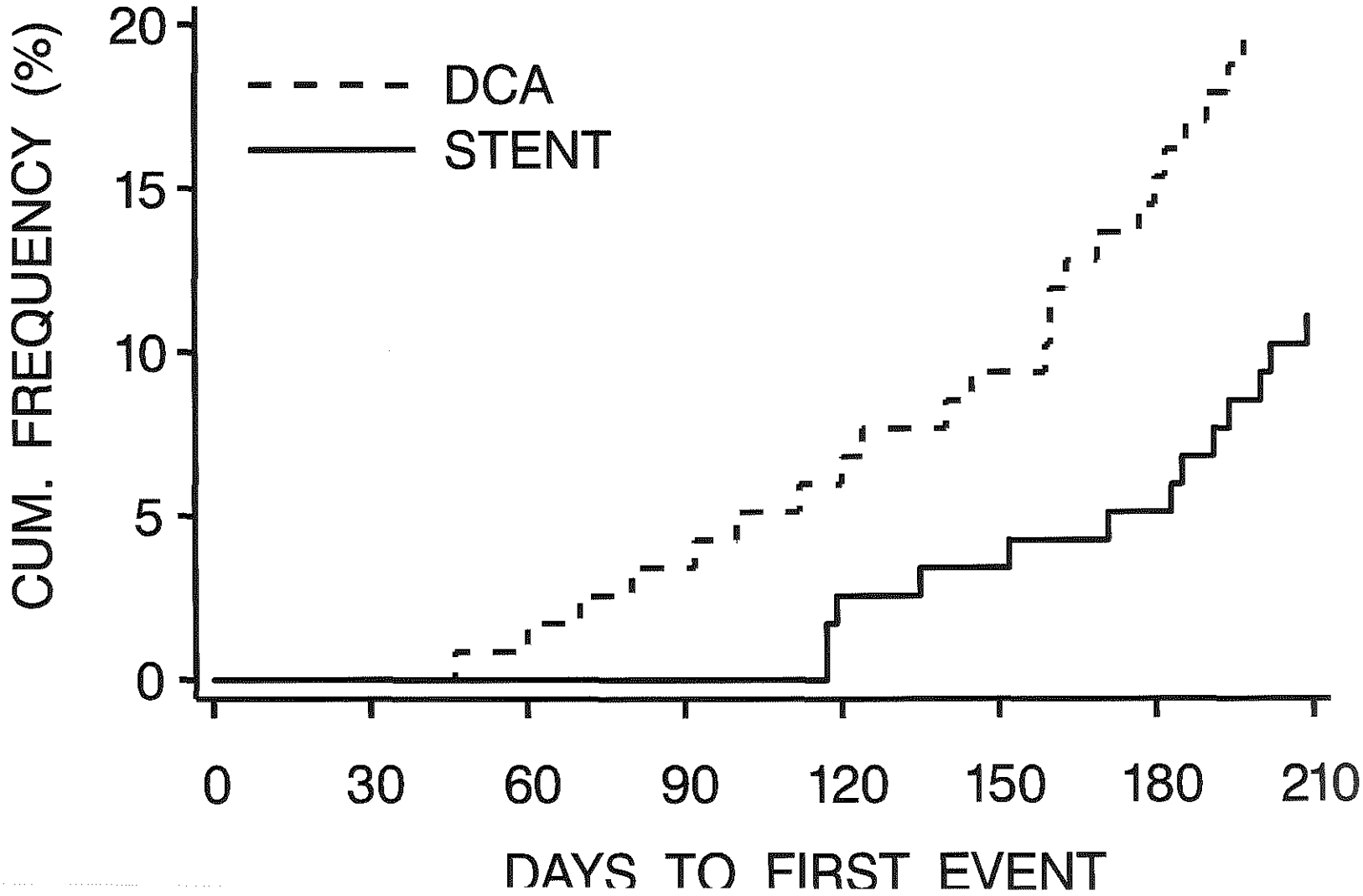
Table 4. Comparison of quantitative angiographic data of 150 matched patients who underwent atherectomy or stent implantation for similar lesion severity and procedural outcome.

	Atherectomy (n=75)	Stent (n=75)	p-value
Reference diameter pre (mm)	3.06 ± 0.43	3.05 ± 0.42	NS
Minimal luminal diameter pre (mm)	1.09 ± 0.25	1.08 ± 0.24	NS
Minimal luminal diameter post (mm)	2.41 ± 0.29	2.42 ± 0.28	NS
Minimal luminal diameter f-up (mm)	1.66 ± 0.53	1.90 ± 0.47	0.0035
Diameter stenosis pre (%)	64 ± 8	64 ± 7	NS
Diameter stenosis post (%)	25 ± 7	22 ± 7	0.0064
Diameter stenosis f-up (%)	43 ± 17	36 ± 12	0.0035
Absolute luminal loss (mm)	0.75 ± 0.57	0.52 ± 0.44	0.0056
Relative luminal loss	0.25 ± 0.18	0.18 ± 0.14	0.0082
Restenosis rate (%)	32	12	0.0003
Lesion length (mm)	6.88 ± 2.34	7.40 ± 2.24	NS
Symmetry index	0.41 ± 0.25	0.36 ± 0.23	NS

DISCUSSION

In this study, we have compared the immediate and long-term clinical and angiographic effects of successful directional atherectomy and stent implantation for primary coronary artery lesions. The major findings of this study are threefold: (1) in matched patients with similar lesion severity and location, stenting is associated with a significantly larger acute lumen which is preserved during follow-up and is reflected by a concomitant reduced need for target lesion revascularizations during the first 6 months, (2) when the procedural result and baseline characteristics are matched, stent implantation is found to provide a superior late angiographic outcome due to significant less luminal renarrowing than after atherectomy and (3) these findings may consider a device specific effect on luminal renarrowing, independent of baseline characteristics or acute procedural result.

Figure 3: Cumulative curves for target lesion revascularization. Fewer patients in the stent treated group than in the atherectomy treated group needed revascularization (repeat angioplasty or coronary artery bypass surgery) of the target artery (p=0.05).



Matching

Despite their clinical necessity, randomized clinical trials of new coronary interventional devices are associated with certain limitations, in evaluating the inherent effect of the device itself on late angiographic results of intervention, since randomization is carried out before intervention and the acute interventional result may differ with the treatment strategies being compared, as shown in recent major trials [1]. In order to specifically evaluate the influence of the device used for intervention, independent of acute procedural results, in this study, we applied the previously validated concept of matching [7,8,15,19,20,22] to the atherectomy and stent populations. In particular, the confounding effects of unequal vessel size and acute luminal gain which have been shown to be independent predictors of restenosis [4,5,9] and which cannot be controlled in randomized studies, are avoided by this matching technique. Furthermore, matching a study population with a reference patient group of similar characteristics can compensate for some of the limitations of nonrandomized studies such as population heterogeneity [21]. Despite a potential patient selection bias in matching studies, our atherectomy and stent patients had comparable angiographic characteristics and acute outcome as the CAVEAT, CCAT and BENESTENT and STRESS patients [10-13]. This indicates that the findings in our comparative study may be applicable to patients selected for stenting or atherectomy and could be useful in planning future trials.

Determinants of a favorable long-term outcome

When we first studied the differences between restenosis after atherectomy and balloon angioplasty in a matched series, we not only observed a linear relationship between acute gain and late loss but in addition recognized that the slope of this regression line may represent an index of luminal renarrowing specific for each treatment modality [7,8,22]. In a subsequent matching study, we further extended this observation and could indeed demonstrate that the process of luminal renarrowing was not only dependent on the extent but also on the mechanism of luminal improvement [20]. These observations may implicate that a beneficial late outcome can be achieved using a device which can associate a large acute gain with a favorable relationship between the degree of vessel wall injury and vessel wall response. In this study, we compared the two available devices which have the capacity to consistently achieve a large acute gain and found that the long-term outcome after stent implantation is significantly superior to atherectomy. A superior acute gain achieved by stenting in patients matched only for baseline characteristics indicates that the improved angiographic outcome of stenting may be due to the combination of the extent and possibly the mechanism of luminal increase.

Why should stent implantation provide superior results to atherectomy ?

The comprehensive analysis of long-term outcome of stent implantation and atherectomy suggests that the scaffolding effect of stenting may lead to less luminal loss with a larger late lumen at follow-up compared to the debulking mechanism of directional atherectomy in matched patients. Multivariate analysis confirmed the significant independent influence of the device used whereby less late loss and a larger lumen diameter at follow-up was predicted for stent implantation compared with directional atherectomy. Earlier observational angiographic studies have demonstrated that this beneficial effect may be secondary to less elastic recoil [23] or to restoring the "Glagovian balance" between plaque and luminal area [24]. Furthermore, by using coronary angioscopy and ultrasound techniques, Baptista et al [25] have demonstrated that stenting reduces the amount of trauma to the vessel wall compared with atherectomy, which ultimately may lead to a reduced vessel wall healing response (i.e. renarrowing). Recently, these suggestions have been shown to be a valid explanation for the favorable long-term stenting effect. In a well controlled IVUS study, Mintz et al have shown that luminal renarrowing after stenting is predominantly the result of intimal hyperplasia with a negligable amount of recoil [26]. Similarly, Kimura et al have documented the timing of restenosis following atherectomy and stenting using serial ultrasound measurements (personal communication). They found an increase in external elastic membrane area (EEM) during the first month after stenting which remained stable thereafter, as opposed to a reduction in EEM area after atherectomy.

Therefore, the favorable stent effect found in this study concurs with the angioscopic findings of a smoother and more circular vessel wall configuration after stenting than atherectomy [27,28] and the scaffolding effect of stenting as demonstrated in serial ultrasound studies [26,29]. It seems unlikely that this favorable scaffolding effect of stenting is attributable to a difference in treatment strategy (optimal stenting versus less optimal atherectomy) since this effect is avoided by matching for baseline characteristics *and* outcome. The post-atherectomy luminal diameter found in this series is comparable with that observed in CCAT and CAVEAT [10,11] although smaller than in the series of Kuntz et al [1,6], while our stent results are comparable to the BENESTENT, STRESS and Palmaz Schatz Stent Study [12,13,30]. Furthermore such an observation does not influence the conclusions of the present study because the linear relationship between acute gain and late loss is maintained at all levels of gain showing a favorable effect (lower slope value) for stenting when compared with atherectomy.

Clinical implications

The favorable angiographic outcome of stenting is further underlined by a significant reduction in the clinical need for target-vessel revascularizations. In accordance with Baim and Kuntz [31], we have refrained from using the composite "any event" clinical end-point criteria to compare stenting with atherectomy to consider the potentially "noise" induced by non-device related cardiac events. Using such "filtered clinical end points [31]", we found an agreement between quantitative angiographic follow-up and the late clinical course emphasizing the need for a dual approach (angiographic and clinical follow-up) in that quantitative angiography demonstrates the mechanistic explanation of the favorable stent results while clinical follow-up provide the clinical implications of this finding. The 12% restenosis rate after successful stenting found in this study is similar to the 14% restenosis rate of successfully stented patients in the BENESTENT trial [12] (i.e. successful stent implantation without subacute occlusion) and comparable to the recent publicised preliminary findings of the pilot phase BENESTENT II [32]. Accordingly, given the choice between these two powerful treatment modalities, at this time, stent implantation would appear to be associated with more favourable acute and long term clinical and angiographic results and must therefore be recommended as first choice over directional atherectomy, in appropriate clinical and morphological circumstances.

LIMITATIONS

It should be emphasized that matching of prospectively collected patients is retrospective in nature and may have led to a selection bias such as the selection of larger vessels. Inherent to the purpose of this study, only patients who underwent a successful procedure were matched and included in this study and we acknowledge that the results apply to a restricted atherectomy or stent population who underwent a successful procedure.

Whether the favorable stent effect observed in this study is only due to a scaffolding effect or could also be due to a difference in anticoagulation therapy, acute recoil or post-procedural vessel wall configuration is beyond the scope of this study. However, various reports have ruled out an effect of anticoagulation [33-35] while in this study the effect of acute recoil was minimized by the use of a meticulous approach as described earlier [7,20]. Criticism of the "sub-optimal result" in the atherectomy group, may be valid in the view of the very latest opinions that a post-procedural stenosis $<20\%$ must be achieved. However such criticism appeals equally to the stent group and we believe does not detract from the findings of a device specific effect of stenting in the context of similar acute results. Confirmation of these findings in the future among optimally treated lesions may be required. In fact our data underscore the need for optimal results, especially for atherectomy, to accommodate late luminal renarrowing.

CONCLUSIONS

In matched patients, successful stent implantation provided a more favorable long-term angiographic outcome, with a reduction in restenosis rate and need for subsequent revascularization, compared with directional atherectomy. This favorable effect is not only related to a larger acute gain but also to a device-specific effect, whereby less renarrowing is provoked by stent implantation for a given degree of acute gain.

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CHAPTER 10

RESTENOSIS AFTER PERCUTANEOUS INTERVENTION: IS THERE A DEVICE SPECIFICITY ?

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HANDBOOK OF INTERVENTIONAL CARDIOLOGY,

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The burning question in interventional cardiology is, apart from different physical capacity of devices for acute luminal improvements, is there a device specificity in restenosis provocation? New devices for percutaneous coronary revascularization are increasingly being applied in clinical practice and are being critically compared with conventional balloon angioplasty in randomized clinical trials [1••–4••]. Although directional atherectomy was found to achieve significantly greater acute luminal improvements than balloon angioplasty, this advantage was not convincingly maintained in the long term [1••,2••]. Although observational studies in specialized centers employing a more aggressive approach have reported superior immediate angiographic results [5••,6••] than in the Coronary Angioplasty Versus Excisional Atherectomy Trial (CAVEAT) or Canadian Coronary Atherectomy Trial (CCAT), "stand alone" atherectomy, without adjunctive balloon angioplasty to optimize acute results might partly explain the somewhat disappointing late outcome of these trials. The magnitude of the acute interventional result has been reported to be the greatest determinant of late outcome and reduced binary restenosis rates, regardless of the interventional device used [1••,6••,7]. If this is true, devices that can achieve the greatest acute luminal increase should be favored for intervention, where possible. Randomized comparison of Palmaz-Schatz stent implantation with conventional balloon angioplasty in North America and Europe has shown maintained superior long-term angiographic results after stent implantation [3••,4••]. It can only be speculated, however, that the sole explanation for this was the magnitude of the acute result and not partly a device-specific advantage of the stent itself. Findings of an inherent device-specific advantage or disadvantage in influencing late interventional results, independent of acute luminal increase, would carry considerable implications for their clinical application, as well as for the design of future randomized trials. Because of the variations in bulk and operating characteristics of different devices, as well as suitability of application with respect to clinical factors and lesion morphology, especially vessel size, randomized comparisons between multiple devices are not really feasible at this time. Therefore, most comparative information has been derived from observational experience, which is subject to variable degrees of theoretical and practical limitation due to population size, patient selection bias, practical experience with the device—learning curve, incomplete angiographic follow-up, angiographic measurement methodology—and definition of study endpoints, such as restenosis [8,9••,10••].

COMPARATIVE STUDIES USING A MATCHING APPROACH

To circumvent some of these limitations, our group has implemented two approaches to making comparisons of outcome between patients treated by different devices [9••,11•]. The first involves a priori selection of patients and lesions that are individually matched between the treatment groups to be compared according to a number of key criteria [12,13••,14••]. Initially, with the aim of comparing outcome in small patient groups treated by directional atherectomy and stent implantation compared with similar patients from a large population treated by balloon angioplasty, the criteria for satisfactory individual matching were limited to epicardial lesion location and reference vessel diameter and minimal luminal diameter (MLD) preintervention [12]. With expanding treatment groups, parameters for matching could be extended to gender, anginal status, and presence or absence of diabetes and hypercholesterolemia [13••]. Nevertheless, these additional features did not change the study outcome in terms of comparative late angiographic results [13••], so it would appear that matching on angiographic principles provides a convenient surrogate for a randomized comparison [14••]. The outcome of two studies, in retrospect, could be considered to have predicted the results of the currently completed randomized trials of balloon angioplasty with directional atherectomy and stent implantation. As in CAVEAT and CCAT, no significant difference could be detected in MLD at follow-up between patients treated by directional atherectomy compared with balloon angioplasty [13••], while stent implantation was observed to provide a significantly improved angiographic outcome over percutaneous transluminal coronary angioplasty (PTCA) [14••], as has been reported by the Benestent [3••] and Stent Restenosis Study (STRESS) [4••]. In a study comparing the angiographic outcome of excimer laser angioplasty with balloon angioplasty in matched lesions, virtually identical acute angiographic results were observed in the two groups, thus providing two

groups matched for the acute luminal gain, as well as baseline characteristics [15••]. Significantly greater renarrowing was observed in the excimer laser–treated group, so that at follow-up these patients exhibited significantly smaller residual luminal diameter at the treated site. The results of this study showed that the greater renarrowing observed in the excimer laser–treated group must have been a consequence of greater neointimal formation, which in theory could be related to the specific type of injury caused by excimer laser angioplasty.

To address the issue of device specificity, appropriate comparative evaluation of the long-term angiographic results of stent implantation, directional atherectomy, conventional balloon angioplasty, excimer laser angioplasty, rotational atherectomy, and other devices, the next series of comparative evaluations using this matching approach will compare outcome in patients wherein the immediate result of intervention as well as the baseline characteristics are individually matched. Therefore, possible differences in late results could be interpreted to be due to device-specific effects on the vessel wall in the achievement of the acute result. To facilitate such precise matching in patient groups of adequate size, large pools of patients treated by each device (with comprehensive prospective clinical evaluation and complete and carefully controlled and standardized quantitative angiographic follow-up) will be required. This may take some time.

AN ALTERNATIVE COMPARATIVE APPROACH USING RELATIVE ANGIOGRAPHIC MEASUREMENTS

In the absence of sufficient patient numbers for such specific and sophisticated matching studies, comparative evaluation in nonmatched groups treated by different interventional devices may be carried out where the important confounding parameters are taken into account. In a comprehensive evaluation in over 3000 patients with full quantitative angiographic follow-up after successful balloon angioplasty, our group has recently found that the degree of luminal renarrowing during follow-up and the MLD at follow-up are determined to a significant degree by the reference vessel size [16]. For this reason, as well as the inherent selectivity in application of different devices to vessels of different diameter, this parameter must be taken into account in comparative studies. Despite its clinical utility, percent diameter stenosis measurements are associated with wide variability due to changes in reference diameter as a consequence of intervention and of the restenosis process [8,17,18,19••]. Therefore, these cannot be reliably used as a correction factor for vessel diameter in important research studies. We have therefore adopted the approach of relating changes in minimal luminal diameter after intervention and during follow-up to the measured reference diameter preintervention as a constant point of reference. Furthermore, to avoid the imprecision and poor reproducibility of traditional subjective measurement of reference diameter, the Cardiovascular Angiographic Analysis System provides an automated interpolated reference diameter [20,21]. Thus, relative gain (proportional luminal increase at intervention), relative loss (proportional luminal renarrowing during follow-up) and net gain index (proportional luminal benefit at follow-up as a consequence of intervention) are derived [9••,12,13••,14••,22,23]. In addition, according to this method, proportional luminal diameter at any point in time is measured as a proportional lumen and not as a proportional stenosis, as conveyed by the conventional percent diameter stenosis approach. To clearly differentiate these, we have coined the term *relative lumen* preintervention, postintervention, and at follow-up [11•]. This approach allows comparison of immediate and late luminal changes between patient groups routinely treated by different devices, wherein the average vessel size in which target lesions are located may be widely different, such as those treated by stent implantation compared with balloon angioplasty.

The purpose of the evaluation we describe here was to investigate the possibility of a device specificity in determining the extent of the restenosis process and the late angiographic outcome of intervention in patients treated by either balloon angioplasty, directional atherectomy, or implantation of a self-expanding stainless steel mesh stent (Wallstent, Schneider, Buelach, Switzerland) or a balloon-expandable tantalum coil stent (Wiktor stent, Medtronic Inc., Minneapolis, MN), using this measurement approach to correct for the influence of the expected differences in basic vessel size between such patient groups.

POPULATION AND METHODOLOGY

The study population comprised 1234 patients (1452 lesions) treated by balloon angioplasty, 120 patients (123 lesions) undergoing directional coronary atherectomy, 106 patients (110 lesions) in whom an endoluminal self-expanding stainless steel mesh stent was implanted, and 100 patients (101 lesions) treated by balloon expandable tantalum coil stent implantation for native coronary artery disease. Pertinent baseline demographic data are given in Table 13-1.

Patients treated by balloon angioplasty had been enrolled in two separate European multicenter placebo-controlled restenosis prevention trials, the details of which have already been published [24,25]. In each of these trials the pharmacologic agent under investigation was found to have no significant effect on either clinical or angiographic outcome by both univariate and multivariate analyses, so for the purposes of the present study, all the patients were pooled and considered as one group. Entry criteria for these two studies were similar. All patients with angiographically proven atherosclerotic native primary coronary artery disease affecting single or multiple vessels, and with clinical symptoms of stable or unstable angina pectoris who were scheduled for balloon angioplasty were considered for inclusion. Only those having a successful dilatation, defined by the operator as a reduction in lesion severity to less than 50% diameter stenosis, were actually included in the trials for the ultimate assessment of angiographic outcome. Eventually, a total of 1234 patients with 1452 lesions had full angiographic follow-up (94% angiographic follow-up rate).

Directional coronary atherectomy (DCA) using the Simpson AtheroCath (Devices for Vascular Intervention, Redwood, CA), was performed as a primary procedure in 70% of patients, as a bailout following complicated balloon angioplasty in 5% of patients, and for restenosis following previous intervention in 25% of patients at two specialized institutions. The atherectomy procedure has been previously described in detail elsewhere [12,26].

TABLE 13-1. DEMOGRAPHIC DATA FOR THE COMPLETE PATIENT GROUPS*

	Balloon angioplasty	Directional atherectomy	Balloon-expandable stent	Self-expanding stent
Patients, *n*	1234	120	100	104
Lesions, *n*	1435	123	101	110
Male/Female, *n (%)*	987/247 (80/20)	97/23 (81/19)	85/15 (85/15)	87/17 (84/16)
Age, *y*	56.4±9	57.6±10.8	56.6±11.7	57±11
Lesion type (primary), %	100	70	0	51
Lesion type (restenosis), %	0	30	100	49
Bail-out procedure, %	0	5	0	33
Vessel, %				
LAD	47	65	52	55
RCA	30	22	34	35
LCX	23	13	14	10
Total occlusion preintervention, %	4	0	0	4
Diabetes, %	7	6	12	5
CCS III or IV angina, %	52	73	68	56
Unstable angina, %	28	51	40	26

*Male/female ratios, age, treated vessel, and frequency of diabetes are similarly distributed. The directional atherectomy and balloon-expandable stent groups have a greater frequency of class III and IV and unstable angina. All patients in the percutaneous transluminal coronary angioplasty group had primary lesions, whereas all patients in the Wiktor (Medtronic Inc., Minneapolis, MN) group had previous intervention and lesion treated by directional atherectomy, and Wallstent (Schneider, Buelach, Switzerland) were a mixture of these.

CCS—Canadian cardiovascular class; LAD—left anterior descending; LCX—left circumflex; RCA—right coronary artery.

Patients undergoing implantation of a self-expanding stainless steel mesh stent were recruited at six centers involved in a nonrandomized trial of this particular prosthesis for a number of indications: restenosis following previous balloon angioplasty (49%), as an adjunct to unsatisfactory balloon angioplasty (19%) or failed balloon angioplasty (14%), and primary coronary artery disease (18%, of which 4% were for chronic total occlusion) [27–30]. Balloon expandable tantalum coil stents were implanted for symptomatic angiographically documented restenosis following previous balloon angioplasty, also in a multicenter trial [31–33]. The respective implantation methodology and anticoagulation regimens employed in association with implantation of each of these devices have been previously described [28,32,27].

No specific guidelines for the actual interventional procedures were imposed on participating institutions so that outcome of therapy with each device can be considered representative of routine clinical experience from multiple European catheterization laboratories. Follow-up angiographic restudy was routinely performed 26±2 weeks postintervention. Where repeat angiography was carried out earlier than 16 weeks postintervention and no significant luminal renarrowing had occurred, the patient was asked to undergo further arteriography during the appropriate time window. For the purpose of avoiding the potential confounding effect of their inclusion, lesions that were occluded preintervention were excluded [34,35]. Because of the variable contribution of thrombosis to total coronary occlusion during follow-up, all lesions that occluded during follow-up were excluded from this study, since the subject at issue was the restenosis process and not reocclusion. Thus, after exclusion of 159 lesions that were totally occluded preintervention or at follow-up, 1313 lesions treated by balloon angioplasty, 116 by directional atherectomy, 92 by Wallstent, and 87 by Wiktor stent implantation.

Quantitative Coronary Angiographic Methodology

Coronary angiography was performed in all patients, before and immediately after intervention and at a predetermined follow-up time interval. The angiograms were recorded to facilitate quantitative analysis by the cardiovascular angiographic analysis system (CAAS) using 35-mm cinefilm at a recommended minimum speed of 25 frames per second. All necessary details of the interventional procedure were recorded in the dedicated case record forms.

Standardization of Angiographic Acquisition Procedures by Investigators to Facilitate Quantitative Analysis

Application of the following standardization procedures was requested from all investigators to allow optimum quantitative analysis at the angiographic core laboratory.

1. Intracoronary nitrate before angiography preintervention, postintervention, and follow-up
2. Use of nonionic contrast, ideally prewarmed to 37°C
3. Contrast-empty catheter (at least 6 F) filmed before each injection and removal and enclosure of the distal 20 cm with the cinefilm for micrometric measurement by the core lab
4. Optimal arterial opacification for at least three full cardiac cycles
5. Avoidance of bony structures, or closely parallel-overlapping branches
6. At least two projections ≥ 60° apart for right coronary artery (RCA) lesions and at least 3 ≥ 30° apart for left coronary artery (LCA) lesions
7. Identical projection angulations and table height at preintervention, postintervention, and at follow-up
8. Radiopaque indicators filmed to identify the administration of intracoronary nitrate and device use, including balloon inflations, atherectomy cuts, stent deployment, and additional stent dilatation
9. Guidewire and balloon-atherectomy catheter removed before final postinterventional angiography

Core-Laboratory Standardization Procedures for Quantitative Analysis

The following procedures were routinely observed at the angiographic core laboratory to ensure reproducibility of quantitative angiographic analysis.

1. Analysis performed using an automated edge-detection system (Cardiovascular Angiographic Analysis System; Pie Medical, Maastricht, The Netherlands)
2. Micrometrically measured catheter tip used as scaling device
3. Panel evaluation of projections and cineframes selected by investigator

4. Analysis of optimal end-diastolic frames in least foreshortened projections
5. Automatic corrections for pincushion distortion of image intensifiers
6. Comprehensive range of measurements provided for each segment analyzed
7. Polaroid print of each analysis to confirm matching of projections preintervention, postintervention, and at follow-up
8. Careful evaluation and error check before each analysis was verified and entered on database using double data entry technique
9. Final measurements used are the means of the multiple matched projections

QUANTITATIVE ANALYSIS OF CINEANGIOGRAMS

All cineangiograms were analyzed using the computer assisted CAAS, the basis for which has been described in detail in many previous publications [17,20,21,36–38] and its advantages and limitations and specific modifications in approach that have been applied to cope with application to new coronary interventional therapies have recently been reviewed [39••]. The basic approach involved identification of the coronary segment of interest in a selected cineframe, in which an area measuring 6.9 mm x 6.9 mm (512 x 512 pixels) is digitized with a high resolution charge coupling device camera. After indication of some points within the arterial segment by the analyst (the accuracy of which is unimportant because the computer automatically readjusts the centerline after contour detection), vessel contours are detected automatically, based on the weighted sum of first and second derivative functions, applied to the digitized brightness information, along scanlines (every 0.1 mm) perpendicular to the local centerline directions of the arterial segment.

As previously mentioned, a computer-derived interpolated reference diameter is provided, in contrast to the conventional method of arbitrarily selecting normal-appearing segments proximal and distal to the lesion and taking an average of these as the reference diameter. According to the process of interpolation, the actual lesion itself is excluded, using the curvature analysis (which identifies the proximal and distal ends of the lesion, a process that may be less accurate in diffusely diseased vessels). Then, in a continuous fashion, the arterial contours over the segment containing the lesion are interpolated on the basis of the proximal and distal centerline segments and a first-degree polynomial through all the diameter values, followed by a translation to the 80th percentile level; tapering of the vessel to account for a decrease in arterial caliber distal to sidebranches is allowed. The measurement taken as the reference diameter or interpolated reference diameter is the value of the polynomial (the so-called diameter function curve) at the site of the minimal luminal diameter. Thus, it is believed that by this process the automated algorithm attempts to reconstruct the original disease-free arterial dimension at the site of obstruction. The theoretical basis of, and actual mathematical steps involved in this process, have been described in detail in technical publications [20] and their intricacies are beyond the scope of this text.

The absolute values of the stenosis diameter as well as the reference diameter are derived by the computer using the known contrast-empty catheter diameter (as measured by micrometer) as a scaling device [17,20,21,36–38,39••,40]. The length of the lesion is determined from the diameter function on the basis of curvature analysis and expressed in millimeters. All contour positions of the catheter, the arterial segment, and the intervention device or balloon, are corrected for pincushion distortion introduced by the image intensifiers. Because the algorithm cannot measure total occlusions, a value of 0 mm is substituted for the minimal luminal diameter and 100% for the percent diameter stenosis. In these cases the postintervention reference diameter is substituted for the reference diameter preintervention.

QUANTITATIVE ANGIOGRAPHIC MEASUREMENTS TO BE USED IN THIS STUDY

Gain and loss, respectively, represent the absolute improvement in MLD achieved at intervention, and the absolute change during follow-up, measured in millimeters. The long-term net angiographic benefit is measured as absolute net gain. Thus, relative gain, relative loss, and net gain index represent these absolute measurements corrected for (or normalized for) the individual vessel size [9••,12,13••,14••, 22,23]. Relative lumen is the minimal luminal diameter corrected for the vessel size [11•]. In this study we intend to exam-

ine the influence of the device used on the restenosis process (measured as relative loss) and long-term outcome (measured as relative lumen at follow-up). These relative terms are calculated as follows: relative lumen—MLD/vessel size; relative gain—MLD post MLD pre/vessel size; relative loss—MLD post MLD at follow-up/vessel size; net gain index—MLD at follow-up MLD pre/vessel size. Vessel size is measured as the interpolated reference diameter preintervention, as the closest and most objective approximation of the disease-free vessel diameter. The reference diameter postintervention is subject to the influence of the trauma and expansion at intervention [41•], and at follow-up, to the pathologic process of restenosis [18,42,43••]. Therefore the static point of reference for relative gain, relative loss, net gain index, and relative lumen preintervention, postintervention, or follow-up is the interpolated reference diameter preintervention [9••,12,13••,14••,22, 23]. It is of importance to point out that these relative measurements are not replaceable by percentage diameter stenosis or changes therein, which are traditionally calculated using an arbitrarily selected vessel segment proximal or distal to the target lesion, pre- and postintervention, and at follow-up as the reference diameter.

STATISTICAL METHODS

Statistical analyses were carried out with the assistance of commercially available statistical software packages, *ie*, SAS (SAS Statistical Institute). A lesion-specific approach, as has recently become accepted for this type of evaluation, was used [44•,45••,46•]. Quantitative angiographic data are given as mean ± SD. Multiple linear regression analysis was used to determine the independent influence of the device used on each of relative luminal loss and relative lumen at follow-up, taking into consideration the known determining parameters of relative gain at intervention, lesion severity preintervention (relative lumen preintervention), vessel size, and epicardial lesion location. To determine whether there were unequal influences of these parameters within each treatment group, interaction terms between each parameter and the device category were included in the analysis. To illustrate the findings in multiple linear regression, three dimensional regression planes were constructed, with relative gain on the X axis, relative lumen preintervention on the Z axis, and relative loss or relative lumen at follow-up on the vertical Y axis (Figs. 13-1 and 13-2).

To provide comparisons of estimated relative loss and relative lumen at follow-up after intervention in a lesion of given parameters, a statistical maneuver known as "centering" of the continuous independent variables was carried out. This procedure simply moves the intercept to the location of the mean (center) of the continuous independent variables. In this study, after centering, the intercept in the respective model represents the estimated relative loss and relative lumen at follow-up, after intervention in a lesion of mean relative lumen preintervention, in a vessel of mean size, where a mean relative gain was achieved—thus called the "average lesion." Due to the larger group of patients treated by balloon angioplasty in this study, these means are inevitably biased in that direction, thus a second centering maneuver was carried out, using the mean relative gain, relative lumen preintervention, and vessel size for the three device groups to allow comparison of estimated outcome after intervention on a typical new device lesion.

All multiple comparisons were subjected to Bonferroni correction, before statistically significant differences were considered to be present.

RESULTS

Baseline demographic characteristics of the patient groups are provided in Table 13-1. Although age and gender are similar between the groups and are characteristic of patients undergoing percutaneous intervention, some distinct differences in demographics are also evident between the groups, particularly treated lesions were exclusively primary (no previous intervention) in the balloon angioplasty group and exclusively restenotic in the Wiktor stent group with a mixture of both primary and restenotic in the directional atherectomy and Wallstent groups.

Table 13-2 displays quantitative angiographic measurements pre- and postintervention and at 6-month follow-up. The vessel size varied significantly between the groups, with the directional atherectomy group displaying the largest vessel size and balloon angioplasty the smallest,

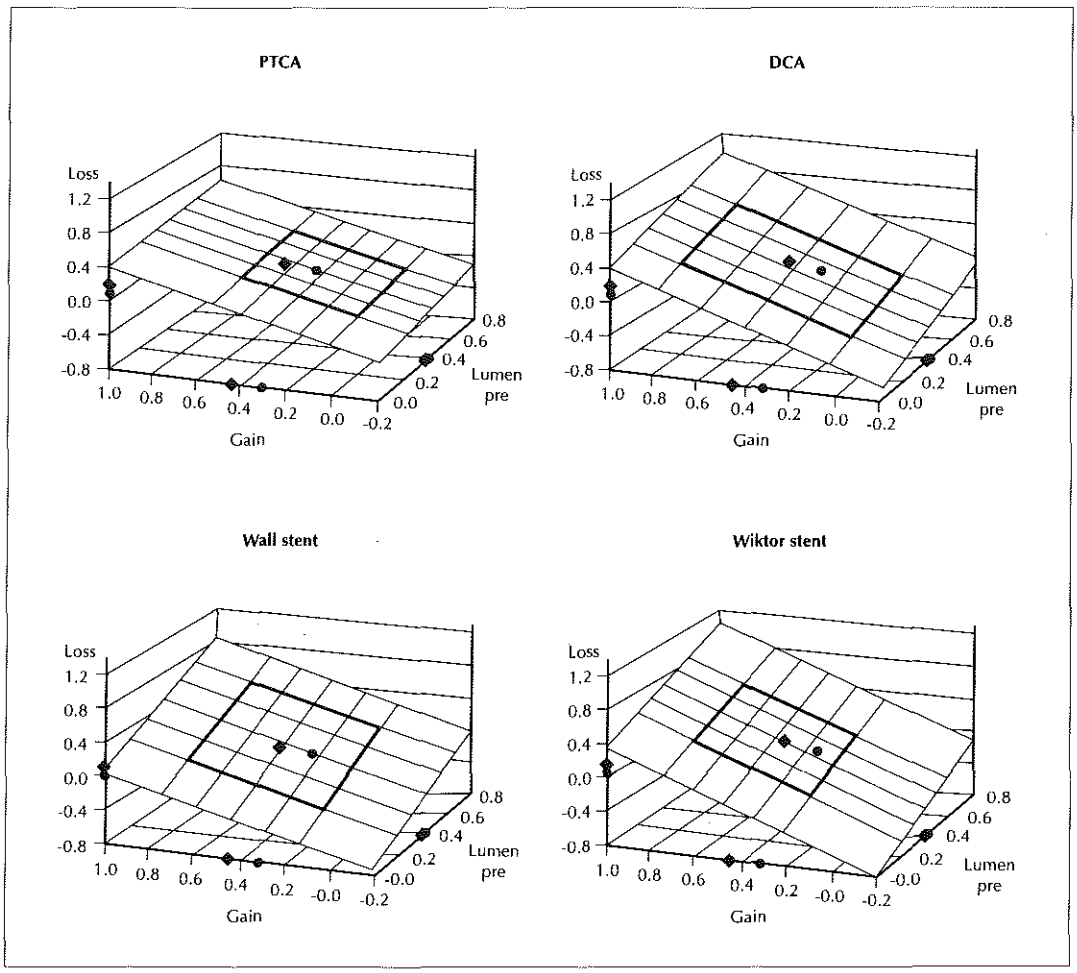

Figure 13-1. Three-dimensional representation of the multiple linear regression models to demonstrate the respective influences of relative luminal gain (GAIN, *X axis*) at intervention and relative lumen preintervention (LUMEN-PRE, *Z axis*) on relative luminal loss (LOSS, *Y axis*) in each of the four patient groups. For comparative purposes, the ranges of each axis are identical for the four patient groups. The parallel lines running from side to side and front to back within each so-called regression plane represent the mean and 1, 2, and 3 SDs of the mean relative gain and relative lumen preintervention, respectively. The bold boundary within each regression plane is to identify the location of most (two SDs, 95%) of the lesions in each group. The dot and diamond symbols on the *Y axis* represent the respective relative loss in each group estimated by the model after intervention in an "average lesion" (relative lumen preintervention = 0.41, relative gain = 0.30, vessel size = 2.72 mm) and "average new device lesion" (relative lumen preintervention = 0.39, relative gain = 0.44, vessel size = 3.08 mm), represented by the corresponding *X* and *Z axis* and regression plane positions of the symbols (*see* text for explanation and Table 13-4 for statistical comparisons). The slopes of the regression planes from front to back and from right to left are calculated from the multivariate model (Table 13-3). Differences in the slopes of the planes from front to back and from side to side between the groups can be appreciated and respectively represent the differences noted in the models in the regression co-efficients of "device × relative lumen preintervention" and "device × relative gain" terms between the groups (Table 13-3).

although no significant difference in vessel size was evident between the patients treated by directional atherectomy or Wallstent or between those treated by Wallstent or Wiktor stent. Table 13-2 shows significant variation between the groups in all parameters displayed, although the variation in loss index was not as statistically significant as the other parameters.

After normalizing for the vessel size, lesion severity preintervention (relative lumen preintervention) was greatest in the directional atherectomy group, although not significantly greater than in the Wiktor stent group. The relative gain at intervention was greatest in the Wiktor stent group, although this was not significantly greater than that achieved by Wallstent

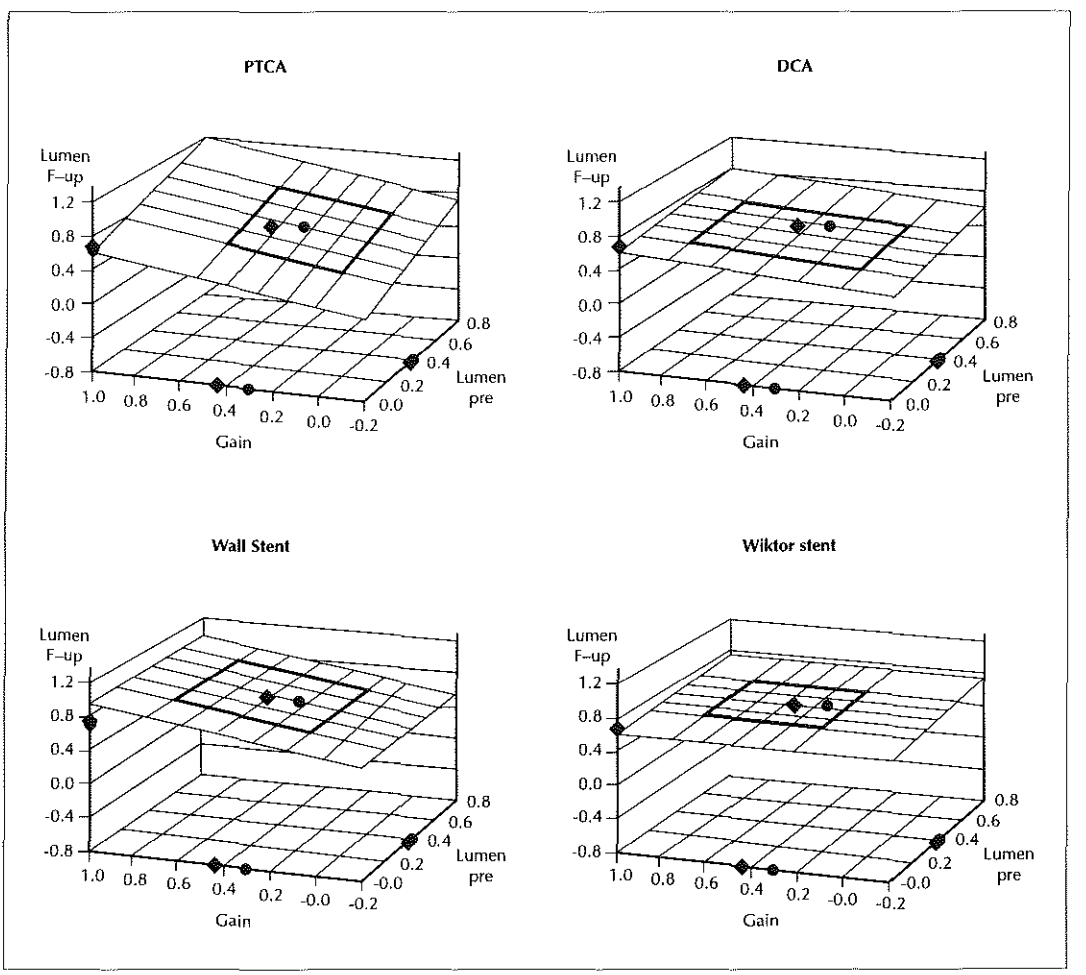

Figure 13-2. Identical graphic construction as in Figure 13-1 to demonstrate the respective influences of relative luminal gain (GAIN, *X axis*) at intervention and relative lumen preintervention (LUMEN-PRE, *Z axis*) on relative lumen at follow-up (LUMEN F-UP, *Y axis*) in each of the four patient groups. For consistency and comparative purposes, the ranges of each axis are identical to Figure 13-1. As in Figure 13-1, differences in the slopes of the regression planes are evident, but are not perhaps as visually convincing, which is mainly due to use of identical axis limits as for Figure 13-1. Although the estimated relative lumen at follow-up for the "average lesion" and the average "new device lesion" are virtually superimposed on the *Y axis*, the significant differences between the patient groups can be appreciated (*see* Table 13-4 for statistical comparisons).

implantation. The relative gain achieved by PTCA was significantly less than in each of the other three groups, so that the relative lumen postintervention was 0.87 in the Wiktor stent group, 0.85 in the Wallstent group, 0.77 in the directional atherectomy group, and 0.70 in the PTCA group. Relative loss during follow-up was significantly lower in the PTCA group, and in the Wallstent group was significantly less than in the Wiktor stent and directional atherectomy groups, leaving the largest relative lumen at follow-up in the Wallstent group (0.70, $P < 0.05$). The Wiktor stent–treated group was next (0.63), followed by the PTCA group (0.61), and the smallest mean relative lumen at follow-up was observed in the directional atherectomy group (0.55, $P < 0.05$, compared with all three other groups). The net gain index from baseline to follow-up was greatest in the Wallstent group (0.28, $P < 0.05$) compared with the atherectomy (0.18) and PTCA groups (0.19), although not significantly greater than in the Wiktor stent group (0.25) in which the net gain index was also greater than in the PTCA group ($P < 0.05$).

Multivariate Analysis

In multiple linear regression analysis, the interventional device was found to be a significant independent determinant of relative luminal loss and relative lumen at follow-up ($P < 0.0001$).

TABLE 13-2. INTERGROUP COMPARISON OF QUANTITATIVE ANGIOGRAPHIC MEASUREMENTS GIVEN AS MEAN ± SD

Angiographic measurements*	Balloon angioplasty ($n = 1247$)	Directional atherectomy ($n = 109$)	Wiktor stent ($n = 86$)	Wallstent ($n = 92$)	Anova (P)
Vessel size, *mm*	2.64±0.53	3.26±0.63	2.87±0.49	3.06±0.49	<0.0001
MLD preintervention, *mm*	1.10±0.30	1.17±0.36	1.11±0.31	1.27±0.44	<0.0001
MLD postintervention, *mm*	1.81±0.35	2.43±0.43	2.45±0.33	2.56±0.49	<0.0001
MLD at follow-up, *mm*	1.59±0.47	1.75±0.56	1.81±0.55	2.12±0.65	<0.0001
Acute gain, *mm*	0.71±0.34	1.26±0.47	1.33±0.32	1.29±0.49	<0.0001
Late loss, *mm*	0.22±0.41	0.68±0.61	0.64±0.53	0.44±0.64	<0.0001
Net gain, *mm*	0.49±0.43	0.58±0.58	0.69±0.53	0.84±0.74	<0.0001
Loss index	0.21±1.51	0.56±0.70	0.48±0.42	0.43±0.86	0.02
Relative gain	0.27±0.13	0.41±0.19	0.48±0.13	0.43±0.15	<0.0001
Relative loss	0.09±0.16	0.22±0.21	0.23±0.20	0.15±0.20	<0.0001
Net gain index	0.19±0.16	0.18±0.18	0.25±0.20	0.28±0.24	<0.0001
Relative lumen preintervention	0.42±0.10	0.36±0.10	0.39±0.10	0.42±0.11	<0.0001
Relative lumen postintervention	0.70±0.12	0.77±0.19	0.87±0.12	0.85±0.12	<0.0001
Relative lumen at follow-up	0.61±0.16	0.55±0.17	0.63±0.18	0.70±0.20	<0.0001

*After Bonferroni correction for multiple comparisons, significant differences ($P<0.05$) were observed between: percutaneous transluminal coronary angioplasty (PTCA) and each of the other three groups, directional coronary atherectomy (DCA), and Wiktor (Medtronic Inc., Minneapolis, MN) stent; Wallstent (Schneider, Buelach, Switzerland) and Wiktor stent and Wallstent and PTCA; PTCA and each of the other three groups; Wallstent and each of the other three groups, PTCA and each of the other three groups; PTCA and each of the other three groups; Wallstent and each of the other three groups, PTCA and each of the other three groups; Wallstent and each of DCA and PTCA, Wiktor stent, and PTCA; borderline corrected difference between DCA and PTCA ($P = 0.06$); PTCA and each of the other three groups, DCA, and Wiktor stent; Wallstent and each of the other three groups, PTCA and each of the other three groups; Wallstent and each of PTCA and Wiktor stent, PTCA and Wiktor stent; PTCA and each of DCA and Wiktor stent, Wallstent, and DCA; DCA and each of the other three groups, PTCA and each of the other three groups; Wallstent and each of the other three groups, PTCA and each of the other three groups.

ANOVA—analysis of variance; MLD—minimal lumen diameter.

Furthermore, the influence of the baseline lesion severity (relative lumen preintervention) was found to differ significantly between the device groups, conveyed by retention in the models of the so-called interaction term device × relative lumen preintervention. The influence of variations in relative gain (device x relative gain, Table 13-3) showed a strong trend toward a significant difference ($P = 0.08$) between the treatment groups. Relative gain, relative lumen preintervention, and lesion location in the left anterior descending artery (LAD) demonstrated

TABLE 13-3. MULTIPLE LINEAR REGRESSION TO EVALUATE THE INFLUENCE OF THE DEVICE USED FOR INTERVENTION ON ESTIMATED RELATIVE LUMINAL LOSS DURING FOLLOW-UP AND RELATIVE LUMEN AT FOLLOW-UP*

	After centering to the average lesion			After centering to the average new device lesion		
	Relative loss	Relative lumen at follow-up	*P*	Relative loss	Relative lumen at follow-up	*P*
Intercept	0.09	0.63		0.17	0.65	
Vessel size	0.03	-0.03	0.0005	0.03	-0.03	0.0005
Relative lumen preintervention	0.30	0.70	<.0001	0.29	0.70	<0.0001
Relative gain	0.63	0.37	<.0001	0.62	0.37	<0.0001
LAD	0.04	-0.04	<.0001	0.04	-0.04	<0.0001
Device			0.01			<0.0001
PTCA	0.00	0.00		0.000	0.00	
DCA	0.05	-0.05	0.01	0.06	-0.06	0.0008
Wallstent†	-0.04	0.04	0.08	-0.07	0.07	0.0003
Wiktor‡	-0.01	0.01	0.64	0.01	-0.01	0.71
Device x relative gain			0.08			0.08
PTCA	0.00	0.00		0.00	0.00	
DCA	0.18	-0.18	0.04	0.18	-0.18	0.04
Wallstent	-0.06	0.06	0.63	-0.06	0.06	0.63
Wiktor	0.26	-0.26	0.09	0.26	-0.26	0.09
Device x relative lumen preintervention			0.0003			0.0003
PTCA	0.00	0.000		0.000	0.00	
DCA	0.39	-0.39	0.02	0.42	-0.39	0.02
Wallstent	0.59	-0.59	0.001	0.60	-0.59	0.001
Wiktor	0.48	-0.48	0.03	0.49	-0.48	0.03

*Takes account of the respective influences of vessel size, relative lumen preintervention, acute relative luminal gain, and lesion location. For comparative purposes, the models have been constructed after "centering" the continuous independent variables to their mean values (*see* statistical methods). Thus, relative loss and relative lumen at follow-up are estimated for the four devices after intervention in the "average lesion" and in the "average new device lesion." To take account of possible differences in the effect of relative lumen preintervention and relative gain at intervention between the four groups, relevant "interaction terms" have been included in the models. The *P* values convey the probability of no additional influence on the variability of relative luminal loss by addition of the independent variable, after all the others have already been entered and retained. The model co-efficients given represent balloon angioplasty, so for the other devices the co-efficients must be adjusted by the relevant co-efficient associated with the particular device and the "interaction term."

†Schneider, Buelach, Switzerland.

‡Medtronic Inc., Minneapolis, MN.

DCA—directional coronary atherectomy; LAD—left anterior descending artery; PTCA—percutaneous transluminal coronary angioplasty.

significant independent influences on relative loss and relative lumen at follow-up. Vessel size was observed to also exert a significant, if numerically minor, influence.

To further illustrate the dynamic interrelationships between the principle continuous determinants on each of relative loss and relative lumen at follow-up and the influence of the device, three-dimensional regression models were constructed for each patient group, with relative loss and relative lumen at follow-up on the relevant vertical Y axis, relative gain on the X axis, and relative lumen preintervention on the Z axis. No variations in the influence of LAD or vessel size throughout the four groups could be detected and are not included in the graphs, but effectively would act as constants, causing parallel elevation of the regression plane in the loss graph and lowering of the plane in the relative lumen at follow-up graphs by a factor of 0.03 × vessel size and 0.04 for LAD location, respectively.

The slopes of the regression planes from front to back and right to left in Figures 13-1 and 13-2 convey, respectively, the regression coefficients associated with relative lumen preintervention and relative gain in the models, appropriately modified for the coefficients associated with the "device × RL preintervention" and "device × relative gain" terms in the models. Thus, with progressively less severe lesions (increasing relative lumen preintervention) while relative gain is constant, greater increase in relative lumen at follow-up (and a concomitant smaller increase in relative loss) could be expected by balloon angioplasty, compared with the other three devices. Similarly, greater increase in estimated relative lumen at follow-up (and lesser increase in relative loss during follow-up) after PTCA or Wallstent compared with directional atherectomy or Wiktor stent implantation, is predicted by the models and can be appreciated from the figures.

Differences in Estimated Outcome after Treatment of the Average Lesion and Average New Device Lesion

The differences between the devices in estimated relative luminal loss and relative lumen at follow-up at given levels of relative lumen preintervention and relative gain can be appreciated from Table 13-4 and from the figures conveyed by the locations of the Y axis values for intervention in the average lesion (represented as the round dots in the figures) and the average new device lesion (represented by the diamond symbols). According to the models, intervention using the Wallstent is associated with the greatest relative lumen at follow-up and the least relative loss, after treatment of both the average lesion and the average new device lesion, although no significant advantage over Wiktor stent implantation is observed for treatment of the average lesion ($P = 0.42$), but a significant advantage is present after treatment of the average new device lesion ($P = 0.002$). It is appreciated from Table 13-4 that the apparent superiority in outcome observed with Wallstent implantation for treatment of the average lesion is magnified by application to the average new device lesion. Also, superior results of Wallstent and Wiktor stent implantation, as well as PTCA, over directional atherectomy are apparent for treatment of the average new device lesion.

According to these results, in the patients and lesions studied, the device used for intervention was found to exert a significant independent determining influence on late angiographic outcome of intervention, independent of lesion severity preintervention, luminal increase, vessel size, and lesion location.

DISCUSSION

Luminal Renarrowing and Late Angiographic Outcome are Influenced by the Device used for Intervention

Many investigators have reported the influence of the acute result of intervention on long-term outcome [6••,7,13••,14••,16,45••,46•,47••,48,49••,50,51]. Greater luminal increase at PTCA was reported by Beatt and coworkers [50] to be associated with a greater incidence of restenosis defined as luminal loss ≥ 0.72 mm, a finding which at that time was considered paradoxical. More recently performed studies using continuous measures of restenosis have demonstrated a direct linear relationship between luminal increase at intervention and luminal loss during follow-up [6••,7,13••,14••,48,49••], which is considered to be a clinical correlate of the generally accepted experimental and pathologic description of restenosis as a neointimal hyperplastic response to vessel wall injury [52,53,54••].

Despite this angiographic finding of increasing luminal renarrowing with improving acute luminal results, the acute postprocedural minimal luminal diameter itself has been shown to be directly predictive of the late lumen and a

powerful predictor of freedom from restenosis, defined as a diameter stenosis greater than or equal to 50% at follow-up angiography [6••,7]. Moreover, application of a multivariate generalized model of restenosis to examination of late results of directional atherectomy, stent implantation, and balloon angioplasty, did not detect any specific influence of the device, so that the greatest determinant of late angiographic results was concluded to be the acute postprocedural lumen [6••,7]. However, comparative evaluation of late angiographic results after balloon angioplasty and directional atherectomy found that despite no significant difference in minimal luminal diameter at follow-up angiography, greater estimated relative luminal loss was predicted by linear regression analysis at increasing levels of relative luminal gain in lesions treated by directional atherectomy (Fig. 13-3) [13••]. The matching approach was later applied to compare acute and late results of stent implantation with balloon angioplasty, which revealed maintained superior late angiographic results after stent implantation, thanks to the considerably larger acute luminal increase achieved by stent implantation, although no significant relative gain or relative loss relationship was detected, which was believed to be due to the rather wide variability in the time to angiographic follow-up in the stent group [14••]. Comparative evaluation of excimer laser angioplasty with balloon angioplasty in matched lesions revealed similar immediate results between the two groups, but significantly greater luminal renarrowing during follow-up in the laser-treated group [15••]. Furthermore, linear regression analysis predicted significantly greater degrees of relative luminal loss after excimer laser compared with balloon angioplasty, with increasing relative gain. This was speculated to be due to the nature of wall injury inflicted by excimer laser in the achievement of luminal increase.

In accordance with the suggestion of the findings of these matching studies of a possible device effect, the device used for intervention was observed to exert a significant independent influence on relative luminal loss and relative lumen at follow-up. Specifically, significantly less

TABLE 13-4. ESTIMATED RELATIVE LOSS AND RELATIVE LUMEN AT FOLLOW-UP FOR EACH PATIENT GROUP*

Average lesion†

	Relative loss	Relative lumen at follow-up	PTCA	DCA	Wallstent¶	Wiktor§
PTCA	0.09	0.63		0.07	0.48	0.64
DCA	0.13	0.59	0.07		0.01	0.42
Wallstent	0.04	0.68	0.48	0.01		0.84
Wiktor	0.07	0.65	0.64	0.42	0.84	

Average new device lesion‡

	Relative loss	Relative lumen at follow-up	PTCA	DCA	Wallstent	Wiktor
PTCA	0.17	0.65		0.005	0.002	0.71
DCA	0.23	0.59	0.005		<0.001	0.13
Wallstent	0.10	0.72	0.002	<0.001		0.01
Wiktor	0.18	0.65	0.71	0.13	0.01	

*P values are corrected for multiple comparisons.
†Relative gain 0.3 in a lesion of 0.41 relative lumen preintervention in a 2.72-mm vessel.
‡Relative gain 0.44 in a lesion of 0.39 relative lumen preintervention in a 3.08-mm vessel.
¶Schneider, Buelach, Switzerland.
§Medtronic Inc., Minneapolis, MN.
DCA—directional coronary atherectomy; PTCA—percutaneous transluminal coronary angioplasty.

relative loss and a greater relative lumen at follow-up could be anticipated after Wallstent implantation than directional atherectomy or PTCA, after treatment of the so defined average lesion and indeed superior late results with Wallstent implantation compared with all three other devices were estimated for treatment of the defined new device lesion. Estimated outcome by the models using the simple statistical maneuver of centering the continuous independent variables to their mean values presents a method of comparative evaluation of the devices at tangible levels. Because the patient population is numerically dominated by lesions treated by balloon angioplasty, the geometric mean lesion indices are heavily influenced and lean toward a typical balloon angioplasty lesion. Therefore, the mean relative lumen preintervention, relative gain, and vessel size for lesions treated by the other three devices were also used as a point for comparative evaluation. What emerges from use of these comparative points is in fact that the apparent generally superior long-term angiographic results of stent implantation, especially Wallstent, over directional atherectomy and PTCA become more significant from the average lesion, to the average new device lesion.

These overall differences in estimated outcome between the devices observed at average lesion values cannot be explained by variability in the influence of vessel size, relative gain, or relative lumen preintervention, because these are already accounted for in the models. Any attempt to explain these differences would be speculative. Differences in demographic factors must be considered, the greatest difference being that lesions treated by Wiktor stent implantation all had previous balloon angioplasty, whereas lesions treated by balloon angioplasty had no previous intervention. Because restenotic lesions are widely believed to be associated with a greater propensity to further renarrowing, this might partly explain the less favorable late results after Wiktor stent implantation compared with Wallstent. However, most lesions treated by directional atherectomy, which was associated with the worst estimated relative loss and relative lumen at follow-up, were primary lesions. In the absence of definitive tangible explanations for the differential estimated outcome after intervention with the different devices, it must be speculated that differential degrees of vessel injury may be caused by the different devices in the achievement of similar quantitative angiographic acute luminal increase. Confirmatory evaluation of such an etiology might be possible using quantitative angiography, in patients with similar demographic characteristics, by identically matching lesions [13••,14••] for severity preintervention and acute postprocedural luminal increase, then comparing the late outcomes at follow-up. Such an investigation, in a large patient population with comprehensive quantitative angiography pre- and postintervention and

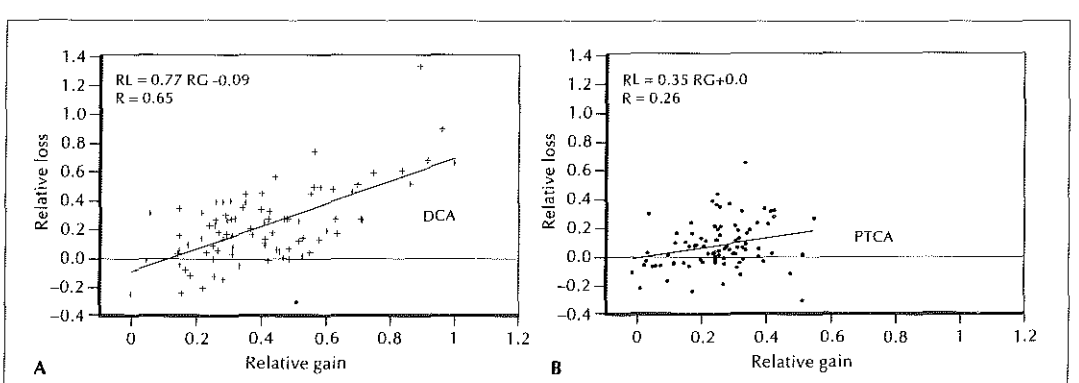

Figure 13-3. Linear regression analysis of relative loss (RL) and relative gain (RG) measurements for 79 matched pairs of coronary lesions treated by directional atherectomy (DCA) (**A**) or balloon angioplasty (percutaneous transluminal coronary angiography [PTCA]) (**B**). As conveyed by the regression (*R*) co-efficients obtained and provided in each graph, greater incremental increase in RL is estimated for increasing RG by DCA compared with balloon angioplasty ($P = 0.07$). This finding suggests some device effect in vessel wall injury in the achievement of similar levels of luminal increase, which provokes greater degrees of subsequent renarrowing after DCA than by balloon angioplasty (*From* Umans and coworkers [13••]; with permission.)

at follow-up, with standardized angiographic acquisition and analysis using an objective and reproducible automated quantitative analysis system, would be extremely valuable. But ample patient numbers for a sufficiently powerful study may not be available just yet. Accurate evaluation using intravascular ultrasound might be an even more useful approach than quantitative angiography and would perhaps require fewer patients to provide as powerful an evaluation. However, at this time the technology to guarantee reliable and reproducible luminal or plaque measurements in a wide variety of clinical circumstances (*eg*, severe or extremely eccentric lesions, in tortuous vessels, or distally located) is not yet available, although rapid progress is being made and such a study might be feasible in the not too distant future.

Differential Influences of Variations in Baseline Lesion Severity and Luminal Increase According to the Device

The influence of variations in lesion severity preintervention on relative loss and relative lumen at follow-up differs significantly between the devices (Tables 13-3 and 13-4, Figs. 13-1 and 13-2). This means that with a constant vessel size, where a given relative luminal gain is achieved, increasing relative lumen preintervention (thus reducing lesion severity) is associated with significant differences in the incremental consequent change in estimated relative loss and relative lumen at follow-up between the patient groups. Specifically, with increasing relative lumen preintervention, intervention with PTCA is estimated to be associated with the least increase in predicted relative loss and greatest increase in relative lumen at follow-up, conveyed by the observation that the PTCA group exhibits the gentlest slope of the regression planes from front to back in the relative loss graph and the steepest slope in the relative lumen at follow-up graph. This finding holds despite the finding of overall superior estimated relative lumen at follow-up for Wallstent implantation compared with DCA and PTCA, at the average lesion and for all three other devices at the average new device lesion, which is conveyed in the relative loss and relative lumen at follow-up graphs by the respective Y axis locations of the two points representing the average lesion (the dots) and the average new device lesion (the diamonds).

The influence of variations in relative gain on relative loss or relative lumen at follow-up did not differ quite as significantly between the patient groups, although differences in the right to left slopes of the regression planes can be appreciated, particularly when comparing each of PTCA and Wallstent with DCA and Wiktor stent in the relative lumen at follow-up graphs. It is possible that with increasing patient numbers in the new device groups, the observed differences provided in Table 13-4 might become statistically significant. In fact, if it were assumed, in the current study, that the influence of variations in relative lumen preintervention on relative loss and relative lumen at follow-up is the same for all devices and would thus not be included in the analysis as an independent term, then significant differences would be unveiled in the influence of variations in relative gain between the devices. This would appear to be mainly due to the significantly greater incremental increase in estimated relative lumen at follow-up (and less incremental increase in relative loss) if increasing relative gain is achieved by PTCA or Wallstent implantation compared with each of the other two devices (all $P < .01$). However, when the possibility of variable influence of changes in relative lumen preintervention is taken into consideration and held constant, the differential influence of changes in relative gain between devices is no longer apparent, and only the differential effect of the changes in relative lumen preintervention is retained, apparently due to the strong linear association between relative gain and relative lumen preintervention.

It can be concluded from this information that intervention in progressive milder lesions, at a given vessel size and luminal increase, is independently associated with the most favorable improvement in outcome parameters if PTCA is used for intervention, compared with the other three devices. If intervention is performed with progressively increasing relative luminal gain at a given relative lumen preintervention and vessel size, then Wallstent or PTCA are estimated to provide better improvement in outcome compared with directional atherectomy or Wiktor stent implantation.

Thus, apart from the detected differences in estimated outcome between the devices, which cannot be explained by differential influences in the variables studied, variation in the influence of changes in lesion severity at baseline (relative lumen preintervention), and to a lesser independent extent variations in relative luminal gain, determine differential late angiographic out-

come between the devices. These findings are completely at variance with previous reports evaluating late angiographic outcome after directional atherectomy, stent implantation, or balloon angioplasty [6••,7]. These reports concluded that the device used for intervention was essentially irrelevant, late angiographic outcome being predominantly determined by the acute postprocedural lumen. Identifiable differences between those studies and this include the use of digital calipers or videodensitometry to measure coronary luminal dimensions compared with automated edge detection in our study. These different approaches are known to provide differing absolute measurements of luminal dimensions pre- and postintervention as well as of reference diameter (vessel size), exclusion of totally occluded lesions at baseline and at follow-up in this study, use of relative measurements in this study compared with absolute measurements in the previous studies, application of a deliberately selective multiple linear regression model with avoidance of overlapping variables (for example acute gain and luminal diameter postintervention), and inclusion of interaction terms to consider potentially confounding influences.

Speculation on Intergroup Differences in Estimated Outcome

Based on experimental, pathologic, angioscopic, and ultrasound information already available, it is possible to speculate that the mode of vessel wall injury imparted by the different devices in the achievement of luminal increases may be inherently different and provoke inherently varying degrees of thrombo-fibro-proliferative response. Traumatic removal of portions of diseased and healthy vessel wall with frequently extensive exposure of intramural tissue components by directional atherectomy may provide a more intense provocation of the healing response than the vessel stretching, plaque compression, fissuring, and dissection caused by balloon angioplasty, injuries that may be minimized by varying degrees by placement of an endoluminal prosthesis. In addition, variable degrees of elastic recoil after treatment with these different devices may exert considerable influences on the propensity for late luminal renarrowing. The specific composition and structure of stents may also exert some influence on healing according to the completeness of opposition of acute elastic recoil, smoothness of the intrastent luminal surface (protrusion of intimal flaps between struts, filaments or helical coil, effect on local hemodynamics in the region of the lesion), and thrombotic and local tissue reaction to the stent components.

Arterial luminal increase by balloon dilatation has been reported by intravascular ultrasound studies to be predominantly due to plaque fracture and compression with a minor and inconsistent contribution from stretching of the vessel wall [55–57,58•,59••,60•,61•], although a recent study has reported vessel stretching, perhaps facilitated by plaque fracture, to be the main reason for luminal increase after balloon angioplasty [62••]. Elastic recoil after balloon angioplasty is known to be associated with a mean loss of 50% of achievable luminal area gain and 33% of achievable diameter gain [63,64]. The contribution of elastic recoil to late restenosis is controversial; however, many studies using quantitative angiography report recoil to be an immediate phenomenon [63,64] with no detectable long-term effects [41•,65,66], while preliminary reports using intravascular ultrasound suggest chronic recoil may be the predominant feature of late renarrowing after successful intervention [67••]. Directional atherectomy has been reported to achieve its luminal increase by a combination of plaque removal, plaque compression, and vessel stretching, in various combinations, varying widely between individual patients and between reported series [60•,61•,62••,68,69•], as well as achieving a reduction in acute elastic recoil compared with balloon angioplasty [70•]. Nevertheless, it may be speculated that traumatic removal of arterial tissue, which is a feature to some extent in all patients undergoing successful atherectomy, imparts a more extensive type of injury than plaque compression, fracture, and vessel stretching by balloon angioplasty, although a consistent relationship between depth of tissue retrieval at atherectomy and degree of subsequent luminal renarrowing has not been reported [5••,47••,71] and needs to be clarified by further larger prospective studies, ideally with the assistance of intracoronary ultrasound.

Stent implantation, particularly if optimally expanded, produces smoothing or wound edge apposition effects and creation of a circular luminal configuration [72,73] at the site of intimal fracture and disruption. This may reduce turbulence and shear stress [32,72], which may facilitate rapid endothelial recovery and therefore retard smooth muscle cell proliferation [74]. The Wallstent, a self-expanding stainless steel mesh stent, was initially reported to exhibit a dilating function [72,75] as well as an additional propen-

sity to further luminal improvements by 24 hours after implantation [76]. This clearly indicates its negation of elastic recoil and justifies its description as "self-expanding" [77]. Evaluation of the early clinical experience with this device was unduly disconcerting, however, with an unacceptably high frequency of acute and subacute stent thrombosis [28], which diluted, at least temporarily, the early enthusiasm of some of its proponents [78]. The balloon-expandable tantalum coil (Wiktor) stent was found to produce similar geometric improvements [32] as had been previously reported for the self-expanding stainless steel mesh stent. The smaller mean diameter of the stented segment (2.88 ± 0.43 mm) compared with the mean diameter of the fully inflated balloon (2.98 ± 0.44 mm) suggested some minor recoil in the stented segment (3% diameter reduction, compared with a mean of approximately 33% diameter reduction after conventional balloon angioplasty [63]). In addition, it was noted that the balloon did not achieve the diameter specified (3.35 ± 0.36 mm) at the recommended inflation pressures for stent deployment, perhaps due to the opposing forces of both the stent and the arterial wall itself. Haude and coworkers [79••] have recently investigated the occurrence of elastic recoil immediately after sequential balloon angioplasty and Palmaz-Schatz (Johnson & Johnson Interventional Systems, Warren, NJ) stent implantation and found that this device almost completely eliminated recoil (31% diameter recoil [48% area recoil] for balloon angioplasty compared with 3.5% [5.1% area] after stent implantation), thus decreasing the impact of long-term intimal hyperplasia on the residual lumen dimensions. Thus, the antirecoil effects of stent implantation represent perhaps the most important contribution of this interventional device in improving long-term outcome of intervention.

There are many confounding factors introduced by the long-term presence of an endocoronary prosthesis: the scaffolding effect of the device, the cutting and embedding effect of the stent filaments, the ration of metal filament to intimal surface area covered by the stent, the long-term presence of a foreign body with its inherent sometimes overwhelming thrombogenic effect and potential inflammatory effects, the potential molecular effect of the electrical charge of the stent molecules, and the unquantifiable persisting barotraumatic injury of the self-expanding stent on the vessel wall [32,77,78,80]. Karas and coworkers [80] have reported a greater proliferative response to implantation of a balloon-expandable tantalum coil stent than balloon dilatation in similarly injured porcine coronary arteries and attributed this to the continuous force of the stent on the vessel wall. These and other as yet unknown considerations potentially alter the association of vessel wall injury and tissue response in stented patient groups (compared with those treated by atherectomy or balloon angioplasty), although Schwartz and coworkers [54••] described the proportional relationship between injury and subsequent hyperplasia in a stented porcine model.

Explanations for the apparently superior long-term angiographic outcome after Wallstent implantation compared with the other three devices and of Wiktor stent implantation compared with PTCA and DCA in new device lesions in this study are not readily apparent. It must be recognized that the patients evaluated in this study underwent successful intervention (diameter stenosis less than 50% after intervention and freedom from any major adverse cardiac events) and completed 6-month angiographic follow-up. Thus, patients experiencing acute and subacute stent thrombosis, a considerable problem in the early experience with both of these devices [28,31], are not considered. Although these untoward thrombotic events are largely unpredictable and not necessarily related to the degree of acute luminal increase at stent implantation, there is some apriori selection of patients with better outcomes, so the results must be interpreted in the context of patients not succumbing to acute or subacute stent thrombosis. Accepting this limitation, it may be speculated that perhaps there are inherent properties of stent implantation, particularly the Wallstent, which create a beneficial luminal environment providing improved late angiographic benefit. If this is so, then is it the scaffolding effect of the device, the self-expanding aspect, the mesh configuration, the stainless steel content, or a combination of these that is important? Could these observations indicate a favorable long-term effect of this particular device when acute thrombotic events can be avoided, or could the same reasoning be applied to other endoluminal prostheses? These questions are not readily answerable at this time because the patient group treated by mesh stent implantation in this study is a nonhomogenous mixture of various clinical syndromes and they represent the early clinical experience with this device. Application of this methodologic approach to recently completed randomized trials of Palmaz-Schatz stent versus balloon angioplasty [3••,4••] will undoubtedly provide more

objective and valuable information. Ultimately it will require either matched comparisons or randomized trials of different clinically efficacious stents to determine device-specific advantages, ideally using intravascular ultrasound as well as quantitative angiographic endpoints.

Influence of Lesion Location on Loss and Angiographic Outcome

Previous studies using multivariate analysis have reported a definite independent influence of epicardial lesion location on late angiographic outcome of intervention, namely, either an adverse influence of LAD location [5••,6••,7,16,81•] or a favorable effect of location in the right coronary artery [46•]. In agreement with previous work, location in the LAD was associated with a greater relative loss and smaller relative lumen at follow-up in the study described here, independent of variations in luminal increase, vessel size, or lesion severity preintervention. No differences were detected between the groups in the degree of effect of LAD location on late results of intervention. Despite the consistency of this finding in several current studies, there is as yet no explanation why the LAD should exhibit a greater propensity to restenosis. Quantitative angiographic studies have reported that acute elastic recoil, adjusted for vessel size, is significantly greater in the LAD than the other two vessels [63]. If chronic recoil is indeed a major contributor to late renarrowing, then on the basis of the acute findings, it is conceivable that chronic recoil might be most marked in the LAD. Such phenomena may be evaluated in serial intravascular ultrasound studies. The only published pathologic finding that might indicate a different biologic substrate in LAD lesions was of increased frequency of primary intimal myocytic hyperplasia in atherectomy specimens retrieved from LAD compared with right or circumflex coronary arteries [82•]. It seems logical that the hyperplastic response to injury may be more aggressive when the intimal myocytes are already activated. Why this should be more frequent in the LAD has not been elucidated, but increasing experience with analysis and culture of retrieved atherectomy specimens may provide some insight in the near future.

LIMITATIONS

This is an observational study that includes only patients who underwent successful percutaneous intervention on nonoccluded lesions that did not progress to occlusion during follow-up and had satisfactory quantitative angiographic analysis of angiograms performed pre- and postintervention and at follow-up. Thus, this could be delineated as a deliberately circumscribed population, particularly in the stent groups, where all patients experiencing acute and subacute occlusion were excluded. This is especially evident in the Wallstent group in which the early experience with the device was associated with unacceptably high occlusive thrombosis rates [28]. The findings must therefore be cautiously applied to the general interventional patient population and recommendation of the Wallstent as the ultimate device for intervention should not be construed.

The limitations of the angiogram as an imaging modality are widely recognized as inherent and must be accepted as such; however, we believe that analysis by computer-based quantitative analysis systems, strict quality control and standardization of image acquisition, and use of multiple matched projections pre- and postintervention, and at follow-up is the most objective means to maximize its potential value.

The relative influence of various suspected clinical risk factors for a greater intimal hyperplastic response could be considered as possibly modifying the relationship between the identified angiographic determinants of luminal renarrowing and late angiographic outcome. It is worth noting, however, that three previous studies failed to demonstrate any such confounding influence [45••,46•,47••]. Thus, the addition of clinical variables might improve the predictive power of the models rather than influencing the nature of the relationships demonstrated. The parameters of interest for comparative evaluation of the interventional devices as independent determining variables were selected based on previous experience, whereby each of the following, lesion severity preintervention, luminal increase at intervention, vessel size, and lesion location, have been found to be independently associated with the long-term angiographic outcome after successful balloon angioplasty [16,45••,46•,47••,66]. Furthermore, basic clinical principles would suggest that prior to planned coronary intervention, regardless of the clinical circumstances, an interventionalist is faced with a set of certain circumstances such as lesion severity and vessel size and that he or she may choose from a number of interventional devices. The interventionalist will seek to achieve some degree of luminal increase, the magnitude of which he or she may control to some extent. The question here is whether there might be inher-

ent device-specific characteristics that influence late angiographic outcome, considered as an ubiquitous and continuously variable process [49••,83••]. In these circumstances, where the angiographic parameters of interest may differ widely between the patient groups to be evaluated, multiple linear regression analysis presents the only valid approach.

Conclusions, Clinical Relevance, and Implications of the Findings

The degree of renarrowing and the lumen diameter at follow-up after successful coronary intervention in nonrandomized patient groups were demonstrated to be influenced by the type of device used for intervention, independent of, and in addition to lesion severity preintervention, luminal increase at intervention, lesion location, and vessel size. Variations in lesion severity preintervention and luminal increase are associated with variable effects on late outcome according to the device used. These findings are at variance with previous studies that reported no device effect in determining late angiographic results of intervention. Whether these contradictory findings are a consequence of methodologic differences in quantitative angiographic measurements (automated versus user-dependent methods) or comparative approach, or can be explained by actual population demographic differences or variations in interventional approach, remains to be determined. In general, stent implantation, particularly Wallstent, emerged from this study with the most favorable predicted late angiographic outcome after initially successful intervention of nonoccluded coronary lesions, which did not completely occlude during follow-up. This finding supports continued clinical investigation of stent implantation, with particular focus on overcoming thrombotic occlusion and the need for stringent systemic anticoagulation and its attendant risks. Similarly, the comparatively unfavorable outcome predicted for intervention by directional atherectomy, in line with the conclusions of recent randomized trials [1••,2••], must conclude that the general use of directional atherectomy for treatment of coronary artery disease remains to be determined. Despite its widely criticized inherent limitations in consistently achieving optimal acute luminal results, balloon angioplasty, with its comparative ease of use, high acute success rates, and applicability to lesions with a wide range of severity and in a broad range of vessel sizes, must still be considered a cornerstone of interventional cardiologic therapeutics.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published recently, have been highlighted as:
- • Of special interest
- •• Of outstanding interest

1.•• Topol EJ, Leya F, Pinkerton CA, *et al.* for 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.

Randomized multicenter international trial to determine whether directional atherectomy could lower the rate of long-term restenosis compared with balloon angioplasty in 1012 patients. Atherectomy achieved greater acute luminal results but was associated with a higher incidence of acute major complications as well as death and myocardial infarction during follow-up and greater in-hospital costs. There was a trend toward lowering of the binary restenosis rate (diameter stenosis ≥ 50% at follow-up) and a larger minimal luminal diameter at follow-up in the atherectomy group.

2.•• Cohen EA, Adelman AG, Kimball BP *et al.*: A comparison of directional atherectomy with balloon angioplasty for lesions of the left anterior descending coronary artery. *N Engl J Med* 1993, 329:228–233.

Randomized multicenter Canadian trial to determine whether directional atherectomy could lower the rate of long-term restenosis compared with balloon angioplasty in left anterior descending coronary artery lesions in 247 patients. Procedural success was greater in the atherectomy group, and there was no difference in acute or in-hospital complications or in long-term clinical or angiographic outcome, despite the fact that atherectomy achieved a significantly greater acute luminal increase than balloon angioplasty.

3.•• Serruys PW, de Jaegere P, Kiemeneij F, *et al.*: A comparison of balloon-expandable stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med* 1994, 331:489–495.

In this randomized, multicenter trial comparing Palmaz-Schatz stent implantation with balloon angioplasty for treatment of primary coronary lesions in patients with stable angina in vessels greater than 3 mm, acute procedural success was greater and acute and in-hospital major cardiac complications were lower in the stent-treated group. Stent implantation achieved significantly greater acute angiographic results, which were maintained in the long-term, with lower restenosis rates and greater minimal luminal diameter at follow-up in the stent group, with a concomitant reduction in the incidence of major adverse cardiac events (death, myocardial infarction, bypass graft surgery, or repeat percutaneous intervention). Bleeding complications, mainly localized to the arterial puncture site, were greater in the stent-treated group.

4.•• Fischman DL, Leon MB, Baim DS, *et al.*: A randomized comparison of coronary artery stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med* 1994, 331:496–501.

This randomized, multicenter trial is similar in design and outcome to that by Serruys and coworkers [3••].

5.••Kuntz RE, Hinohara T, Safian RD, *et al.*: Restenosis after directional coronary atherectomy: effects of luminal diameter and deep wall excision. *Circulation* 1992, 86:1394–1399.

In this retrospective observational study, an aggressive approach to directional atherectomy is shown to yield improved long-term angiographic results, which are not jeopardized by retrieval of deep vessel wall tissue.

6.••Kuntz RE, Safian RD, Carrozza JP, *et al.*: The importance of acute luminal diameter in determining restenosis after coronary atherectomy or stenting. *Circulation* 1992, 86:1827–1835.

A multiple linear regression model applied to evaluate late results of stent implantation and directional atherectomy showed that the acute luminal diameter immediately after treatment to be the greatest determinant of late luminal diameter and freedom from late restenosis (diameter stenosis ≥ 50%), independent of the device used to achieve the acute result. The overall predict of late outcome was found to be poor, which was proposed to be due to the multifactorial nature of the restenosis process.

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9.••Serruys PW, Foley DP, Kirkeeide RL, *et al.*: Restenosis revisited—insights provided by quantitative coronary angiography. *Am Heart J* 1993, 126:1243–1267.

This review from prominent investigators in the field of quantitative angiography applied to evaluation of the acute and late results of percutaneous interventions provides a historical perspective on development of the angiographic evaluation of restenosis, detailed review of ongoing controversies, and proposes new conceptual approaches to comparative evaluation of long-term angiographic outcome of percutaneous interventions.

10.••Kuntz RE, Baim DS: Defining coronary restenosis: newer clinical and angiographic paradigms. *Circulation* 1993, 88:1310–1323.

Like the study from Serruys and coworkers [9••], this paper provides historical perspective on the development of the angiographic evaluation of restenosis.

11.• Foley DP, Serruys PW: Restenosis after percutaneous coronary interventions, the evolving angiographic perspective. *Coronary Artery Dis* 1994, 4:1129–1136.

Similar subject matter as in Kuntz and Baim [10••] but shorter and somewhat more updated.

12. Umans VA, Beatt KJ, Rensing BJ, *et al.*: Comparative quantitative angiographic analysis of directional coronary atherectomy and balloon angioplasty: a new methodologic approach. *Am J Cardiol* 1991, 68:1556–1563.

13.••Umans VA, Hermans WR, Foley DP, *et al.*: Restenosis after directional coronary atherectomy and balloon angioplasty: comparative analysis based on matched lesions. *J Am Coll Cardiol* 1993, 21:1382–1390.

In this study, acute and late angiographic outcome was compared among 76 patients treated by directional atherectomy matched for clinical as well as angiographic characteristics with 76 patients treated by balloon angioplasty. In addition to confirming the results of the previous study in smaller groups, this study showed that with increasing levels of acute luminal increase, the estimated degree of renarrowing was greater after atherectomy than angioplasty, suggesting some device-specific effect whereby atherectomy might cause more injury than balloon angioplasty in achieving similar luminal gain.

14.••de Jaegere P, Strauss BH, de Feyter P, *et al.*: Stent versus balloon angioplasty; matching based on QCA, a surrogate for randomized studies. *Am Heart J* 1993, 125:310–318.

In this study, 93 patients treated by Wallstent implantation were compared with 93 patients matched for lesion location and severity and vessel size. The acute result was significantly greater in stent-treated patients and despite a significantly greater late loss in the stent-treated group also, the superior acute result was maintained at follow-up. Based on the findings, the authors provided models of population sample sizes required for a randomized comparison of the two devices and speculated that the results of their study might actually forecast the results of such a trial.

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First results of a randomized comparison of excimer laser and balloon angioplasty, where after similar initial angiographic results were observed in the two groups, significantly greater late loss developed in the laser-treated group, leaving a smaller minimal luminal diameter at follow-up and associated with a greater binary restenosis rate. This was speculated to be a consequence of the specific type of injury imparted by excimer laser in the achievement of similar acute luminal increase as balloon angioplasty.

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19.••Foley DP, Strauss BH, Escaned J, *et al.*: Quantitative coronary angiography in interventional cardiology: clinical application of QCA measurements. *Prog Cardiovasc Dis* 1994, 36:363–384.

Extensive review of the clinical application of quantitative angiography to evaluation of the immediate and long-term results of percutaneous coronary interventions.

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This is a comprehensive description of the edge detection and videodensitometric quantitative analysis approaches used by the Cardiovascular Angiographic Analysis System, providing basic explanations of the process involved, their respective general limitations and advantages, and particularly the practical difficulties that have been encountered through their application to assessment of different coronary interventional devices.

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41.• Foley DP, Deckers J, van den Bos AA, *et al.*: Is there a need for repeat coronary angiography 24 hours after successful balloon angioplasty, to evaluate early luminal deterioration and facilitate quantitative analysis. *Am J Cardiol* 1993, 72:1341–1348.

In this study quantitative angiographic measurements at 24 hours are compared, in multiple identically repeated projections, with those postangioplasty in 118 patients. No differences were detected in minimal luminal diameter or cross-sectional area but there was a significant increase in reference diameter at 24 hours so percent diameter stenosis was also significantly greater at 24 hours. Consequently, it was concluded that use of percent diameter stenosis measurements should be discouraged in clinical studies. Using the findings, the postangioplasty lesion measurement variability of the Cardiovascular Angiographic Analysis System could be identified as ± 0.20 mm.

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To investigate angiographic morphologic changes occurring during follow-up after successful angioplasty, 668 lesions with quantitative angiography preintervention, postintervention, and at follow-up were deliberately categorized as restenosis or no restenosis by a traditional binary cut-off criteria (diameter stenosis ≥ 50%) and a loss criteria (loss ≥ 0.40 mm). Comparing angiographic characteristics of the two groups of lesions according to the two criteria showed that lesions that deteriorated by greater than or equal to 0.40 mm also demonstrated significant reduction in reference diameter and mean diameter of the dilated segment and had been subject to a greater initial gain at angioplasty. It was concluded that the restenosis process is particularly stimulated by greater degrees of initial luminal gain and tends to affect not only the target lesion but the entire segment dilated, which carries implications for reliability of percent diameter stenosis measurements in accurately conveying changes in lesion severity over time. Categorical criteria for definition of restenosis were discouraged as being misleading.

44.• Gibson MC, Kuntz RE, Nobuyoshi M, *et al.*: Lesion-to-lesion independence of restenosis following treatment by conventional angioplasty, stenting, or directional atherectomy: validation of lesion based restenosis analysis. *Circulation* 1993, 87:1123–1129.

No correlation in the rate or magnitude of restenosis could be found between different lesions treated by balloon angioplasty, directional atherectomy, or stent implantation within the same patient, leading to the conclusion that lesion-based analysis is valid for evaluating results of interventional procedures.

45.••Rensing BJ, Hermans WRM, Vos J, *et al.* 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, 88:975–985.

Multiple linear regression analysis to determine the degree of luminal renarrowing after successful coronary balloon angioplasty from clinical, procedural, and angiographic parameters demonstrated luminal loss to be poorly predictable. Individual parameters that were independent predictors of increased luminal loss included: diabetes mellitus, short duration of angina preangioplasty, longer lesions preangioplasty, greater gain at angioplasty, and presence of angiographically detected thrombus postangioplasty.

46.• Hermans WRM, Rensing BJ, Foley DP, *et al.* on behalf of the MERCATOR study group: Patient, lesion and procedural variables as risk factors for luminal re-narrowing after successful coronary angioplasty: a quantitative analysis in 653 patients with 778 lesions. *J Cardiovasc Pharm* 1993, 22:S45–S57.

In this study, relative luminal gain at angioplasty and LAD coronary artery lesion location were independently associated were greater luminal loss during follow-up after successful balloon angioplasty in 653 patients.

47.••Umans VA, Robert A, Foley D, *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, 23:49–58.

Investigation of determinants of the restenosis process and of late angiographic outcome emphasized the need to consider both these aspects of long-term results of intervention. Although greater luminal loss was predicted by greater relative luminal gain and preprocedural minimal luminal diameter, a larger minimal luminal diameter at follow-up was predicted by a greater acute postprocedural minimal luminal diameter, greater vessel size and non-LAD lesion location. No clinical or histologic factors were independently associated with late outcome.

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To determine whether new devices have a lower incidence of restenosis and if so what the explanation could be, 223 coronary lesions treated by directional atherectomy, stent implantation, or laser balloon angioplasty had quantitative measurements preintervention, postintervention, and at follow-up. Similar degrees of late loss were found in the three groups but significant differences in restenosis rates, which could be explained by greater acute luminal gain in the stent group than in the atherectomy group, which in turn was greater than the laser balloon angioplasty group. Percent stenosis and late loss measurements were demonstrated to be normally distributed within the treated population.

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In 66 lesions, intravascular ultrasound allowed classification of the effects of balloon angioplasty into six groups according to the observed morphologic effects. Ultrasound and angiography correlated well for the presence of dissection but not calcification, which was significantly more frequently observed by ultrasound. Calcified plaque by ultrasound fractured more frequently after angioplasty. Angiographic restenosis (diameter stenosis ≥ 50% at follow-up) occurred more frequently if angioplasty left a concentric ring of plaque without fracture or dissection.

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Using intravascular ultrasound, plaque fractures, and compression of plaque were found to be the principle factors responsible for luminal increase after balloon angioplasty of iliac arteries, with an additional minor contribution of vessel stretching.

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In 30 patients after directional atherectomy and 15 after balloon angioplasty, intravascular ultrasound showed similar minimal luminal cross-sectional area and diameter in each group. However, balloon angioplasty caused both vessel stretch and dissection, which were uncommon after atherectomy, which was observed to be effective by removing plaque, although measurements of these respective components were not possible in this study.

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In this study, plaque compression (48%) and removal (37%) and vessel expansion (15%) were responsible for the increase in lumen after directional atherectomy in 40 patients, whereas compression (94%) and vessel expansion (6%) accounted for luminal increase after balloon angioplasty in 25 patients.

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Contrary to the previously referenced study (Suneja and coworkers [61•]), plaque removal provided the main contribution (78%) and vessel increase (22%) the remaining portion of increase in lumen after atherectomy in 25 patients, while vessel expansion accounted for 81% of luminal increase after balloon angioplasty in 30 patients.

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These preliminary results of serial intravascular ultrasound in 20 patients reported for the first time that the predominant cause of luminal renarrowing after successful angioplasty using balloon angioplasty, directional or rotational atherectomy, or excimer laser is chronic recoil of the stretched vessel, which accounted for 68% of the loss of luminal cross sectional area, compared with 32% luminal loss due to increase in plaque and media area during follow-up.

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69.• Umans VA, Haine E, Renkin J, *et al.*: On the mechanism of directional coronary atherectomy. *Eur Heart J* 1993, 14:505–510.

Quantitative analysis by edge detection and videodensitometry of angiography recorded before and after directional atherectomy in 113 patients as well as after passage of the device and before activation in 10 patients demonstrated that the Dotter effect makes an important contribution to the luminal increase provided by this device. The finding of a comparatively small discrepancy between cross-sectional area measurements by edge detection and videodensitometry after atherectomy was interpreted as suggesting that, in general, a circular lumen is created by the device.

70.• Kimball BP, Bui S, Cohen EA, *et al.*: Comparison of acute elastic recoil after directional atherectomy versus standard balloon angioplasty. *Am Heart J* 1992, 124:1459–1466.

In 25 patients treated by directional atherectomy, elastic recoil led to loss of 23.5% of achievable minimal luminal diameter compared with loss of 41.6% of luminal diameter in 25 comparable lesions treated by balloon angioplasty. The ratio of device size to the vessel size influenced the degree of recoil in both groups, and although no morphologic features influenced recoil after atherectomy, lesion length and symmetry influenced recoil after balloon angioplasty.

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Serial angiography before and after balloon angioplasty and Palmaz-Schatz stent implantation and at late follow-up in 60 patients showed elastic recoil amounting to loss of 48% in area and 31% in diameter after balloon angioplasty and a loss of 5.1% in area and 3.5% in diameter after subsequent stent implantation. A follow-up mean luminal loss was 0.59±0.51 mm and 14% of lesions had a stenosis greater than 50% while 80% of lesions had

a stenosis less than the stenosis observed after balloon angioplasty and before stent implantation. It was concluded that Palmaz-Schatz stent implantation can almost completely eliminate elastic recoil and thus diminish the impact of subsequent intimal hyperplasia and improve late angiographic results of angioplasty.

80. Karas SP, Gravanis MB, Santoian EC, *et al.*: Coronary intimal proliferation after balloon injury and stenting in swine: an animal model of restenosis. *J Am Coll Cardiol* 1992, 20:467–474.

81.• Kuntz RE, Hinohara T, Robertson GC, *et al.*: Influence of vessel selection on the observed restenosis rate after endoluminal stenting or directional atherectomy. *Am J Cardiol* 1992, 70:1101–1108.

Among 367 lesions treated by directional atherectomy or stent implantation, multivariate regression analysis showed LAD location to be the strongest independent determinant of the likelihood of binary restenosis (diameter stenosis ≥ 50%) and of a greater lesion severity (% diameter stenosis) at follow-up. This was speculated to be due to the increased propensity of the LAD for neointimal response after intervention, conveyed by the greater loss index (late loss-acute gain) observed in the LAD.

82.• Miller MJ, Kuntz RE, Friedrich SP, *et al.*: Frequency and consequences of intimal hyperplasia in specimens retrieved by directional atherectomy of native primary coronary artery stenoses and subsequent restenoses. *Am J Cardiol* 1993, 71:652–658.

Smooth muscle cell proliferation was identified in more than 90% of atherectomy specimens retrieved after treatment of 55 lesions treated for restenosis. Among 102 lesions having atherectomy as a first intervention (primary lesions), 44% showed evidence of smooth muscle cell proliferation, which was more prevalent in younger patients and in LAD lesions. Nevertheless, although restenotic lesions demonstrated a higher binary restenosis rate than primary lesions, no difference in late angiographic outcome was observed among primary lesions between those with and without smooth muscle cell proliferation.

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Evaluation of quantitative angiographic measurements of luminal diameter before and after successful balloon angioplasty and at follow up in 1445 lesions, demonstrating an approximate normal Gaussian distribution for all parameters, with the implication that in clinical studies evaluating restenosis, late angiographic outcome should be compared as the mean luminal change between the groups being compared, rather than by incidence of categorically defined restenosis.

CHAPTER 11

DIFFERENCES IN RESTENOSIS PROPENSITY OF DEVICES FOR TRANSLUMINAL CORONARY INTERVENTION

A quantitative angiographic comparison of balloon angioplasty, directional atherectomy, stent implantation and excimer laser angioplasty

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ABSTRACT

Background: With the increasing clinical application of new devices for percutaneous coronary revascularization, maximization of the acute angiographic result has become widely recognized as a key factor in maintained clinical and angiographic success. What is unclear, however, is whether the specific mode of action of different devices might exert an additional independent effect on late luminal renarrowing.

Purpose: The purpose of this study was to investigate such a difference in "restenosis propensity" among 3660 patients, who had 4342 lesions successfully treated by balloon angioplasty (BA, n=3797), directional coronary atherectomy (DCA, n=200), Palmaz-Schatz stent implantation (PS, n=229) or excimer laser coronary angioplasty (ELCA, n=116) and also underwent quantitative angiographic analysis pre- and post- intervention and at 6 month follow up.

Methods: To allow valid comparisons between the groups, because of significant differences in coronary vessel size (VS) (BA=2.62±0.55mm, DCA=3.28±0.62mm, ELCA=2.51±0.47mm, PS=3.01±0.44mm; $p<.0001$), the comparative measurements of interest selected were the "relative loss" in luminal diameter (RLoss=loss/VS) to denote the restenosis process, and the "relative lumen at follow up" (RLfup=minimal luminal diameter (MLD) at follow up/VS) to represent the angiographic outcome. For consistency, lesion severity pre was represented by the "relative lumen pre" (RLpre=MLD pre/VS) and the luminal increase at intervention was measured as "relative gain" (RG=gain/VS). Differences in restenosis propensity between devices was evaluated by univariate and multivariate analysis. Multivariate models were constructed to determine relative loss and relative lumen at follow up, taking account of relative lumen pre, lesion location, relative gain, vessel size and the device used. In addition, model estimated relative loss and relative lumen at follow-up, at fixed relative lumen pre, relative gain and vessel size, were compared between the 4 groups.

Results: Significant differences were detected between the groups with respect to these estimates, whereby, Palmaz-Schatz stent implantation was associated with the most favourable angiographic outcome and excimer laser coronary angioplasty the least ($p<.01$). Significant effects of lesion severity and location, as well as luminal increase on late angiographic outcome were noted. In addition, the influence of luminal increase achieved at intervention on late angiograpic results differed significantly between the devices ($p=.02$).

Conclusion: These findings indicate that propensity to restenosis after apparently successful intervention is influenced by the device used for intervention. In view of the clinical implications of such findings, further evaluation in larger randomized patient populations is warranted.

INTRODUCTION

Over the last decade, a number of new devices for transluminal coronary revascularization, have been introduced, aiming to improve acute and long term clinical and angiographic results of coronary balloon angioplasty [1,2]. Through a variable combination of plaque removal, compression and vessel stretching [3-6], directional coronary atherectomy (DCA) can achieve significantly greater acute luminal results than conventional balloon angioplasty [7-10], but randomized trials have failed to demonstrate long term superiority of this apparent mechanical advantage [7,8]. By vaporization of atherosclerotic plaque, excimer laser coronary angioplasty (ELCA) has been associated with improved acute success compared with balloon angioplasty, especially in complex coronary lesions [11,12,13], but restenosis rates in registry and observational reports have been relatively high [11,13,14,15] and the results of randomized trials are still awaited. Stent implantation, through vessel expansion, opposition of natural elastic recoil [16] and establishment of a smooth and circular coronary lumen [17-19], has the capacity to consistently achieve superior procedural luminal increase compared with balloon angioplasty [17-22]. Although 2 randomized comparisons of Palmaz-Schatz stent implantation with balloon angioplasty, in native primary coronary stenoses, indicate long term maintenance of the acute advantage of stent implantation [23,24], it is not yet known whether this is simply due to the greater acute luminal increase, or to additional benefits of specific mechanical or physical properties of the stent itself.

Despite the mechanistic differences between these 4 devices, observational studies have concluded that the magnitude of the post procedural lumen alone determines late angiographic outcome, without any detectable independent contribution of the device used to achieve it [10,25]. Conversely, studies in angiographically matched lesions, comparing balloon angioplasty with each of directional atherectomy [9,26], stent implantation [22] and excimer laser [15], as well as unmatched general comparisons in patients treated by atherectomy, balloon angioplasty or stent implantation, have reported definite differences in restenosis propensity and late angiographic results [27,28]. Because these prior studies comprised comparatively early experience with directional atherectomy, as well as Wallstent and Wiktor stent implantation in heterogenous patient groups, this study was designed to ratify the previous findings by investigating the possibility of an independent influence of the device used for intervention, among patient groups treated by 4 different devices : balloon angioplasty (BA), directional atherectomy (DCA), Palmaz-Schatz stent implantation (PS) or excimer laser coronary

angioplasty (ELCA), in contemporary clinical experience.

POPULATION AND METHODOLOGY

The study population was made up of 3660 patients (4342 lesions) treated for native coronary artery disease by BA (n=3797 lesions), DCA (n=200 lesions), PS (n=229 lesions) and ELCA (n=116 lesions). Patients treated by BA had been enroled in 4 international multicentre placebo controlled restenosis prevention trials, the details of which have already been published [30-33]. In each of these trials the pharmacological agent under investigation was found to have no significant effect on either clinical or angiographic outcome by both univariate and multivariate analyses, so, for the purposes of the present study, all the patients were pooled and considered as one group. Patients treated by PS had been recruited during the BENESTENT trial (a European multicentre randomized comparison with BA, for treatment of native primary coronary artery lesions (associated with stable anginal symptoms) with a reference vessel diameter ≥3mm [23]). Final quantitative angiographic follow up was 93%. Patients treated by ELCA were treated at a single institution, using a Xenon Chloride device (Dymer 200+, Advanced Interventional Systems, Inc., Irvine, California), which emits laser pulses with a wavelength of 308nm, duration of 210 nsec and at a repetition rate of 20Hz. Over-the-wire laser catheters of 1.3, 1.6 and 2.0mm, with concentric multifiber arrangement around a central lumen were employed at a fluence of 45-65 mJ/mm^2. The excimer laser procedures were carried out according to conventional practice as previously reported [34]. Adjunctive BA was carried out in 98% of lesions. Quantitative angiographic follow up among eligible patients was 94%. Patients were treated by DCA at two specialised institutions (The Thoraxcenter, Rotterdam, Netherlands and St Luc University Hospital Brussels, Belgium; both of which participated in the Coronary Angioplasty Versus Excisional Atherectomy (CAVEAT) trial), using the Simpson atherectomy catheter (Devices for Vascular Intervention, San Diego, California). Primary lesions were treated in 80% of cases and 20% of lesions had undergone previous intervention. A 6F device was used in 61% and 7F in 39% of cases, with a mean of 5.9±2.8 cuts made per lesion. Adjunctive BA was carried out in 16% of lesions. Overall quantitative angiographic follow up was 93%. In all component studies, all aspects of intervention were left to the discretion of the individual physician. Successful intervention was universally considered as a post-procedural diameter stenosis of < 50% visually assessed by the individual investigator.

Quantitative coronary angiographic (QCA) methodology: Coronary angiography was performed, in multiple projections pre intervention and identically repeated immediately after intervention and at a pre-determined 6 month follow-up. The angiograms were recorded to facilitate quantitative analysis by automated edge detection (using the Cardiovascular Angiographic Analysis System (CAAS)), in the angiographic core laboratory, with universal application of specific standardization procedures, as previously described [29,35,36].

Quantitative angiographic measurements of interest in this study: Due to the wide range of coronary vessel size treated by modern interventional devices, (as confirmed in table 2 in the results section), QCA measurements were normalized for reference vessel size, deriving measurements of "relative gain" and "relative loss" in luminal diameter, as previously introduced [9,22,28,37,38]. The vessel size was represented as the interpolated reference diameter **pre-intervention**, on account of changes in reference diameter aafter intervention and during follow up, as previously described [16-23,28,29,38-40]. Accordingly, relative measurements of lumen dimensions pre and post intervention and at follow up were also derived by normalizing minimal luminal diameter for the interpolated reference diameter pre, producing the measurements of "relative lumen" pre, post and follow up, as previously described [41]. These novel parameters thus represent measurements of luminal patency as a fraction of the ideal luminal diameter. **Relative gain** = Gain/Vessel Size; **Relative loss** = Loss/Vessel Size; **Net gain index** = Gain-Loss/Vessel Size; **Relative lumen** = Minimal luminal diameter/Vessel Size. Conventional binary measures of restenosis were also estimated applying a number of commonly used angiographic criteria (table 2).

Statistical methods

Statistical analyses were carried out with the assistance of a commercially available statistical software package (SAS, SAS Institute, Inc.). A lesion based approach was applied, as previously justified [42-44,45]. Analysis of variance was used to compare continuous parameters and restenosis rates were compared using a chi-square test. In keeping with the findings of previous studies [6,9,10,14,15,21,22,25-29,42,44], and a recent specific evaluation [46], a linear relationship was assumed between relative luminal gain at intervention and relative luminal loss during follow up. To investigate the influence of the device used on the restenosis process and late angiographic outcome, the relationship between relative luminal gain at intervention and each of relative luminal loss during follow up (representing the restenosis process) and relative lumen at follow up (as the late angiographic outcome), was investigated first in simple linear regression analysis. Then the entire patient population was considered as a single group and a previously described multiple linear regression model was constructed, to take account of the respective determining influence of the vessel size, lesion severity pre-

intervention (relative lumen pre), the influence of the physician (relative luminal gain at intervention) and the epicardial lesion location [29].

To investigate whether a difference could exist between the 4 devices in the degree of relative loss provoked by increasing relative gain (so called "effect modification"), an "interaction term" between "device" and "relative gain" (denoted in the model as : "device x gain") was entered as an independent variable. The same procedure was performed for relative lumen pre, vessel size and lesion location. If an "interaction term" is found to contribute significantly to the final model, this would imply a significant difference between the devices, with respect to the influence of that particular factor on the late angiographic results. Inter-group comparisons can then be performed to locate the source of the detected difference.

For additional comparative purposes, the multivariate model was interrogated to provide estimates of relative luminal loss and lumen at follow up for each device group at hypothetical, but clinically relevant, interventional scenarios. Accordingly, we chose to compare estimated outcome between the 4 devices in this study: firstly for the "average intervention", thus, where mean relative gain (0.30, table 2) is achieved in a lesion with the mean relative lumen pre (0.38, table 2), in a vessel of mean diameter (2.67mm, table 2). Because of the preponderance of lesions treated by BA, the overall mean values for these parameters tend to reflect a typical BA scenario (table 2), so a typical "stent/atherectomy intervention" was also used to compare outcome where a relative gain of 0.44 is achieved in a lesion with a relative lumen pre of 0.37, in a vessel of 3.12mm. Finally, the third level of comparison was chosen to reflect "optimal intervention", whereby a relative lumen post of 1.0 is achieved through a relative gain of 0.61 in a lesion of mean severity (0.39, table 2), in a vessel of 3.2mm. Statistical comparisons are provided, without systematic automatic correction for "multiple comparisons", in order to display all potential differences and trends between the groups. To graphically illustrate the findings, 3 dimensional regression planes were constructed, as previously described [29].

RESULTS

Baseline demographic features of the patient groups are provided in table 1, showing that the patient groups are broadly similar, with the exception that 20% of the patients treated by DCA had had prior angioplasty (in a previous specific analysis of this population [48], so called "restenotic lesions" were not associated with a greater propensity to subsequent renarrowing so all patients were included in this study) and no totally occluded lesions were treated by DCA compared with 15% treated by ELCA.

Table 1. Demographic data for the 4 patient groups.

	Balloon Angioplasty	Directional Atherectomy	Excimer Laser	Palmaz-Schatz Stent
Patients	3135	190	106	229
Lesions	3796	200	116	229
Male/Female	(80%/20%)	(81%/19%)	80%/20%	80%/20%
Age (years)	56±9	58±11	56±9	55±9
Lesion (primary/restenosis)	100%	80%/20%	100%	100%
Vessel: LAD	43%	67%	36%	65%
RCA	33%	20%	35%	22%
LCX	24%	13%	29%	13%
Total occlusion pre	6%	0	15%	4%
Diabetes	7%	6%	6%	7%
CCS III or IV angina	62%	73%	72%	64%
Non-exertional angina	46%	40%	52%	48%

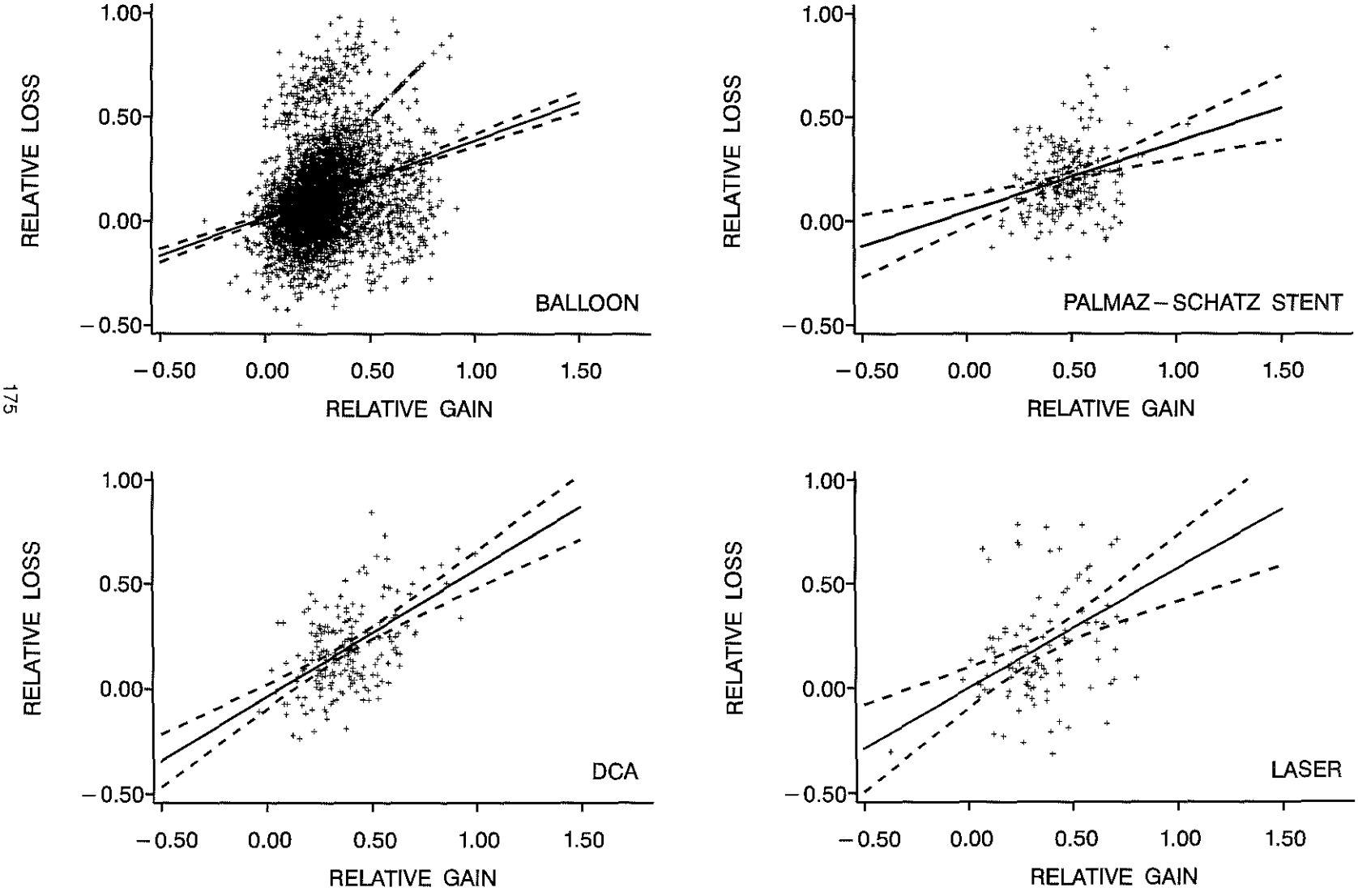
After normalization for vessel size, significant differences were detected between the groups for all parameters : Pre-procedural lesion severity was greatest in the ELCA group, which had the greatest frequency of total occlusion pre (relative lumen pre 0.31 or % diameter stenosis 69%). Luminal increase was greatest after PS (relative gain of 0.48, or 48% increase in lumen) as was post procedural relative lumen (0.84 or 84% of vessel diameter). Despite having greatest relative loss (0.21, 21% loss in vessel diameter) PS also retained the greatest relative lumen at follow up (0.64, or 64% of ideal) and displayed greatest ultimate net benefit (net gain index 0.28, 28% net increase in vessel diameter).

Table 2. Quantitative angiographic measured and derived parameters per device group, given as mean and standard deviation (std). Vessel size differed widely ($p < .0001$), justifying the use of "relative" rather than "absolute" measurement parameters in the study evaluation.

	BALLOON Mean	± sd	DCA Mean	± sd	LASER Mean	± std	STENT Mean	± std	ALL Mean	± std	ANOVA 'p'
Reference diameter pre(mm)	2.62	0.55	3.28	0.62	2.51	0.47	3.01	0.44	2.67	0.57	<.0001
Reference diameter post(mm)	2.67	0.53	3.34	0.52	2.68	0.49	3.19	0.41	2.73	0.55	<.0001
Reference diameter f-up(mm)	2.69	0.58	3.32	0.54	2.60	0.60	2.96	0.47	3.09	0.51	<.0001
MLD pre (mm)	0.99	0.40	1.21	0.38	0.76	0.44	1.08	0.33	1.00	0.40	<.0001
MLD post (mm)	1.73	0.37	2.41	0.43	1.66	0.39	2.51	0.36	1.80	0.40	<.0001
MLD f-up (mm)	1.42	0.58	1.83	0.60	1.17	0.71	1.91	0.54	1.46	0.60	<.0001
Diameter stenosis pre (%)	61.3	14.6	63.2	10.0	68.8	18.3	63.9	10.1	61.8	14.4	<.0001
Diameter stenosis post (%)	34.7	9.6	27.5	9.8	37.8	10.5	20.9	7.5	33.7	10.1	<.0001
Diameter stenosis f-up (%)	46.5	19.4	41.0	16.4	55.7	23.6	35.5	14.1	45.9	19.3	<.0001
Absolute gain (mm)	0.73	0.42	1.20	0.47	0.90	0.53	1.43	0.42	0.80	0.46	<.0001
Absolute loss (mm)	0.30	0.53	0.58	0.60	0.50	0.72	0.60	0.50	0.34	0.55	<.0001
Absolute net gain (mm)	0.43	0.58	0.62	0.60	0.40	0.70	0.83	0.58	0.46	0.59	<.0001
Relative lumen pre	0.39	0.15	0.37	0.10	0.31	0.18	0.36	0.10	0.38	0.14	<.0001
Relative lumen post	0.67	0.12	0.75	0.16	0.67	0.14	0.84	0.11	0.68	0.13	<.0001
Relative lumen f-up	0.55	0.21	0.56	0.17	0.47	0.27	0.64	0.16	0.55	0.21	<.0001
Relative gain	0.29	0.16	0.38	0.18	0.36	0.21	0.48	0.14	0.30	0.17	<.0001
Relative loss	0.12	0.21	0.19	0.21	0.20	0.29	0.21	0.17	0.13	0.22	<.0001
Net gain index	0.17	0.23	0.19	0.19	0.15	0.28	0.28	0.19	0.17	0.23	<.0001
Loss index	0.51	3.99	0.52	0.75	0.73	1.61	0.44	0.37	0.51	3.75	.34
Restenosis rates:											Chi-square
1. %ds ≥ 50% at fup	36.3%		28.5%		50.9%		16.2%				<.0001
2. Loss ≥ gain/2	41.1%		45.0%		46.6%		35.4%				.17
3. Loss ≥ 0.4mm	31.5%		59.8%		38.1%		64.9%				<.0001
4. %ds at fup > .9%DS pre	25.3%		16.1%		27.8%		9.2%				<.0001

Restenosis definition 1 = diameter stenosis ≥ 50% at follow up; 2 = loss ≥ half the initial gain; 3 = loss ≥ 0.4mm (twice the post-PTCA variability of CAAS [39]; 4 = recurrence of stenosis to within 10% of baseline severity. BALLOON = balloon angioplasty; DCA = directional coronary atherectomy; LASER = excimer laser coronary angioplasty; STENT = Palmaz-Schatz stent; MLD = minimal luminal diameter. %DS = percent diameter stenosis.

Figure 1. Linear regression analysis (and 95% confidence intervals), displaying the influence of relative gain on relative loss. Significant differences are evident between groups in the rate of the relative loss response to increasing relative gain (p=.006). Balloon = balloon angioplasty; DCA = directional coronary atherectomy; laser = excimer laser coronary angioplasty.



Binary Restenosis Rates (table 2)

Differences between the groups in binary restenosis depended on the definition applied (table 2). ELCAwas associated with the highest frequency of a stenosis ≥ 50% at follow up at 51%, followed by BA at 36%, DCA at 29% and PS stenting at 16% ($p<.0001$), although PS had the greatest frequency of a loss ≥ 0.4mm during follow up.

Linear regression analysis (figure 1)

Significant differences were detected between the device groups in the relative loss response to increasing relative gain ($p=.006$, by analysis of variance; 0.61 in the DCA group, 0.57 in the ELCA group, 0.37 in the BA group and 0.33 in the PS group) and in the relative lumen at follow up response to increasing relative gain ($p=.003$; -0.22 for ELCA, 0.01 for BA, 0.17 for DCA and 0.22 for PS).

Multiple Linear Regression Analysis (table 3, figure 2).

Inter-device differences in predicted angiographic results: Each of relative luminal gain, relative lumen pre and lesion location in the LAD were found to be significant independent determinants of both relative loss and relative lumen at follow up. Having already controlled for the influence of vessel size, by virtue of the use of relative parameters, no significant further independent influence of this parameter on outcome was noted. Significant differences were observed between the devices with respect to the influence of relative gain on each of relative loss and relative lumen at follow up ($p=.02$; reflected by the observed differences in the slopes of the 3 dimensional regression planes, from right to left in figure 2). The principle source of this difference appeared to be between the BA and each of the ELCA ($p<.01$) and the DCA ($p=.04$) groups, whereby, for a given relative luminal gain, 43% would be retained as improved relative lumen at follow up if BA was used, compared with 23% for DCA and 12% for ELCA. By PS, 41% of relative gain was predicted to be retained as relative lumen at follow up, which was not found to be statistically different from that predicted for DCA and ELCA ($p=.07$ versus ELCA).

Comparison of estimated outcome between devices at the 3 pre-designated levels of comparison, as already described, revealed the following: for "average intervention", significant differences in model estimated relative loss and relative lumen at follow up were detected between the device groups, primarily due to significant differences between ELCA and each of the other 3 groups (table 3b, figure 2); for "average DCA/stent intervention", PS was associated with less relative loss and greater relative lumen at follow up than both ELCA ($p<.0001$) or DCA ($p=.01$), also, each of BA and DCA were associated with superior late results than ELCA ($p<.0001$ and $p=.005$, respectively). No significant difference in estimated outcome was observed between BA and either PS or DCA (table 3b, figure 2). At the third predesignated level of comparison, thus after "optimal intervention", similar inter-group differences as in the previous comparison were evident and, in addition, BA was estimated to be associated with less relative loss and a greater relative lumen at follow up than DCA ($p=.006$).

Influence of totally occluded lesions: Due to the greater prevalence of totally occluded lesions at baseline in the ELCA group compared with the others (table 2), particularly DCA and PS, multivariate analysis was repeated after excluding such lesions from all groups, to be certain that the observed differences could not be explained merely by this factor. Of the 24 successfully treated totally occluded lesions in the ELCA group, 9 (37%) had re-occluded at follow up, compared with 59 of 286 (20%) in the BA group and 0 of 5 in the PS group. Exclusion of totally occluded lesions at baseline from the population to be analyzed resulted in no fundamental change in the findings of significant differences between devices in the influence of relative gain on outcome and in estimated outcome, as described.

DISCUSSION

Restenosis rates

Conflicting findings regarding late angiographic results were evident from the use of different categorical criteria for angiographic restenosis. Such disclosure is not new having been described many times in the past [29,47]. According to the widely used "diameter stenosis ≥50%" criteria, PS stent implantation appeared to provide the greatest 6 month angiographic results and ELCA the least, with BA and DCA in between.

These findings although not providing any insight to the problem or a possible mechanistic explanation, concur quite well with the results of the more comprehensive multivariate analyses.

Simple Linear Regression - useful but incomplete information

In simple linear regression, the renarrowing response to increasing luminal enlargement was found to differ significantly between the groups, with the least favourable response displayed by the ELCA group (figure 1). The most favourable outcome was predicted for the PS stent group, with least increase in relative loss and greatest increase in relative lumen at follow up predicted, with increasing relative gain. In addition, at the 3

Table 3 (a): Multiple linear regression model to evaluate the influence of the device used for intervention on estimated relative luminal loss during follow up and relative lumen at follow up. Opposite the independent variable "Device" [1], [2], [3], are "p' values representing analysis of variance of estimated RLoss and RLfup between the 4 devices at the selected levels of comparison as described in the statistical methods section ([1] represents "average intervention", [2] represents "average DCA/stent intervention", [3] represents "optimal intervention". The respective influences of relative gain and relative lumen pre on outcome for each individual device are provided in the 4 x 4 tables immediately below the relevant term. The 'p' values convey the probability of no additional influence on the model by addition of the relevant independent variable, after all the others have already been entered. In the 4 x 4 tables, automatic pre-correction for multiple comparisons has not been applied.

	Rel Loss (r^2 = .14)	RLFup (r^2 = .12)	p
Device [1]	*	*	.0006
Device [2]	*	*	<.0001
Device [3]	*	*	.0007
Vessel size	0.00	0.00	.87
LAD	0.02	-0.023	.03
RLumen pre	0.32	0.68	<.0001
Relative Gain	0.61	0.39	<.0001
Device x RG	*	*	.02

Inter-group comparisons of the influence of RG on outcome :

	Estimated RLoss	Estimated RLFup	PS	BA	DCA	ELCA
PS	0.59	0.41	.	.98	.10	.07
BA	0.57	0.43	.78	.	.006	.001
DCA	0.77	0.23	.10	.006	.	.23
ELCA	0.86	0.14	.07	.001	.23	.

Device x RLpre	*	*	.23

Inter-group comparisons of the influence of RLpre on outcome :

	Estimated RLoss	Estimated RLFup	PS	BA	DCA	ELCA
PS	0.56	0.44	.	.85	.20	.08
BA	0.32	0.68	.85	.	.09	.008
DCA	0.61	0.39	.20	.09	.	.48
ELCA	0.38	0.62	.08	.008	.48	.

Device x Vessel size	*	*	.56
Device x LAD	*	*	.11

Table 3 (b)

Estimated relative loss and relative lumen at follow up for each patient group, according to the "centering" procedures performed, as described in the text, with inter group comparisons using a 4 x 4 table (p values are not corrected for multiple comparisons), after :

(i) the "average intervention" : ie where a relative gain of 0.3 is achieved in a lesion with a relative lumen pre of 0..39, located in a 2.67mm vessel.

	Estimated R Loss	**Estimated RLfup**	PS	BA	DCA	ELCA
PS	0.11	0.58	.	.34	.33	.006
BA	0.13	0.55	.34	.	.80	.002
DCA	0.13	0.55	.33	.80	.	.02
ELCA	0.19	0.49	.06	.002	.02	.

(ii) the "average DCA/stent intervention" : ie where a relative gain of 0.44 is achieved in a lesion with a relative lumen pre of 0.37, in a 3.12mm vessel.

	Estimated R Loss	**Estimated RLfup**	PS	BA	DCA	ELCA
PS	0.18	0.62	.	.14	.01	<.0001
BA	0.20	0.60	.14	.	.08	<.0001
DCA	0.23	0.57	.01	.08	.	.005
ELCA	0.31	0.49	<.0001	<.0001	.005	.

(iii) the "optimal intervention" : ie where a relative gain of 0.61 is achieved in a lesion of 0.39 relative lumen pre, located in a 3.2mm vessel.

	Estimated R Loss	**Estimated RLfup**	PS	BA	DCA	ELCA
PS	0.28	0.72	.	.73	.01	.0006
BA	0.30	0.70	.73	.	.006	.0003
DCA	0.36	0.64	.01	.006	.	.03
ELCA	0.47	0.53	.006	.0003	.03	.

Table 4 (a). Repeat multiple linear regression analysis, after exclusion of totally occluded lesions pre-intervention. Format is similar to table 3.

	Rel Loss (r^2 = .14)	RLFup (r^2 = .12)	p
Device [1]	*	*	.06
Device [2]	*	*	.001
Device [3]	*	*	.003
Vessel size	0.00	0.00	.31
LAD	0.02	-0.023	.0009
Relative Gain	0.70	0.30	<.0001
RLumen pre	0.23	0.77	<.0001
Device x RG	*	*	.03

Inter-group comparisons of the influence of RG on outcome :

	Estimated RLoss	Estimated RLFup	PS	BA	DCA	ELCA
PS	0.56	0.44	.	.85	.20	.03
BA	0.59	0.41	.85	.	.03	.008
DCA	0.77	0.23	.20	.03	.	.48
ELCA	0.89	0.11	.03	.008	.48	.

Device x RLpre	*	*	.004

Inter-group comparisons of the influence of RLpre on outcome :

	Estimated RLoss	Estimated RLFup	PS	BA	DCA	ELCA
PS	0.56	0.44	.	.06	.92	.33
BA	0.23	0.77	.06	.	.04	.008
DCA	0.61	0.39	.92	.04	.	.26
ELCA	0.69	0.31	.33	.008	.26	.

Device x Vessel size	*	*	.37
Device x LAD	*	*	.25

Table 4 (b)

(i) the "average intervention" : ie. where a relative gain of 0.28 is achieved in a lesion with a relative lumen pre of 0.41, located in a 2.67mm vessel.

	Estimated R Loss	**Estimated RLfup**	PS	BA	DCA	ELCA
PS	**0.12**	**0.57**	.	.65	.47	.04
BA	**0.13**	**0.55**	.65	.	.57	.008
DCA	**0.13**	**0.55**	.47	.57	.	.09
ELCA	**0.18**	**0.51**	.04	.008	.02	.

(ii) the "average DCA/stent intervention" : ie. where a relative gain of 0.43 is achieved in a lesion with a relative lumen pre of 0.37, located in a 3.14mm vessel.

	Estimated R Loss	**Estimated RLfup**	PS	BA	DCA	ELCA
PS	**0.18**	**0.62**	.	.06	.02	.0001
BA	**0.21**	**0.59**	.06	.	.34	.002
DCA	**0.23**	**0.57**	.02	.34	.	.06
ELCA	**0.29**	**0.51**	.001	.002	.02	.

(iii) the "optimal intervention" : ie where a relative gain of 0.61 is achieved in a lesion with a relative lumen pre of 0.29, located in a 3.2mm vessel.

	Estimated R Loss	**Estimated RLfup**	PS	BA	DCA	ELCA
PS	**0.28**	**0.72**	.	.03	.02	.0006
BA	**0.34**	**0.66**	.03	.	.39	.009
DCA	**0.37**	**0.63**	.02	.39	.	.06
ELCA	**0.47**	**0.53**	.006	.009	.06	.

levels of comparison chosen, ELCA was associated with least favourable estimated outcome and PS stent the most favourable. These findings are strongly suggestive of differences between the device groups in renarrowing response to luminal increase. However, because of the considerable differences in pre-procedural lesion severity, epicardial location and coronary vessel size between the groups and the known confounding effects of these factors on late angiographic outcome [10,14,25,26,42,44,48,49], emphatic conclusions would be premature without taking account of these factors in multiple linear regression.

Luminal renarrowing and late angiographic outcome are influenced by the device used

Multiple linear regression analysis confirmed the existence of significant differences between the devices with respect to the renarrowing response to luminal increase at intervention, independent of variations in vessel size, lesion severity or location and luminal increase at intervention. Retrospective exclusion of totally occluded lesions at baseline, on the grounds of significantly greater frequency in the ELCA group, did not lead to any fundamental change in the differences found by multivariate analysis between ELCA and the other 3 groups, or to improvement in the overall predictive power of the model (although some changes in the final model were indeed detected). Accordingly, the discussion will focus on evaluation of the complete lesion populations, without this a priori stratification.

Evidence for device specific influence on late angiographic results was twofold. Firstly, comparison of estimated angiographic results between devices at 3 pre-designated levels of intervention revealed significant differences, which became more apparent at increasing levels of relative luminal gain in larger vessel size (from the "average" to the "optimal" intervention). In particular, PS and BA emerged with the most favourable predicted angiographic results in the selected circumstances. Late results of ELCA were least favourable at each comparative level. Secondly, the influence of luminal increase on late results differed significantly between devices, whereby, for any given luminal increase significantly more favourable late angiographic results could be anticipated by BA, than by DCA or ELCA. These findings confirm our previous reports of inherent device specific effects on the restenosis process and late angiographic outcome [9,15,22,26-28] and prompt questioning of the reported "generalized model" of restenosis after intervention [10,14,25], according to which, the device used for intervention exerts no independent influence on late angiographic results.

Differences with previous studies

Although it is possible that differences in patient selection, demographic factors, interventional practices and quantitative angiographic methodology, may contribute to the differing findings between this and prior studies [10,14,25], 3 methodological variations may also potentially explain the conflict. Firstly, in previous studies, absolute coronary luminal measurements were employed and the wide differences in coronary vessel diameter between patient groups treated by different devices [10,14,25] may have exerted some confounding influence, according to our recent report of the influence of vessel size on late angiographic results [29]. A priori normalization of key angiographic parameters for vessel size in this study adequately controlled for this confounding influence. Secondly, prior studies did not specifically investigate potential differences between devices by considering so called "effect modification" - by including "interaction terms" (as explained in the statistical paragraph), in the multivariate models. Accordingly, if such differences did actually exist (as we have found here), they would not have been detected. Thirdly, we used the multivariate model to allow additional and practically useful, if hypothetical, direct comparison of estimated outcome between devices, whereas previous studies constructed models to allow prediction of the likelihood of "binary restenosis" from the post procedural result, based on the multivariate findings [10,25].

Clinical Implications: optimization of the acute result

Although our findings, of an independant influence of the device itself on late results, question the universal applicability of the previously reported "generalized model of restenosis" [10], in agreement with previous reports [7,9,10,25,26,29,48,50], we have also found that maximization of the acute result tends to provide more favourable late results. Accordingly, such an approach should be recommended as the practical goal of all interventions (since it is predicted by our multivariate models that, depending on the device, 14% - 43% of acute angiographic luminal increase will be retained as larger lumen at follow up). By the same token, it must be acknowledged that such an approach does not actually "prevent restenosis", but in fact provokes renarrowing, because 57% - 86% of luminal increase (depending on the device) is subsequently "lost" as luminal renarrowing. Ultimately, optimization of the acute result is not a conclusive solution to restenosis, merely creating a greater lumen to accommodate the inevitably greater degrees of subsequent renarrowing. Thus, although the binary restenosis rate is perceptibly lower after stent implantation than balloon angioplasty, significantly greater measured luminal renarrowing develops after stenting (table 2). Moreover, from our findings, it would appear that through systematic optimization of acute angiographic results, as has been previously recommended [7,9,10,25,26,29,48,50], differences in late angiographic outcome between devices become more apparent, thus, evaluation of current studies investigating the clinical value of optimal atherectomy and stent implantation will provide interesting ratification of the predictive models we have used. In fact, recent

Figure 2a. 3 d graphs of the multiple regression analysis (table 3), already used in chapter 10. 'X' axis = relative gain, 'Z' axis = relative loss, Y axis = relative loss (figure 2a), relative lumen at follow up (figure 2b). Symbols represent parameter values at the three selected levels of comparison of outcome, whereby, the dot represents "average intervention", the diamond "average DCA/stent intervention" and the star "optimal intervention" (contd. on caption 2b).

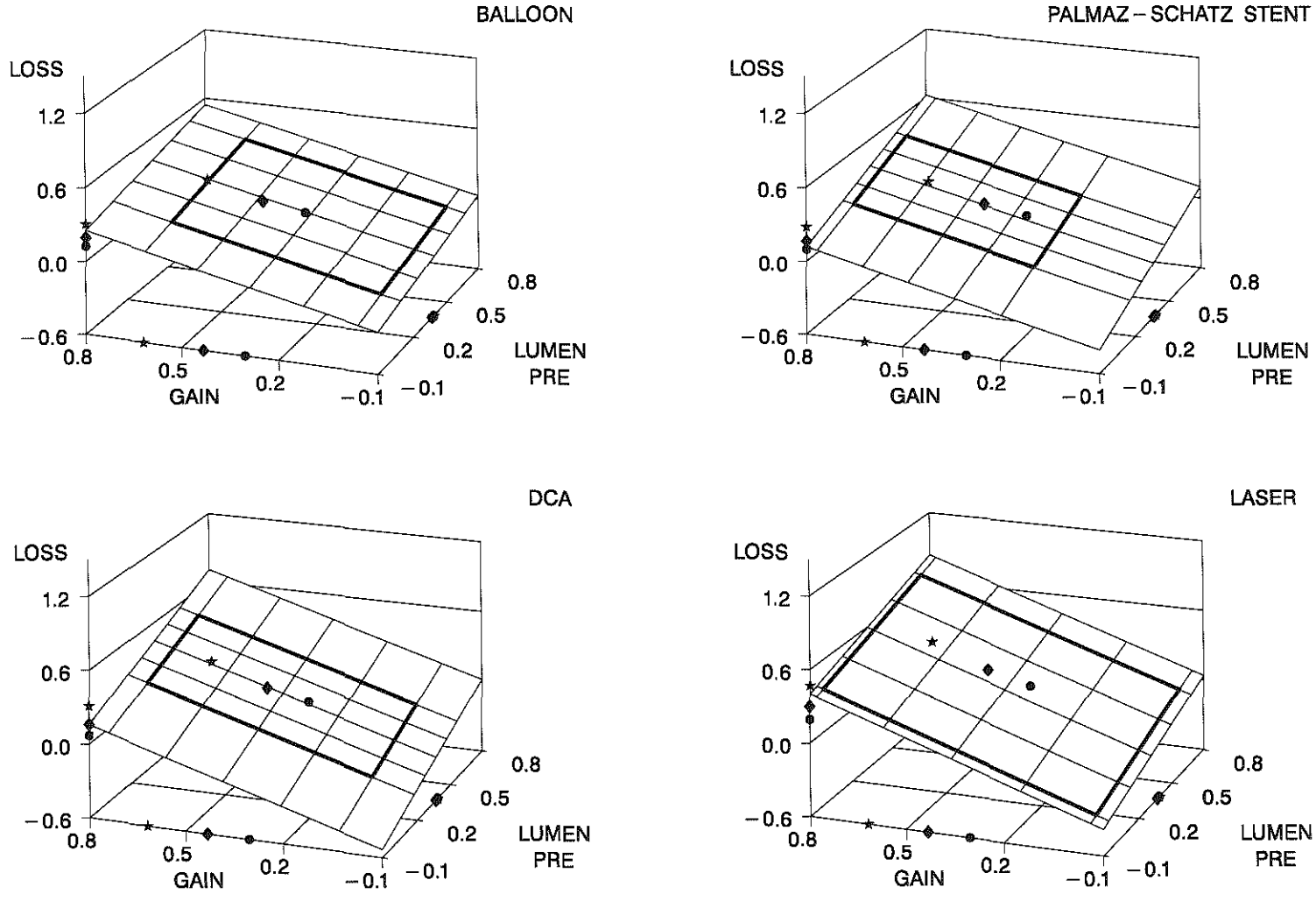
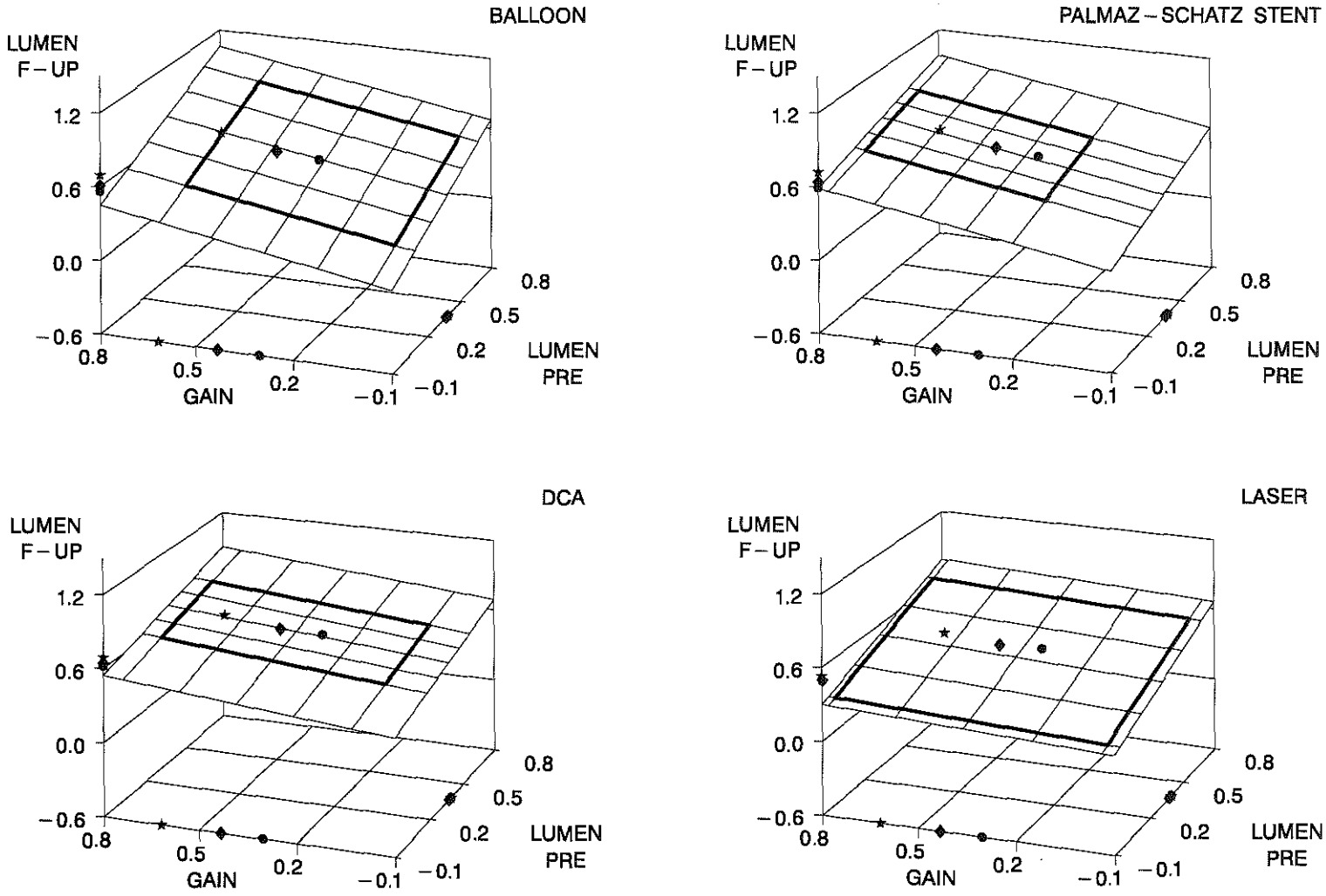


Figure 2b. (contd from 2a). "Average intervention" is in the centre of BA and ELCA planes, but below centre in DCA and PS planes, whereas "optimal intervention" is at the upper extremity of the BA plane, but within one standard deviation in the PS plane. Balloon = balloon angioplasty; DCA = directional atherectomy; laser = excimer laser. Loss = relative loss; Gain = relative gain; lumen pre = relative lumen pre; lumen f-up = relative lumen at follow up.



comparison of atherectomy with each of balloon angioplasty [26] and Palmaz-Schatz stent implantation [51] in lesions matched for the acute procedural result, as well as baseline severity, has shown significantly superior late angiographic results by balloon angioplasty and stent implantation, supporting the findings of this study.

Implications for interpretation of outcome of clinical trials and selection of devices for intervention

Since late angiographic results were predicted to be similar for PS and BA in this study, the reported superior results after PS compared with BA in both the Benestent and Stress trials [23,24], may now be concluded to be simply a consequence of the greater acute luminal results achieved by stent implantation and not because of any difference in actual restenosis propensity. Accordingly, for two rapidly emerging practical reasons, stent implantation may soon be considered the device of choice above BA, when the choice exists. Firstly, stent implantation, with or without adjunctive balloon dilatation, can consistently achieve optimal luminal results, whereas balloon angioplasty alone clearly cannot and the hypothetical "optimal intervention" for balloon angioplasty is rarely observed. Secondly, studies with optimization of stent deployment [52,53], suggest that stringent anticoagulation, which carries the considerable side effect of bleeding complications [23,24], may no longer be required to combat the previously reported high risk of acute and sub-acute occlusion [20].

Since DCA was associated with less favourable predicted late angiographic results than BA in this study, it could be speculated that in CAVEAT [7] and CCAT [8], its consistent achievement of greater acute luminal results adequately compensated for this apparently increased restenosis propensity, providing similar late angiographic results for DCA as BA, as had been previously described by our group, in a comparison of matched coronary lesions [9]. Although optimization of the acute result by DCA was predicted to provide improving late angiographic lumen in this study, as previously reported [6,25,26], the main concern raised here regarding DCA is the greater propensity to restenosis, compared with BA and PS stent. Namely, with comparable increase in relative luminal gain, if DCA is used then 77% of the increase will subsequently be lost as luminal renarrowing, compared with 57% for BA and 59% for PS), findings which, as previously mentioned, are in alignment with a recent comparative study [26]. The place of DCA in the interventional armimentarium, thus, remains to be finally clarified.

It would be foolhardy to suggest that there is no place for laser technology in interventional cardiology, based on the findings of this study, since the technology and application methodology is continuously evolving. In addition, its value in initially recanalizing unfavourable lesions has been well documented [12,54]. However, the 37% reocclusion rate following recanalization of total occlusions by ELCA in this study and the unfavourable late angiographic results in multivariate analysis, compared with the other devices, are not encouraging for the particular approach employed in the patients described in this study (which was the conventional therapy during the period 1991-93). Combination therapy of successful recanalization of occluded vessels by laser technology followed by optimization of the result by stent implantation is a potentially interesting area which remains to be clinically explored. However, it is more likely that newer treatment applications, such as use of continuous local saline infusion during laser ablation but even more importantly, integral improvements in catheter design to improve light delivery and increase ablative power while reducing trauma to the vessel wall.

Potential mechanistic explanations for differences in predicted outcome between the devices

Differences in distribution or influence of clinical or angiographic morphological factors between the patient groups may theoretically influence outcome, but previous studies, including such variables, have not shown any major confounding effects, which might distort the relationships demonstrated between the angiographic parameters on which this study has been concentrated [9,10,25,26,42,44,48,49,55]. In particular, a recent comparison of late clinical and angiographic outcome among our patients with stable and unstable angina treated by directional atherectomy revealed no significant difference in restenosis tendency [56]. Furthermore, the greater frequency of total occlusion at baseline in the ELCA and BA groups in this study did not unduly influence the findings. Accordingly, we have focused on the principal quantitative angiographic factors which are known to exert fundamental influence on late angiographic results.

(i) Rheological considerations - chronic recoil and vessel remodelling

It must be stated at the outset that any mechanistic attempt to explain the observed differences in predicted outcome would be somewhat speculative and is not based on the findings of this study, but rather represents an attempt to understand the findings of this study, in the light of current knowledge and emerging findings of ongoing investigations. Our hypothesis, based on experimental, pathological and ultrasound evidence, is that since the mode of vessel wall injury imparted by the different devices appears to be considerably different, the "rheo-fibro-proliferative" response of the vessel also differs significantly, between lesions treated by different devices. In the first place, it is already known that acute "elastic recoil", which is an inherent feature of BA [57-59] and thus also ELCA [34], is partially reduced by DCA [60] and virtually abolished by PS [16]. Consequently, if "chronic elastic recoil" and late "vessel remodelling" are confirmed as important factors in late luminal renarrowing [61-64], it would be expected that devices with differing rheological effects

would produce differing late outcome, despite apparently similar acute angiographic results (thus similar acute luminal increase, in apparently angiographically similar lesions, could conclude in considerably different late angiographic results, as has been found by our multivariate models in this study).

(ii) Fibro-proliferative aspects of intimal response due to device specific injuries

Secondly, if the major non-elastic component of renarrowing is fibroproliferative neointimal hyperplasia and if this is proportional to the degree of injury imparted during intervention [65], it seems logical that device specific injuries may provoke particulate response levels. Ablation of tissue by ELCA, with generation of shockwaves [66] and of vapour bubbles [67], can cause extensive intimal dissection, medial necrosis and internal elastic lamina abrasion [67,68] and ultraviolet radiation may be somewhat mutagenic [69]. Similarly, excision of vessel wall components, with exposure of intramural tissue [5,6,48], as well as plaque fracture, compression and vessel stretching by DCA [3,4], might create greater injury to the vessel wall than the plaque fracture, compression and vessel stretching caused by BA [3,4,5,70-72]. Stent implantation presupposes some of the features of balloon injury, but creates a larger lumen of a mainly smooth and circular contour [17-19]. Accordingly, it seems reasonable to speculate that these mechanistic differences may, at least partly, explain the observed differences in predicted restenosis propensity and late angiographic outcome between the devices studied here.

Limitations

First, although most of the patients evaluated in this study were recruited during major multicentre randomized trials and overall quantitative angiographic follow up was 93 % of eligible patients, this is ultimately an observational study and final outcome certainly requires verification through similar evaluations in randomized comparisons of interventional devices. Second, it could be argued that specific lesion morphological indications for the use of the 4 devices may differ considerably and so influence late results, however, we have previously demonstrated that the principle angiographic determinants of late angiographic outcomeafter coronary intervention are the quantitative angiographic parameters included in this study [9,26,42,44,48,49]. Third, according to current interventional practice today, the post procedural results of DCA and stent implantation might not be considered "optimal" and the paucity of lesions with "super-optimal" results may have affected the reliability of the model in predicting late angiographic results for each device after optimal intervention. Nevertheless, these angiographic data are comparable with those obtained in STRESS, BENESTENT, CAVEAT and CCAT [7,8,23,24], thus representative of diverse multinational multicentre experience. Fourth, focusing on angiographic parameters does not take account of the potentially confounding effects of clinical factors, but, as previously stated, prior studies have demonstrated no distortion of angiographic relationships, when clinical factors are included, so we feel justified in concentrating on the key angiographic parameters in this study.

CONCLUSION

Definite differences in the propensity to restenosis were detected between patient groups treated by Palmaz-Schatz stent implantation, directional atherectomy, balloon angioplasty and excimer laser coronary angioplasty, independent of variations in lesion severity and location, coronary vessel size and procedural results. These differences, which may represent inherent device specific characteristics of the "rheo-fibroproliferative" response to unique vessel wall injury, require further study in larger patient groups, ideally with optimal interventional strategies and intravascular ultrasound evaluation, for corroboration and possible mechanistic explanation.

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Conclusion, reflections and implications of the findings in this thesis

Principal findings

In the first part of the thesis, it emerges that quantitative angiography does not help to identify patients at greater risk of lesion related complications after angioplasty, nor does angiographic imaging per se seem to be useful for reliable identification of thrombus in the coronary lumen or for exclusion of the presence of intimal dissection. Accordingly, it seems wise to apply angiography to investigations in which it can provide the most reliable, reproducible and useful information, thus, for the serial measurement of luminal changes as a consequence of coronary interventions. With respect to important methodological aspects of the application of quantitative angiography to investigation of results of intervention, particularly in the quantification of the deterioration in the lumen of treated vessels - the angiographic evaluation of the process of restenosis - chapter 4 demonstrates that quantitative analysis from multiple projections is necessary to provide reliable serial measurements; the findings in chapter 5 are reassuring for the clinician, insofar as post-angioplasty angiography is found to be as reliable for analysis as angiography postponed for 24 hours (despite the problems of intimal dissection and contour haziness), and furthermore, no significant luminal deterioration is observed during that time.

Scrupulous standardized quantitative angiographic analysis, of serial angiograms acquired according to specific guidelines (as described in the early chapters of this thesis and emphasized in each chapter), in large patient groups treated by different coronary devices, provided the substrate for the investigations described throughout the thesis and particularly in part 2. Essentially 2 messages emerge from the investigations in part 2 : firstly, among other important factors, coronary vessel size is found to be a fundamental determinant of the late angiographic outcome of intervention, whereby lesions located in larger vessels are inherently associated with a more favourable outcome. Accordingly, this factor must thus be taken into account in comparative studies of the late results of intervention, between different devices which may be systematically and preferentially applied to smaller or larger vessels. Secondly, use of comparative measures which control for differences in vessel size, allowed demonstration of intrinsic differences in restenosis propensity between different interventional devices - perceptible as varying levels of angiographic luminal loss after similar levels of luminal gain in lesions of similar severity, location and vessel size. These differences in restenosis propensity are speculated to be a consequence of the fundamentally differing mechanistic effects of the devices, which result in varying nature and degree of vessel wall trauma, through achievement of given degrees of luminal enlargement, thereby provoking inherently varying degrees of neointimal and/or remodelling response.

These device specific differences are essentially unveiled for the first time in collected studies in this thesis, and it must be stated that such findings do not meet with universal agreement. Other investigators have reported in several studies, that the post procedural result is the principle determinant of late angiographic outcome, regardless of the device used, implying that essentially the device used is irrelevant, as long as a policy of maximization of the acute result is universally applied. We believe the findings of chapters 8 to 11 in this thesis emphatically demonstrated that the device used actually exerts a significant independent influence on late results of intervention, and this must be taken into account clinically when choosing devices for intervention.

Future interventional perspectives, in the light of these findings

Balloon angioplasty

What are the clinical implications of device specific effects on restenosis, for the future use of these different devices ? Firstly, it must be concluded that balloon angioplasty, according to this scheme of things, may have a limited future as an independent "stand alone" therapy in interventional cardiology. Now in 1995, 18 years after the first balloon angioplasty procedure, restenosis remains as big a problem as ever after balloon dilatation and failure, sub-optimal results and acute vessel closure are still a real problem in a not inconsiderable proportion of cases. In addition, "plain old balloon angioplasty" does not have the capacity to consistently provide "optimal" acute results, due to the natural phenomenon of elastic recoil, and if recoil is overpowered, unwanted dissection of the vessel wall occurs (which, as seen in chapter 3, is more common than is angiographically apparent and in chapter 6, is shown to be a strong predictor of unfavourable short term outcome). In fact, with the type of "optimal" acute angiographic results which increasing numbers of clinicians are now achieving through the use of stent implantation, the definition of what constitutes a "sub-optimal" results will most probably change, because a "diameter stenosis less than 50%" may not for much longer be

considered an acceptable definition of successful intervention. Requirement for a post-procedural result of less than 20% diameter stenosis is already being applied in a number of ongoing clinical trials of directional atherectomy (OARS, BOAT and EUROCARE) and stent implantation (BENESTENT II, MUSIC, MUST, SOBIG, WEST). Thus, since the nature of the typical acute result offered by balloon angioplasty has not really changed over the years, if the "goalposts" are moved, by a change in the definition for acute procedural success, the frequency of so-called "sub-optimal" acute results of balloon angioplasty will probably considerable increase in the coming years. This will lead to progressively greater use of stent implantation to provide "optimal" acute results, so reducing the use of balloon angioplasty as a successful "stand-alone" device. It seems certain therefore, that the only manner in which balloon angioplasty can retain an important place as a sole and independently useful device in the interventional armamentarium is, if local delivery of effective biological agents can : **a)** reduce recoil (for example "Biostent", a compound directed at inhibition of actin polymerization); **b)** perhaps "mend" intimal dissection (each of which would improve the acute result); and/or **c)** control the rheo-fibro-proliferative neointimal response to vessel wall injury, which would improve the long term result. In other words, the "restenosis propensity" must be favourably altered, and according to our methodological proposal, studies in this area may best be evaluated by using either the univariate relative gain/relative loss relationship, as described in chapter 2, or the multivariate approach used in chapters 7 - 11, where additional confounding factors are also taken into account. (The concept of "primary angioplasty" for acute myocardial infarction, may actually provide a new avenue of survival for conventional balloon angioplasty, since recently published randomized trials demonstrate significant improvement in survival after angioplasty compared with "best thrombolysis", although the long term results of such studies, in terms of restenosis, remain to be reported.)

Directional atherectomy

Directional atherectomy does not emerge from these comparisons with a favourable profile in terms of restenosis propensity. Despite the attractive concept of plaque debulking, it is clear that this procedure provokes extensive luminal renarrowing and even when achieving the same acute results as stent implantation, a significantly greater degree of restenosis is provoked, as observed in chapters 9 - 11. From the practical point of view, despite what the greatest proponents of this device claim, it is not really "directional" at this time, since it cannot be consistently and reliably directed at the site of greatest plaque, as evident from the tissue removed being frequently normal vessel wall structures, without atherosclerotic plaque. Accordingly, advances in catheter design, to include ultrasound guidance allowing truly directional atherectomy and also the development of forward-cutting, rather than side-cutting, catheters, will represent considerable advances, which would require thorough evaluation but might save this concept of plaque removal from being consigned to the scrap heap of medical treatment philosophies. Optimization of the acute result of all atherectomy procedures by systematic balloon angioplasty is a fine and noble idea, but introduces considerable cost increases and does not solve the problem of fibro-proliferative neointimal hyperplasia (encapsulated by the univariate or multivariate gain/loss relationships demonstrated in chapters 9-11). The idea of adjunctive post procedural local drug delivery, may be a theoretical consideration, but is not logistically or practically attractive and would lead to further spiralling of costs per procedure. The future of directional atherectomy must therefore be considered to be in serious doubt at this time, without the technological advances mentioned, which, although exciting and promising, may not, of themselves, reduce its restenosis propensity.

Excimer laser

What about excimer laser assisted coronary angioplasty ? This device emerges from these studies with a very poor prognosis for the future because of its apparently unfavourable inherent restenosis propensity and requirement for systematic adjunctive balloon angioplasty. This statement must be qualified however, by recognizing the evolution of procedural aspects of excimer laser therapy over the past 3 years, with the introduction of saline infusion at the catheter tip, to reduce the problem of fast imploding and exploding vapour bubble formation and their traumatic consequences, as well as the current ongoing renovation of catheter design to provide homogenous light distribution (HLD) at the target site, which, the evidence suggests, may favourably alter the tissue ablation/damage ratio. Imminent clinical introduction of such catheters may provide a metamorphosis in laser therapy from interventional villain to ultimate hero. Certainly, the provision of a new channel through totally occluded lesions or diffusely diseased vessels, sufficient to allow introduction of a dilating balloon, may be perceived as an important contribution to revascularization, but it is unlikely to be sufficient to mandate the expense of this therapy, for most catheterization laboratories. In order to maintain a place in the interventional arsenal, laser must provide more than a means to make a channel, so the clinical results of new technology which claims to allow more tissue ablation with less tissue damage will be eagerly awaited. If the slope of the relative gain/relative loss relationship (or loss index, as used in chapter 8) can be

favourably affected by technological advances, then the status of excimer laser in intervention may well be secure.

STENT IMPLANTATION

The stent, in general, emerges from these evaluations as the most ideal device of those compared. The Wallstent treated lesions in chapter 10 are associated with significantly superior predicted late results in multivariate analysis compared to the other 3 devices. However, before recommending universal application of this albeit extremely useful device, it must be remembered that these patients represent the "best case scenario", among the patients treated by Wallstent during the initial European investigation of this device, all patients with acute and sub-acute occlusion having been excluded (in the initial report in 1991, 21% of patients experienced presumed thrombotic occlusion in the short term). Nevertheless, it can be concluded that when unfavourable early events are avoided, the late results, in terms of reduction of angiographic restenosis propensity are extremely favourable with this device and the current policy of maximizing the acute result, with attendant reported reduction in thrombotic events, should augur well for this stent in the future.

In the study described in chapter 10, the Wiktor stent had been implanted only for restenosis and quite a high percentage of the patients presented with "unstable angina" (see chapter 10), representing quite an unfavourable combination, in terms of the likelihood of subsequent luminal renarrowing. It is thus perhaps not a fair evaluation of the Wiktor stent to chastise it on the basis of the moderate results observed in this study, compared with the Wallstent and balloon angioplasty.

Palmaz-Schatz stent implantation provided significantly superior angiographic and clinical results in a direct comparison with directional atherectomy in chapter 9 and is associated with the most favourable late angiographic outcome in the evaluation in chapter 11. The progressively more widespread use of this stent in the last 2 years is therefore not surprising. However, like the other 2 stents investigated, the Palmaz-Schatz stent is also associated with considerable degrees of luminal renarrowing, compared with balloon angioplasty, for example, and it was mainly the ability to really provide greater acute results to compensate for the inevitable luminal renarrowing, which constituted the advantage of this device.

Thus, stent implantation is also not the perfect intervention, since luminal renarrowing still represents a considerable problem and reaches clinical relevance in 10 - 20% of cases (chapter 9 for example). This must be considered to represent a major improvement over the 35 - 50% of patients conventionally reported to be affected by clinically relevant "restenosis" following balloon angioplasty therapy, but it remains a problem which must and is being addressed by researchers in the area. In order to further reduce the restenosis propensity of the stent, the concept of drug eluting stents, which deliver biologically active agents over a period of time to inhibit the proliferative vessel wall response, represents an exciting avenue of hope and initial clinical results of the BENESTENT II trial, evaluating a heparin coated Palmaz-Schatz stent for reduction of restenosis, are very promising indeed. Additionally, the idea of biodegradable stents also coated with biologically active agents is not far from being applied in the clinical arena and may introduce a new era in stent implantation. Also, local drug delivery balloon catheters may be used after stent implantation, just as after balloon angioplasty or other procedures and may be of some interest for restenosis reduction. If these advances can further reduce the slope of the "gain/loss" relationship (as displayed in univariate form in chapters 2 and 7 and in 3 dimensional form in chapters 7, 10 and 11), associated with stent implantation, then it may approach the description of the "ideal device". If this were the case, then stenting would undoubtedly occupy the largest niche in the interventional armamentarium and only unfavourable morphological circumstances would mitigate against universal use. The challenge for the future for stent implantation, will thus partly focus on reduction of intimal hyperplasia, but also on increasing the clinical applicability, for example in lesions located in, or distal to, tortuous coronary segments, in the presence of established coronary thrombus and, especially, in smaller vessels, which still represent the majority of interventional practice (in chapter 7, more than 70% of lesions treated by balloon angioplasty in 4 major clinical trials involving over 3000 patients were located in vessels less than 3mm, which is still the generally accepted threshold for safe stent implantation).

Final reflections on the future for intervention and imaging

DEBULKING VERSUS DILATING - RESTORING OR RE-ESTABLISHING GLAGOVIAN BALANCE ?

It is evident from the findings in this thesis that the search for the "holy grail" in the percutaneous treatment of coronary artery disease is far from over, although considerable advances have been made in recent years. Nonetheless, of the devices compared, stent implantation shows the most promise as the ideal device for revascularization and further modification of its restenosis propensity may be anticipated by addition of antithrombotic or drug eluting coatings. Considerable technological improvements will be required if directional atherectomy and excimer laser angioplasty are to retain an important role in coronary intervention and the future

of balloon angioplasty as a sole interventional device must be considered to be limited, unless adjunctive effective biological agents to reduce its restenosis propensity can be introduced in the near future. However, if we return to the fundamental pathophysiology of coronary artery disease and focus, in particular, on the phenomenon described by Glagov, of compensatory enlargement of the coronary arteries in response to increasing plaque burden, it may be considered that the concept of debulking plaque represents something biologically more attractive (in allowing **restoration** of the "Glagovian balance"), than plaque compression and vessel stretching, by stent implantation (which may thus **establish a new** Glagovian balance). It is as yet unknown what happens to the plaque which is displaced, compressed or crushed by stent implantation. In addition to the known tendency to neointimal hyperplasia within the stent, could this compressed plaque also form a nidus for atherosclerotic advancement, which might stimulate further compensatory vessel enlargement, or does it remain an "innocent bystander" ?. It must be remembered that debulking procedures up to now have been extremely crude and uncontrolled. The sequelae of accurate and optimal plaque debulking and of the method of debulking (ablation versus excision), remains to be determined, so that this approach to coronary intervention cannot yet be glibly dismissed, especially now, with the apparently imminent clinical introduction of exciting advances in the design of atherectomy and laser catheters.

CORONARY IMAGING - IS QUANTITATIVE ANGIOGRAPHY A "BATTERED GOLD STANDARD" ?

Despite the increasing use of intracoronary ultrasound, quantitative coronary angiography can continue to play a key role in the evaluation of new approaches to coronary intervention and the investigation of biological approaches to restenosis reduction, as long as technical advances in automated analysis algorithms continue to be explored, validated and appropriately introduced (such as gradient field transformation, allowing faithful border detection in complex and angulated lesions, a limitation of current systems), careful standardization of image acquisition in multiple projections continues to be serially and consistently applied and the data derived are intelligently and sensitively evaluated. Furthermore, since intracoronary ultrasound is even more invasive than angiography, with introduction of a potentially traumatic guide wire and echo catheter, non-invasive angiographic methods, particularly Magnetic Resonance Imaging and Emission Beta Tomography, present the opportunity for a whole new era of contrast angiography. If further developments allow consistent provision of sharply defined images of both the coronary vessel wall, as well as the lumen, to facilitate automated quantitative analysis, the currently battered gold-standard would indeed have struck back at its critics to re-establish its rightful place in coronary imaging.

Curriculum Vitae

The author was born in Limerick, Ireland on May 9, 1961. After completing his school education at St Mary's Primary School, Askeaton, County Limerick and St Clement's Redemptorist College, Limerick, he enroled in University College Dublin to study medicine in 1978, graduating with MB BCh BAO degree in June 1984. During his undergraduate hospital residency apprenticeship, he took an elective period of 2 months at the division of cardiology of the Beth Israel Hospital, Harvard Medical School, Boston, in 1983, where the first flickers of an ensuing passion for interventional cardiology were initially kindled. After graduation, he completed his internships in internal medicine and surgery at the Mater Hospital, Dublin, during which time his cardiological penchant was further stimulated by attachments to both the department of cardiology and of cardiovascular surgery. His training in internal medicine was fulfilled at the Louth Hospital Dundalk and the Mater Misericordiae Hospital, Dublin, in the departments of internal medicine and gastroenterology. During this time he was almost lured into the realms of gastroenterology while undertaking a population screening study for colonic neoplasia and developing expertise in gastrointestinal endoscopy, as well as considerable useful experience in clinical research. After completing 3 years training and experience in internal medicine, he undertook and satisfied the examination for, and received the degree of, Member of the Royal College of Physicians in Ireland, in June 1987. In July 1988, he finally answered the irresistible call of cardiology and took a fellowship position at the department of cardiology of St James' Hospital and Trinity College Medical School Dublin. Over the next 3 years, a compelling fascination for interventional cardiology burgeoned, culminating in his move to the Thoraxcentre, Erasmus University, Rotterdam, after completion of his clinical cardiology fellowship and being awarded a Travelling Fellowship in Cardiology by the Irish Heart Foundation, in September 1991. At the Thoraxcentre, under the promotion of Prof Patrick Serruys, he became engaged in clinical research in the expanding field of interventional cardiology (leading to the preparation of this thesis) and through active involvement in the catheterization laboratory, has considerably expanded his prior clinical interventional experience to the use of new devices for coronary investigation and therapeutic intervention. In addition, he has been intimately involved in the design and co-ordination of a number of multicentre European and North American clinical trials of various pharmacological agents and new transcatheter devices for the prevention of restenosis after coronary intervention, as well as supervising activities at the angiographic core laboratory, at Cardialysis, Rotterdam, which is one of the largest and most renowned in the world. In November 1992 he was awarded the Young Investigator of the Year award of the Irish Cardiac Society for original clinical research. In June 1993, his prior internal medical and cardiological training was certified by the Medical Council of Ireland, and he was entered on the Netherlands Register of Medical Specialists in July 1993. In June 1993 he was invited to become a Fellow of the Scientific Council of the American College of Angiology and, in January 1994, a Fellow of the Royal Academy of Medicine in Ireland. He continues to be deeply involved in clinical research in interventional cardiology and is currently engaged as an interventional cardiologist at the catheterization laboratory of the Thoraxcentre, Erasmus University Academic Hospital of Rotterdam.

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