Stent implantation in human coronary arteries.
Clinical and angiographic aspects

Stent implantation in human coronary arteries.
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Stent implantatie in menselijke kransslagaders
Klinische en angiografische aspecten

PROEFSCHRIFT

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To my father who dreamt his son would become a cardiologist but never saw this dream come true,

To my mother whose remarkable personality is a continuous impetus for the family my father left behind,

To my dearest and truly beloved wife Sophie, and our three lovely boys Thomas, Matthias and Louis for their tolerance, encouragement and never ending love, patience and company,

To Pauline and Arthur, in the hope that one day the fruits of science will cure the incurable.

CONTENTS

Part II Clinical aspects

INTRODUCTION

Atherosclerotic cardiovascular disease remains one of the most important causes of morbidity and mortality in the industrialized world. Treatment is basically aimed at palliation and consists of either pharmacological intervention or revascularization. The first significant advances in the latter were largely surgical [1]. However, the pressing need for treatment with less invasive and potentially less expensive techniques, have stimulated the development of non-surgical revascularization techniques. Percutaneous transluminal coronary balloon angioplasty, which was first performed by Andreas Gruentzig in 1977, is one of the most successful examples and provided the stimulus for a rapid technological growth of interventional cardiology [2]. It is now widely accepted as a safe and effective treatment of obstructive coronary artery disease. However, the risk of abrupt vessel closure during or immediately after the intervention and the risk of late luminal renarrowing or restenosis continue to compromise its overall safety and efficacy [3,4]. To improve the immediate and long-term results of balloon angioplasty, a number of new technologies such as intracoronary stenting, directional or rotational atherectomy and laser therapy have been developed and represent the leading edge in the battle against atherosclerosis [5-8]. The intracoronary stent has been shown to be effective in the treatment of acute or threatened vessel closure due to balloon angioplasty induced coronary dissection, alleviating the need for emergency bypass surgery [9]. Furthermore, it has been hypothesized that intracoronary stent implantation may reduce the incidence of restenosis by optimizing the immediate angiographic results which should lead to improved long-term clinical outcome.

The work presented in the following chapters encompass the clinical and angiographic aspects of intracoronary stent implantation in human coronary arteries.

The first part of this thesis, deals with the technical aspects of intracoronary stenting. In particular, since it has been postulated that improved immediate angiographic results may reduce the incidence of angiographic restenosis, the changes in lesion morphology immediately after stent implantation were studied. Coronary angiograms before and after stent implantation were analyzed with the computer-assisted Cardiovascular Angiography Analysis System using automated contour detection. In the first chapter, the principles of this quantitative analysis method are briefly reviewed and the potential pittfals in the setting of intracoronary stenting are discussed.

Chapters 2, 3, 4 and 5 detail the immediate changes in stenosis geometry following stent implantation and compare these changes between two types of stents and with other interventional techniques.

Obviously, the main task of the medical practictioner is palliation of symptoms and eventually improve longevity in addition to palliation. Therefore, the second part of this thesis reflects on the clinical aspects of intracoronary stent implantation.

The immediate and long-term clinical and angiographic results of Wiktor stent implantation in native coronary arteries because of restenosis are reviewed in chapter 6 and 7. The potential role of stent implantation in venous bypass grafts is discussed in chapter 8.

It goes without saying that one of the methods to assess the proper role and merits of intracoronary stenting is the conduction of a randomized trial. Some of the aspects of the design of such a study are discussed in chapter 9. These data were of use for the power calculations for the Benestent Study, of which the results of the pilot phase are presented in chapter 10. This study is an international randomized study comparing the safety and efficacy of stent implantation versus balloon angioplasty for a de novo lesion in a native coronary artery.

In the final chapter, an attempt has been made to critically review the role of intracoronary stent implantation with some reflections on how we may improve the results.

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Part 1

Angiographic aspects

CHAPTER 1

CRITICAL APPRAISAL OF QUANTITATIVE CORONARY ANGIOGARPHY AND ENDOLUMINAL STENT IMPLANTATION

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INTRODUCTION

To objectively evaluate the coronary anatomy and its changes following therapeutic procedures, a computer assisted analysis procedure was developed in the Thoraxcenter by H. Reiber and colleagues [1]. This computer assisted Coronary Angiography Analysis System or CAAS system has extensively been validated with respect to its accuracy and precision on the basis of perspex models filled with contrast [2–4]. In addition, the overall short-, medium-, and long-term variations in arterial dimensions from repeated coronary angiograms have been determined [2]. This method, commonly called Quantitative Coronary Angiography (QCA), has become the gold standard in the assessment of the immediate and long-term results of various coronary interventions, both pharmacological and mechanical. In particular, the incidence of restenosis or late luminal renarrowing after coronary intervention have become an important field of investigation [5]. Initially, it was intended as a system to assess the extent of disease within the coronary artery. But with the advent of novel therapeutic interventional techniques such as intracoronary stenting, several new and unforeseen problems have emerged. In some circumstances, the principles had to be adapted to more complicated and complex situations related either to the device itself or to the effect of the intervention on the angiographic appearance of the treated artery. To appreciate the role and potential pitalls of QCA in the assessment of the angiographic results of intracoronary stent implantation, one has to understand its basic principles and how the angiographic parameters are defined. This will be discussed in this chapter and additionally the capabilities of the CAAS system will be reviewed as well as some of the methodological problems and shortcomings of the system that have become evident from our experience with intracoronary stenting. Although most of our studies are based on the use of automated contour detection, some data on the use of videodensitometry will be discussed as well.

GENERAL PRINCIPLES OF THE CAAS SYSTEM

Automated edge detection

It is beyond the scope of this chapter to review in detail the technical aspects of the CAAS system using automated edge detection. However, for the purpose of reader, the general aspects are briefly summarized. They are discussed in detail elswhere [6].

To analyze a coronary segment in a selected frame of a 35 mm cinefilm, an optically magnified portion of the image encompassing that segment is converted into video format by means of a cine-video converter. For the computer-assisted definitions of the boundaries of this selected coronary segment, the following steps need to be distinguished:

1) definition of the coronary segment to be analyzed;
2) edge definition;

Definition of the coronary segment

The user indicates a number of pathline or centerline points with a sonic pen which are subsequently connected by interpolation resulting in the pathline or centerline. This line functions as an initial model for subsequent contour detection. The only requirement of this line, is that it is situated within the arterial boundaries. A disavantage of this technique is that the amount of user-interaction may become significant, particularly in curved segments or in case of an overlapping side branch, in which the distance between subsequent points must be chosen small to make sure that the connecting lines will not be drawn outside of the arterial segments. Therefore, an update of the pathline or centerline is advocated by computing a new line from the contour positions once these have been detected and possibly corrected manually. Thereafter the contour detection procedure is repeated. By means of this iterative approach the influence of the user definition of the path line points on the detected contour positions can be minimized. Figure 1 illustrates the several steps described above.

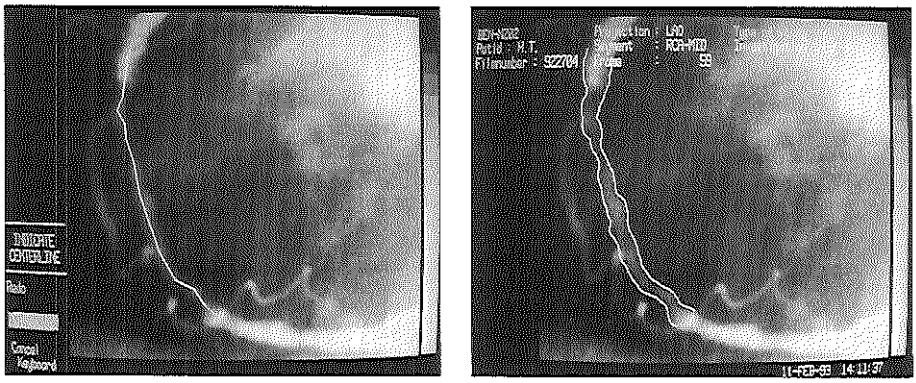

Fig. 1. Following the mannual definition of the beginning and end points of the segment to be analyzed, the pathline or centerline is detected automatically. Using the automatically detected pathline or centerline, the arterial boundaries are detected. The first iteration using minimal cost criteria is followed by a second. In the second iteration, the final contour are detected with the same edge detection technique and using the contours of the first iteration as models.

Edge definition

For the subsequent computation of the edge positions, a number of scanlines perpendicular to the local pathline or centerline are determined. Along these scanlines, the brightness profile of the arterial segment is assessed. The contours are determined on the basis of the weighted sum of the first and second derivative function applied to the brighness information using the minimal cost criteria. The application of the weighted sum of the first and second derivative function is based on the experience that using maximal values of only the first or second derivative

functions underestimates or overestimates the true arterial boundary positions, respectively [2,6].

Contour analysis

From the contours of the analyzed segment, following smoothing, pincushion correction and calibration, a diameter function is determined by computing the distances between the left and right edges. The distances between the left and right edges in pixels is converted into absolute values by using the catheter as scaling device. From these data some relevant parameters are calculated (Figure 2 and 3):

Direct measurements
1. minimal luminal diameter (MLD)
2. maximal diameter
3. mean diameter
4. extent of obstruction or lesion length
5. obstruction area (assuming circular model)
6. reference area (assuming circular model)

Interpolated measurements

1. reference diameter (RD)
2. symmetry
3. area plaque

Derived measurements

1. percent diameter stenosis (calculated from MLD and RD)
2. percent area stenosis
3. curvature
4. inflow and outflow angle
5. roughness

Definition of angiographic parameters (Figure 2 and 3)
The direct measurements are derived from the "diameter function" which represents the size of the analyzed vessel segment at intervals of approximately 0.1 mm as measured by the computed centerline. The diameter values are presented along the y-axis and the vessel length is represented along the x-axis.

The length of the lesion is determined from the diameter function on the basis of a curvature analysis and expressed in milimeters. The curvature is computed as the average value of all the individual curvature values along the centerline of the coronary segment, with the curvature defined as the first derivative of the tangent as it moves along the centerline which for a circle is equal to the reciprocal of the radius.

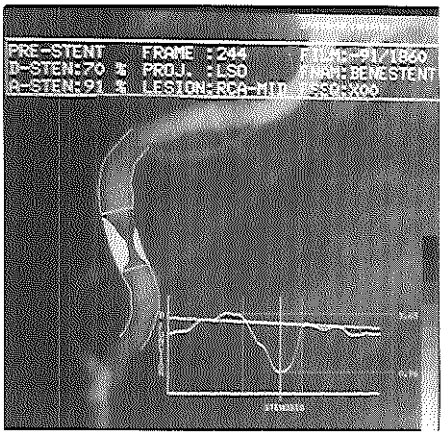

Fig. 2. The final result of the automated contour detection is the diameter function curve from which a number of angiographic parameters are calculated. The X-axis represents the extent of the segment, the Y-axis the value of several lesion characteristics such as minimal luminal diameter and reference diameter, expressed in mm.

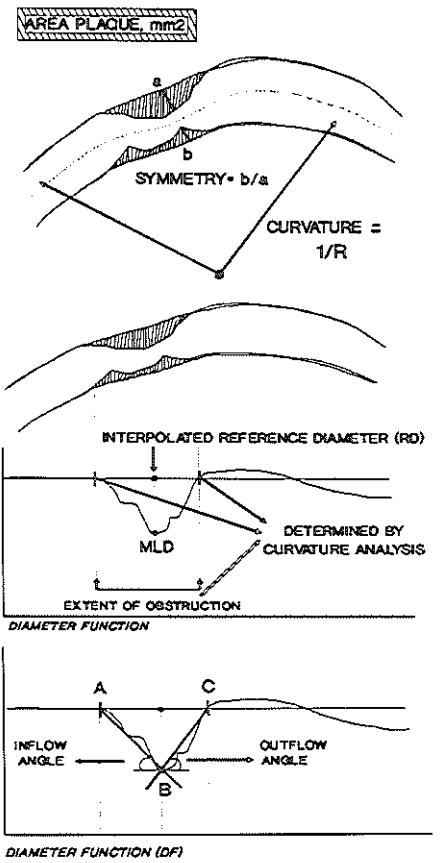

Fig. 3. Graphic display of a diameter function curve derived from a schematic coronary vessel. The definition of several angiographic variables describing the lesion morphology are illustrated.

To estimate the original diameter values over the obstructed region, the reference diameter is computed. The reference diameter can be selected visually as the nearest coronary artery segment that appears normal. However, to standardize this measurement and minimize potential errors, the "interpolated" reference diameter is used in all our studies. This method has the advantage of eliminating the arbitrary choice of a reference diameter, which will vary among individual observers, and also provides a smoothing effect for the segments adjacent to the stenosis so that extreme irregularities in the vessel have little influence on the reference diameter. The interpolated reference diameter is taken as the value of the reference diameter function at the location of the minimal luminal diameter. The latter is the single

smallest diameter value on the diameter function curve. Occasionally, a computer-defined reference diameter can not be obtained. This occurs in situations where there is no reliable proximal or distal obstruction boundary, such as lesions located at the ostia of a vessel or at the origin of side branches or in diffusely diseased vessels. In such circumstances, the analyst may decide to choose a different part of the vessel as reference diameter resulting in a "user-defined" reference diameter. Obviously, every user interaction introduces the risk of bias.

From the miminal luminal diameter and the reference diameter, the percent diameter stenosis can easily be calculated. The same holds for the minimal luminal cross-sectional area, reference area and percent area stenosis. It is important to note that in these calculations a circular cross-section is assumed. An assumption which hardly holds in clinical practice [7-9]. The resulting error may be reduced by incorporating two orthogonal projections.

The plaque area is a measure of the atherosclerotic plaque. This area is calculated as the sum of pixels between the computer-estimated predisease reference contours and the actual detected luminal comtours of the obstructive lesion. Since measurement of plaque area is highly dependent on the length of the stenosis (which is subject to considerable variation) and the determination of the reference contours of the artery in the presumed prediseased state, the usefulness of this parameter is debatable.

The symmetry value is a measure of the eccentricity of a particular lesion. A symmetry measure of 1 denotes a concentric obstruction; the number decreases down to 0 with increasing asymmetry or eccentricity of the obstruction. Unfortunately, this parameter has not been validated with pathologic studies and thus the pathologist and angiographer may not be talking about the same feature. The in- and outflow angle are derived from the slope of the diameter function curve at the defined site of the stenotic segment.

The CAAS system has also attempted to convert information on angiographic parameters into functional significance based fluid-dynamic equations (pressure gradient, Poisseuille and turbulent resistances) [10-13]. The calculated theoretical transstenotic pressure gradient over a particular stenosis describes the hemodynamic impact that a particular lesion would have under a range of flow conditions, within the range of "normal" aortic pressures. These calculations do not account for the effects of pulsatile flow or of curved and tapered vessels, more than one lesion in a vessel, the presence of collaterals, or perfusion of areas of nonviable myocardium. These effects of the entrance and exit angle (along with the absolute lesion diameter, percent narrowing, lesion length, blood flow velocity, and inertial and frictional effects) are important factors that determine the physiologic significance of a stenosis [14]. The pressure gradient across a stenosis is determined by entrance effects, drag effects and exit effects. Although the most important site of energy loss is at the exit of a stenosis where the separation of the fluid column occurs, neither the outflow nor inflow angle have yet been incorporated into the CAAS software package to calculate pressure gradients.

Videodensitometry

Although all our studies describing the changes in stenosis geometry after intracoronary stenting have used automated edge detection, there is some experience with videodensitometry in the setting of coronary stenting.

Videodensitometry assesses the relative area stenosis by comparing the density of contrast in the diseased or treated segment with the density of contrast in the "normal" segment. The advantage of this method is that a single plane densitometric profile is sufficient to obtain meaningful data regardless of the lesion morphology. For absolute measurements (conversion of the relative area stenosis into absolute area stenosis or minimal luminal cross-sectional area), the reference diameter must be determined from the edge detection data with the assumption of a circular cross section. An example of such an analysis is shown in Figure 4.

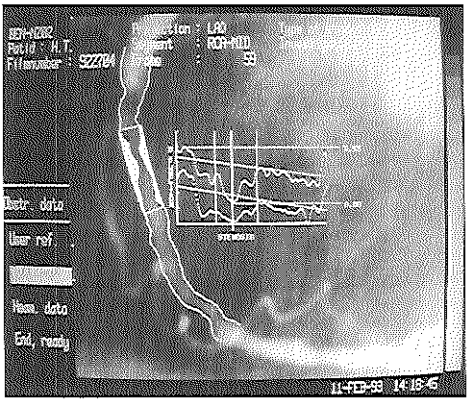

Fig. 4. Single frame angiogram with automated contour and videodensitometric analysis of the obstruction. Superimposed on the videoimage are the diameter function curve (upper curve) and the densitometric area function curve (lower curve). The minimal luminal diameter and minimal luminal cross-sectional area are the single lowest values on the diameter and videodensitometric function curve, respectively. The white areas are the measure for the "atherosclerotic" plaque.

Although videodensitometry is extremely attractive on a theoretical basis, numerous technical problems have limited its use [15]. Videodensitometry is much more sensitive than edge detection to densitometric non-linearities, oblique projection of an artery, and overlap with other vessels. It is easily appreciated that the advent of radiopaque stents has created its own specific problems.

QCA AND INTRACORONARY STENTING

Four types of intracoronary stents are currently used in the Thoraxcenter (Table 1). Three of these stents, the Wallstent, Palmaz-Schatz stent and the Gianturco-Roubin stent are composed of radiolucent stainless steel, whereas the Wiktor stent is radiopaque. The radiopacity of the Wiktor stent is explained by its chemical composition (tantalum) and its greater wire cross sectional area in comparison with the other stents. Tantalum has a higher atomic number than the elements contained in the stainless steel stents. Consequently, the larger electronic cloud surrounding the

nucleus absorbs more X-ray energy. This in combination with the greater wire cross-sectional area result in a higher radiopacity (Figure 5).

Fig. 5. The Wiktor stent is entirely composed of tantalum which explains its radiopaque features on fluoroscopy.

Table 1. Intracoronary stents used in the Toraxcenter

Stent	Date	Indication
Wallstent	Sept.'86	venous bypass grafts
Wiktor stent	Jan. '90	restenosis/bail-out
Palmaz-Schatz	Sept.'90	Benestent Study/bail-out
Gianturco-Roubin	Nov. '92	bail-out

QCA and stainless steel stents

Although it has been postulated that the ideal stent should be, among other factors, radiopaque, poor angiographic visibility does not have to hamper exact stent positioning. However, for the analyst, the lack of radiopacity means that the stent boundaries may be uncertain which may render the analysis of the immediate changes in stenosis geometry at the stented segment difficult and the precise location of late restenosis (within the stent or immediately adjacent) may be in doubt. Nevertheless, in most instances one may discern the position of the stent by carefully reviewing the angiogram without contrast injection. Furthermore, in all our follow-up reports of stenting, we have included restenosis within and immediately adjacent to

the stented segment to ensure restenosis is not underreported due to this problem [16,17].

A second problem with angiographic analysis of stented vessels is due to the superior results immediately post stenting versus PTCA alone. One could focus on the changes in stenosis geometry at the stented segment itself or one could be interested in the overall changes in stenosis geometry of the treated coronary artery. This implies that, in the first situation, the analyst has to interfere with the automated edge detection program in order to let coincide the boundaries of the segment to be analyzed with the boundaries of the stent itself. This, we call a "stent analysis". In the second situation, there is no need for interaction with the choice of computer detected contours. The anatomical landmarks such as vessel branches are used to define the boundaries of the segment to be analyzed and is called "vessel analysis". The use of one or the other significantly influences the results of quantitative coronary angiography. For instance, in case of complete correction or even overdilation of the obstruction segment, a negative value for diameter stenosis may be found when using the "vessel analysis" method. This is explained by the fact that the minimal luminal diameter (defined within the boundaries) is actually larger than the reference diameter which is determined according to the diameter of the proximal and distal segments (Figure 6). In other circumstances, one may also find that the minimal luminal diameter is located outside the stent. This results in a so-called "unmasking of a lesion" (Figure 7). In reporting our angiogarphic studies, we chose the pre and post PTCA frames to be analyzed by vessel, and the post stent and follow-up films according to the stent. This ensures that we obtain information related to the stent and its immediate adjacent segment rather than describing a more severe stenosis somewhere else in the coronary vessel.

The minimal luminal diameter is now widely accepted as ultimate angiographic end point of studies analyzing the immediate and long-term effects of therapeutic interventions [18,19]. However, we have learned that the assessment of this parameter does not reflect all changes in stenosis geometry of the stented coronary artery segment. While there is still some gap between the minimal luminal diameter and the reference diameter, the mean diameter of the stented segment closely approaches the reference diameter of the treated vessel (Figure 8 A & B).

QCA and radiopaque stents

It goes without saying that the radiopacity of the Wiktor stent facilitates exact stent positioning. Furthermore, dislodgement of the stent from the balloon during implantation may easily be recognized, promoting its safety.

It may be argued that the radiopacity of the stent wires interferes with contour detection. However, it is our experience that in case of adequate filling of the coronary artery with a contrast medium at a concentration of 100%, this is not the case. It is, as if automated edge detection ignores the information coming from the radiopaque stent wires. This is true for both the analysis immediately after stent implantation as well as for the assessment of neointimal hyperplasia within the stent

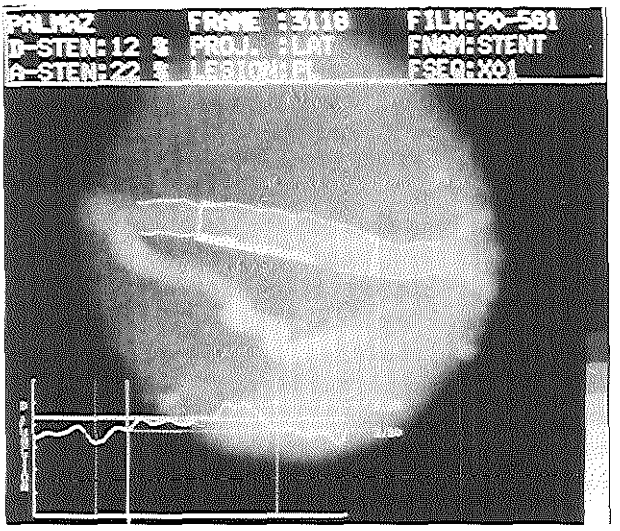

Fig. 6. Overdilatation of the coronary segment after stent implantation results in a minimal luminal diameter which is greater than the reference diameter and as a result in a negative percent diameter stenosis.

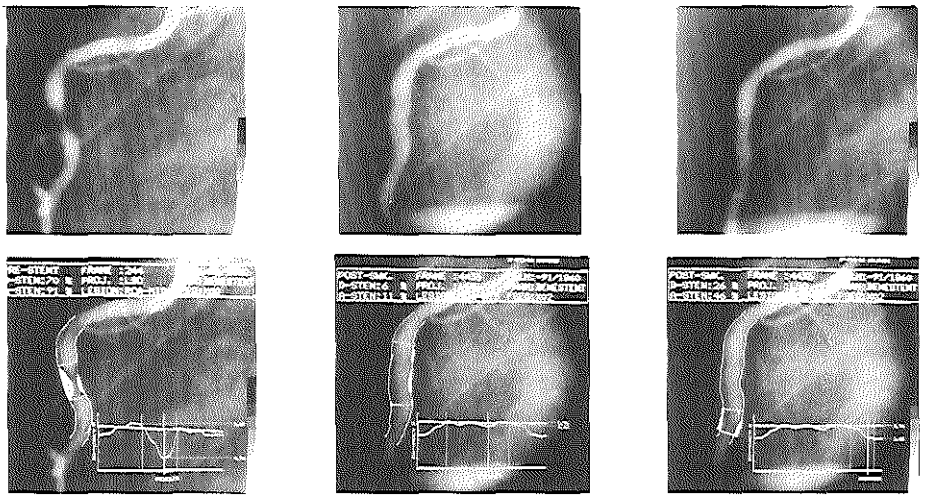

Fig. 7. User-defined extent of the stented segment coinciding with the extent of the stent itself results is a "stent analysis". It forces the computer to analyze the changes in stenosis geometry within the stented segment. This contrasts with a "vessel analysis" in which no attempt has been made to coincide the extent of the analyzed segment with the extent of the stent. Due to the almost perfect improvement of the stenosis geometry after stent implantation, a non-significant lesion distal to the stented segment is now identified as a residual stenosis outside the stent.

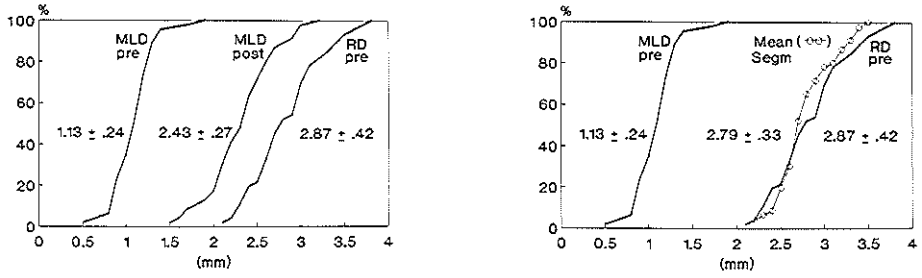

Fig. 8. Cumulative distribution curves of the minimal luminal diameter and its changes after stent implantation (panel A) and the mean diameter post stenting in relation to the reference diameter of the target vessel (panel B). On the X-axis are shown the values of the angiographic variables and on the Y-axis the relative number of the population under investigation. It is evident that, in contrast to the mean diameter of the stented segment, there is still a gap between the minimal luminal diameter and the reference diameter.

at follow-up (Figure 9 & 10). This is in accordance with phantom studies from our laboratory which disclosed that automated edge detection, in contrast to videodensitometry, could adequately define the luminal boundaries of a Wiktor stent-containing plexiglass phantom (Figure 11) [20]. However, in some cases in which neointimal hyperplasia is not clearly defined on the angiogram and appears as haziness within the stent, automated edge detection cannot accurately define the luminal boundaries either. Mannual correction of the contours by the analyst would induce to much bias. It is the only situation in which videodensitometry may offer a solution despite the inevitable densitometric information coming from the stent itself. Accurate stenosis values are obtained by selecting the reference segment ("user-defined" reference diameter) within a non-narrowed segment within the stent itself (Figure 12). Of all the follow-up angiograms of the Wiktor stent, videodensitometry had to be used in 8% of the cases.

Specific data on videodensitomerty

In contrast to the situation after PTCA, there is an excellent agreement between the minimal luminal cross-sectional area determined by edge detection and videodensitometry after stent implantation [21,22]. In 19 patients who underwent balloon angioplasty followed by stent implantation, a significant improvement in the correlation and variability in the measurement of the minimal luminal cross-sectional area between edge etection and videodensitometry was observerd after stenting [22]. This improvement is likely due to smoothing of the vessel contours by the stent and remodeling of the stented segment into a more circular configuration. Therefore, we believe that both methods are appropriate to assess the immediate results after implantation of stainless steel stents. In a separate in-vitro study in which stainless steel and radiopaque stents were placed in known stenoses within plexiglass phantoms, The Wallstent and Palmaz-Schatz stent had minor and clinically

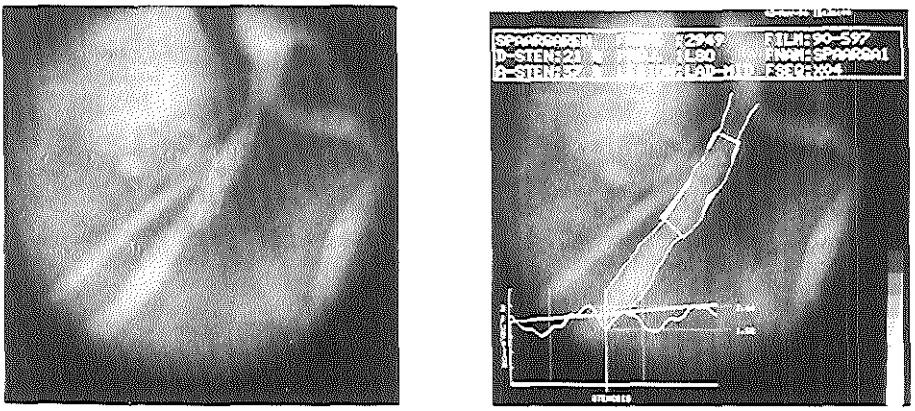

Fig. 9. Example of a computer-assisted Coronary Angiography Analysis using automated edge detection immediately after Wiktor stent implantation. There was no interference of the radiopaque stent wires with the contour detection.

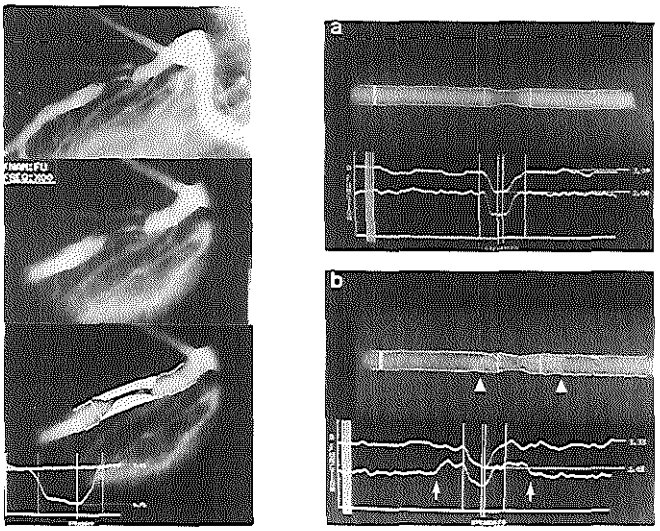

Fig. 10 (left). A significant luminal renarrowing within the Wiktor stent is appreciated on the angiogram. Despite the radiopacity of the stent, automated contour detection resulted in an adequate detection of the luminal contours without user interaction.

Fig. 11 (right). Control (a) and Wiktor stent-containing (b) plexiglass phantoms (3 x 2 mm) filled with 100% and 50% iopamidol contrast medium, respectively. Graphs show the diameter function (upper curve) and the densitometric area function (lower curve). Outside vertical lines on the graph and rightward two vertical lines on the phantom are the lesion boundaries. The inner two vertical lines represent the minimal points on the diameter and densitometric graphs, respectively. The multiple vertical lines in the left part of the graph and the lefward vertical line in the phantom represent the user-defined reference segment. The numbers in the graph represent the maximum and minimum diameters. The boundaries of the Wiktor stent are visible in the phantom (arrowheads) and as a step-up in the densitometry graph (arrow). Reproduced with permission from Strauss et al, Catheterization and Cardiovascular Diagnosis 1991; 24:259–264.

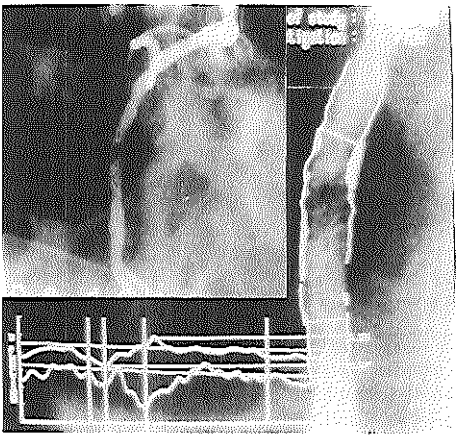

Fig. 12. In case of haziness as expression of restenosis within the Wiktor stent, edge detection cannot define the arterial boundaries. In such circumstances, videodensitometry is used. To obtain accurate values of the minimal luminal cross-sectional area, the user selects the reference in a non-stenosed segment in the Wiktor stent itself.

insignificant contributions to the densitometric determination of the minimal luminal cross-sectional area [20]. Conversely, the radiopacity of the Wiktor stent increased the minimal luminal cross-sectional area in these same narrowings by 10-56% depending on the concentration of contrast medium and specific stenosis [20].

WHY SHOULD WE USE QCA DURING STENT IMPLANTATION?

Restenosis should be considered as the reparative vessel wall response or perhaps as the natural healing process following injury [23,24]. When excessive, this may lead to new symptoms and eventually to repeat intervention [25]. One of the objectives of stent implantation is to reduce the incidence of restenosis in the hope that it will favorably affect the long-term clinical outcome. Stent implantation causes substantial injury to the coronary vessel wall and therefore will invariably be associated with restenosis. Schwartz et al. demonstrated that the extent of late neointimal hyperplasia was directly related to the degree of vessel wall injury following oversized coil stent implantation in porcine coronary arteries [26]. In accordance with these data, we found that the extent of late luminal renarrowing, increases with the amount of luminal gain after stent implantation in human coronary arteries [27]. Resolution of clinical or angiographic restenosis may require the creation of the largest possible luminal diameter and the control of neointimal hyperplasia. On-line quantitative coronary angiography can beneficially be used during stent implantation to minimize vessel wall injury and to guide the operator to obtain the most optimal angiographic result. Minimizing vessel wall injury is achieved by selecting the appropriate stent

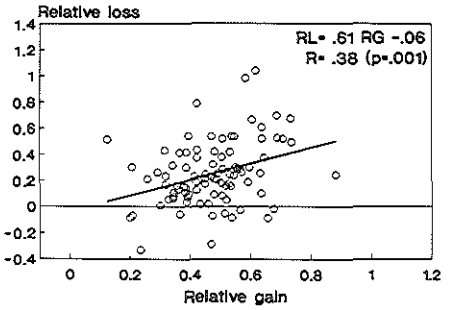

Fig. 13. Graphic display of the relation between the relative gain (RG = increase in minimal luminal diameter immediately after stent implantation normalized to the vessel wall) and relative loss (RL = decrease in minimal luminal diameter at follow-up normalized to the vessel wall). A positive linear relation was found with a correlation coefficient of 0.38 ($p<0.001$) with a slope of 0.61 and an intercept on the Y-axis of −0.06.

size by first measuring the reference diameter of the target vessel. Once the appropriate stent size has been selected and implanted, on-line quantitative coronary angiography can be used to evaluate the immediate changes in stenosis geometry. This may be of importance to the long-term angiographic results. As outlined above, studies using quantitative coronary angiography have shown a positive linear correlation between the relative gain and relative loss (Figure 13). However, one should realize that the greater gains are not fully offset by the increased loss in minimal luminal diameter which is reflected by the slope of the curve (< 1). This once again confirms that the superior improvement in stenosis geometry after stent implantation compensates to some degree for late loss. In addition, data from other investigators who used the categorical approach to define restenosis found that a suboptimal angiographic result after stent implantation was associated with an increased risk for restenosis according to the 50% diameter stenosis criterion [28,29]. On-line quantitative coronary angiography is essential to assess the residual stenosis post stent implantation. If necessary, an additional balloon angioplasty within the stent can be performed to optimize the immediate results (Figure 14). Based on the data of Strauss et al. we perform such an additional dilatation when the residual percent diameter stenosis exceeds 20% [28]. The size and inflation pressure is determined on the basis of the on-line quantitative coronary angiography.

QCA TO EVALUATE DIFFERENT INTERVENTIONAL TECHNIQUES

There are currently several interventional techniques in clinical use. They do not only differ in the mechanisms by which they result in luminal enlargement but also in the immediate angiographic result or gain and late loss [30]. Because of this difference and because the minimal luminal diameter at follow-up has been shown to best describe the functional status of the patients 6 months after coronary intervention, we have proposed the minimal luminal diameter at follow-up as the angiographic end point in studies comparing different interventional techniques provided that the patients included have comparable reference diameter and minimal luminal diameter prior to the intervention [5,18,19].

The angiographic parameters are best used in a continuous approach and displayed in cumulative distribution curves reflecting the entire study population under

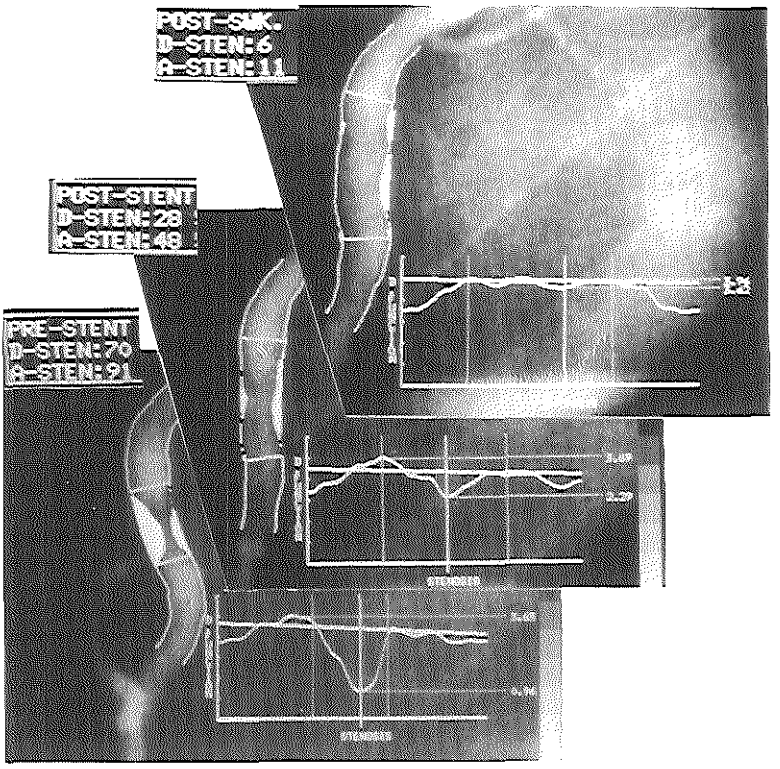

Fig. 14. On-line quantitative coronary angiography disclosed a residual stenosis immediately after stent implantation. This information was used to further optimize the dilatation process by performing an additional balloon dilatation within the stent.

evaluation (Figure 8,15) [19]. The advantage of this method is that the absolute enlargement of the vessel lumen and the absolute loss of the initial gain in luminal size are easily gleaned from the curves and allows the comparison of the immediate and long-term angiographic outcome of different interventional techniques [19]. Furthermore, it depicts the process of restenosis independent of any definition. The medical practictioner who still would like to use the categorical approach ("present/ not present"), can obtain these data from the cumulative distribution curve of the percent diameter stenosis at follow-up (Figure 16).

CONCLUSIONS

Quantitative coronary angiography has been developed to assess objectively the efficacy of modern therapeutic procedures in the catheterization laboratory. The advent of new and innovative therapeutic interventions have raised unforeseen problems. In most instances, they have effectively been addressed and even solved

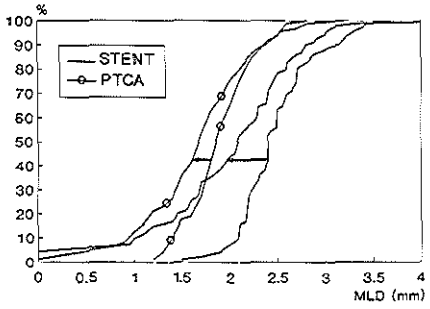

Fig. 15. The graphic display of the minimal luminal diameter post intervention and at follow-up as a continuous variable in cumulative distribution curves offers the unique advantage that it reflects the absolute changes (in this case loss) of the initial gain. This model is particularly valuable in analyzing the value of different interventional techniques and may provide insight into the mechanisms of dilatation and restenosis.

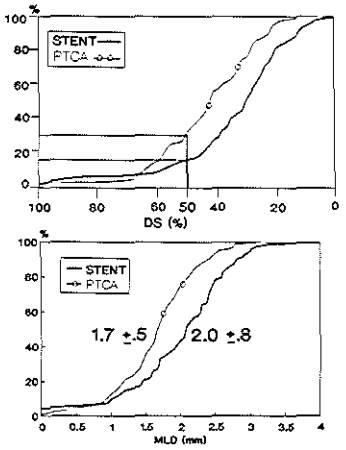

Fig. 16. Every angiographic variable may be displayed as a continuous variable in cumulative distribution curves. The minimal luminal diameter at follow-up, is depicted in the upper graph. The percent diameter stenosis at follow-up is shown on the lower graph. The number of patients with a diameter stenosis > 50% at follow-up can easily be gleaned from this graph.

thanks to the knowledge and understanding of the technical limitations of this analysis method. This system does not only provide accurate assessment of the immediate and long-term changes in stenosis geometry following coronary intervention, but can also be used as a tool to understand the mechanisms of luminal enlargement and the pathophysiology of restenosis.

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CHAPTER 2

MORPHOLOGIC CHANGE IN CORONARY ARTERY STENOSIS WITH THE MEDTRONIC WIKTOR STENT: INITIAL RESULTS FROM THE CORE LABORATORY FOR QUANTITATIVE ANGIOGRAPHY

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Cath and Cardiovasc Diagn 1991; 24: 237-245.

Catheterization and Cardiovascular Diagnosis 24:237–245 (1991)

Feature Topic: Stents in Clinical Practice

Morphologic Change in Coronary Artery Stenosis With the Medtronic Wiktor™ Stent: Initial Results From the Core Laboratory for Quantitative Angiography

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The purpose of this study was to assess the early changes in stenosis geometry after implantation of the Medtronic Wiktor™ stent in human coronary arteries. Morphologic changes were evaluated by quantitative coronary angiography using automated edge detection. The hemodynamic significance of the morphologic changes were assessed by the calculation of the theoretical pressure drop across the dilated and stented stenosis derived from the Poiseuile and turbulent resistances assuming a coronary blood flow of either 0.5, 1, or 3 ml/sec. Fifty patients were studied before and immediately after stent implantation. The stented coronary artery was the left anterior descending artery in 26 patients, the circumflex artery in eight patients, and the right coronary artery in 16 patients. Stent implantation resulted in an additional increase in the minimal luminal cross-sectional area and minimal luminal diameter of the dilated vessel without changing the curvature of the stenosis. Furthermore, there was a significant reduction of the "plaque area." This was associated with a normalization of the calculated resistances to flow and presure drop across the stenosis. To a minimal extent, recoil (0.1 ± 0.36 mm) was observed after stent implantation.

Key words: coronary stent, quantitative analysis, stenosis geometry

INTRODUCTION

Percutaneous Transluminal Coronary Angioplasty (PTCA) is now accepted as a safe and effective therapy for obstructive coronary artery disease. Gained experience and improved catheter technology have resulted in a high initial success rate [1–3]. These favorable initial results are offset by a restenosis rate of 30% to 40% during the first 6 mon after the procedure [4–5]. Stenting of the dilated vessel may offer an alternative approach for the prevention of restenosis [6]. Different prostheses have been developed and tested in animal experiments and implanted in humans [7–11]. The Wiktor™ stent (Medtronic Inc., Mineapolis, Minn. USA) is a new intravascular prosthesis which, in contrast to the Wallstent® (Schneider, Zürich, Switzerland) and Palmaz-Schatz® stent (Johnson & Johnson, Warren, USA), is not a mesh made of stainless steel, but a radiopaque single loose interdigitating tantalum wire which undergoes oxidation after implantation. The resultant oxide (TaO_5) is not only very stable, implying less changes in surface charge, but also corrosion resistant [12]. Potentially, the smaller amount of endothelial surface covered by the stent (less than 10% of the vascular endothelium is covered by a full expanded stent) in conjunction with the electrochemical characteristics of this stent protect against thrombus formation. As a result

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of the loose configuration, it has been hypothesized that the Wiktor® stent accommodates more adequately to the natural bending of the coronary artery in contrast to the stents with a more rigid and stiff mesh architecture such as the Palmaz-Schatz® stent. The Wiktor® stent, like the Palmaz-Schatz® stent, is a balloon expandable endoluminal prosthesis and does not exert an active radial force on the vascular wall after deployment as occurs with the Wallstent® [13]. However, the loose configuration of the Wiktor® stent may have less scaffolding properties compared to the other two intravascular prostheses.

The purpose of this study was to assess the early morphologic changes in stenosis geometry, including the occurrence of recoil, by quantitative coronary angiography and to assess the physiological significance of these changes by calculating the pressure drop across the stenosis for a theoretical blood flow of 0.5 to 3 ml/sec after Wiktor® stent implantation in human coronary arteries.

MATERIALS AND METHODS

Patients

Fifty patients (45 male, five female, median age 57 years—range 30–77) were studied. The patients were treated and investigated in the following centers: Department of Cardiology, Hôpital Cardiologique Lille, France, Department of Cardiology, Klinikum der J.W. Goethe Universität Frankfurt, Germany, Department of Cardiology, Ottawa, Ontario, Canada, Department of Cardiology, University Hospital Gasthuisberg, Leuven, Belgium, Department of Cardiology, Medical Clinic I RWTH Aachen, Germany, Department of Cardiology, Georg August Universität, Göttingen, Germany, and the Catheterization Laboratory, Thoraxcenter, Rotterdam, Netherlands. Written informed consent was obtained from every patient. Wiktor® stent (Medtronic Inc., Minneapolis, Minn., USA) was implanted because of a first restenosis of a native coronary artery in 33 patients, a second restenosis in 12 patients, and a third restenosis in five patients. In all patients objective evidence of ischemia was documented. The dilated and stented coronary artery was the left anterior descending artery in 26 patients (62%), the circumflex artery in eight patients (16%), and the right coronary artery in 16 patients (32%). The nominal diameter of the balloon on which the stent was mounted was 3.0 mm in 23 patients, 3.5 mm in 20 patients, and 4.0 mm in seven patients (14%). The nominal diameter of the balloon for the total study group (mean ± SD) was 3.35 ± 0.36 mm.

Description of the Stent

The endoprosthesis used in this study is a balloon-expandable stent (Wiktor®, Medtronic Inc., Minneapolis, Minn., USA) constructed of a single tantalum wire (0.125 mm in diameter) which is formed into a sinusoidal wave and wrapped into a helical coil structure. This prosthesis is crimped onto the deflated polyethylene balloon of a standard angioplasty catheter (Fig. 1a). The features of this prosthesis design are such that by inflating the balloon the diameter of the stent increases without any alteration in length (14–16 mm, Fig. 1b). The crimped stent profile is approximately 1.5 mm. The maximal diameter of the balloon during inflation determines the ultimate size of the prosthesis on implantation. One inflation at 6–8 atm is sufficient to open the stent and allows the safe withdrawal of the deflated balloon.

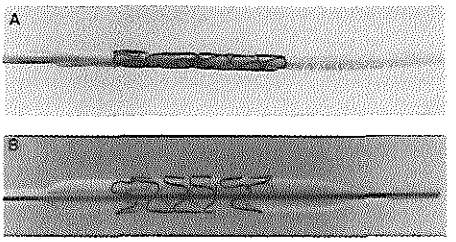

Fig. 1. a: Wiktor® stent crimped onto an polyethylene angioplasty balloon before inflation. b: Wiktor® stent on fully inflated angioplasty balloon.

Stent Implantation

One day prior to stent implantation acetylsalicylic acid 300 mg/day was started. Dextran (100 cc/hr) was administered 2 hr before the implant and continued throughout the procedure. A minimum of 500 cc was infused. A total of 20,000 units of heparin was injected intravenously. Full heparinization was maintained until therapeutic levels of coumadin therapy were achieved. Conventional balloon angioplasty was performed and repeated until the desired angiographic result was obtained. After control coronary angiography for subsequent quantitative analysis, the balloon/stent system was advanced over a 0.014-in steerable guidewire under fluoroscopic control to the treated lesion site. The balloon was inflated until the desired expansion of the stent was achieved. Subsequently the balloon was deflated and the catheter was removed under negative pressure while leaving the stent in place. In case of incomplete expansion of the stent, a repeat balloon dilatation within the stent was performed. After repeat coronary angiography, the guiding catheter was removed. The post-procedure drug therapy consisted of coumadin for a minimum of 3 mon and acetylsalicyclic acid (300 mg/day) for 6 mon.

Quantitative Coronary Angiography

The coronary cineangiograms were analyzed by a computer-assisted Cardiovascular Angiography Analysis System (CAAS), described in detail elsewhere [14,15]. Briefly, this system allows an objective and reproducible quantification of a coronary artery stenosis. A 35-mm cineframe was selected and digitized with a CCD-camera at very high resolution (1330 × 1770 pixels) and electronically a region of interest (512 × 512 pixels) encompassing the arterial segment to be analyzed was selected for subsequent analysis by the computer.

Contours of the arterial segment were detected automatically on the basis of the first and second derivative functions of the brightness profile, and corrected for pincushion distortion from the image intensifiers. A calibration factor was derived from a computer processed segment of the angio-catheter. From the arterial contour data, a diameter function was computed. The minimal luminal diameter and a reference diameter, computer-estimated by the interpolated diameter technique, were expressed in millimeters. On the basis of the proximal and distal centerline segments and the computed reference diameter function, the reference contours over the obstructed region were reconstructed. The extent of the obstruction was determined from the diameter function on the basis of curvature analysis and expressed in millimeters. The curvature is computed as the average value of all the individual curvature values along the centerline of the coronary segment, with the curvature defined as the first derivative of the tangent as it moves along the centerline which for a circle is equal to the reciprocal of the radius. The difference in area between the reference and the detected contours over the lesions ("plaque area," in mm^2) is a measure for the atherosclerotic plaque [16]. The inflow angle is the average slope of the diameter function between the position of the minimal obstruction diameter and the position of the proximal boundary of the stenotic lesion. The outflow angle is the average slope of the diameter function of the minimal obstruction diameter and the position of the distal boundary of the stenotic segment.

The severity of the stenosis can also be expressed as a percentage area stenosis: assuming circular cross-sections at the obstruction and reference position, corresponding luminal areas (mm^2) were calculated by comparing the minimal area value at the obstruction with the reference value obtained following the interpolated diameter technique. An illustration of such a quantitative analysis of a coronary artery is shown in Figure 2.

Elastic recoil was calculated as the difference between the mean diameter of the balloon when fully inflated and the mean diameter of the stented segment immediately after stent delivery and withdrawal of the balloon. Single identical views during complete expansion of the balloon and immediately after stent implantation were chosen for automated edge detection.

Hemodynamic Assessment

To assess the physiological significance of the obstruction and its changes after angioplasty and stenting, the theoretic pressure drop was calculated using the arteriogram and digital computation, according to the formulae described in the literature: Pgrad = Q.(Rp + Rt), where Pgrad is the theoretic transtenotic pressure decrease (mm Hg) over the stenosis, Q is the mean coronary blood flow (ml/sec), Rp is the Poiseuille resistance, and Rt is the turbulent resistance [17,18].

These resistances have been defined as follows:

$Rp = C1.(\text{length obstruction})/(\text{minimal cross-sectional area})^2$,
where $C1 = 8.\pi.(\text{blood viscosity})$ with blood viscosity = 0.03 g/cm.sec;

and

$Rt = C2.(1/\text{minimal cross-sectional area} - 1/\text{normal distal area})^2$,
where C2 = (blood density)/0.266 with blood density = 1.0 g/cm^3.

The theoretic transstenotic pressure drop was calculated for theoretic coronary blood flow of 0.5, 1, and 3 ml/sec. The Poiseuille and turbulent contributions to the flow resistance were determined from stenotic geometry assessed by quantitative coronary angiography.

Statistical Analysis

All values are expressed as mean with the standard deviation of the mean. Comparisons between measurements obtained after PTCA and stenting were made after variance analysis with the Student's *t*-test for paired observations. A statistical level <0.05 was considered as significant.

RESULTS

The morphologic and hemodynamic data (mean ± SD) are presented in Tables I, II, and III.

Stent implantation after balloon angioplasty resulted in an additional increase in minimal luminal cross-sectional area and minimal luminal diameter with a concommitant decrease in percentage area and percentage diameter stenosis compared with the postangioplasty state (Table I). Moreover, there was a significant decrease in plaque area and inflow and outflow angles while the curvature of the lesion was respected (Table II).

This morphologic improvement was associated with a decrease in both the calculated turbulent and Poiseuille resistance, as well as the virtual disappearance of the theoretical transstenotic pressure drop for a theoretical flow of 0.5, and 3 ml/sec (Table III).

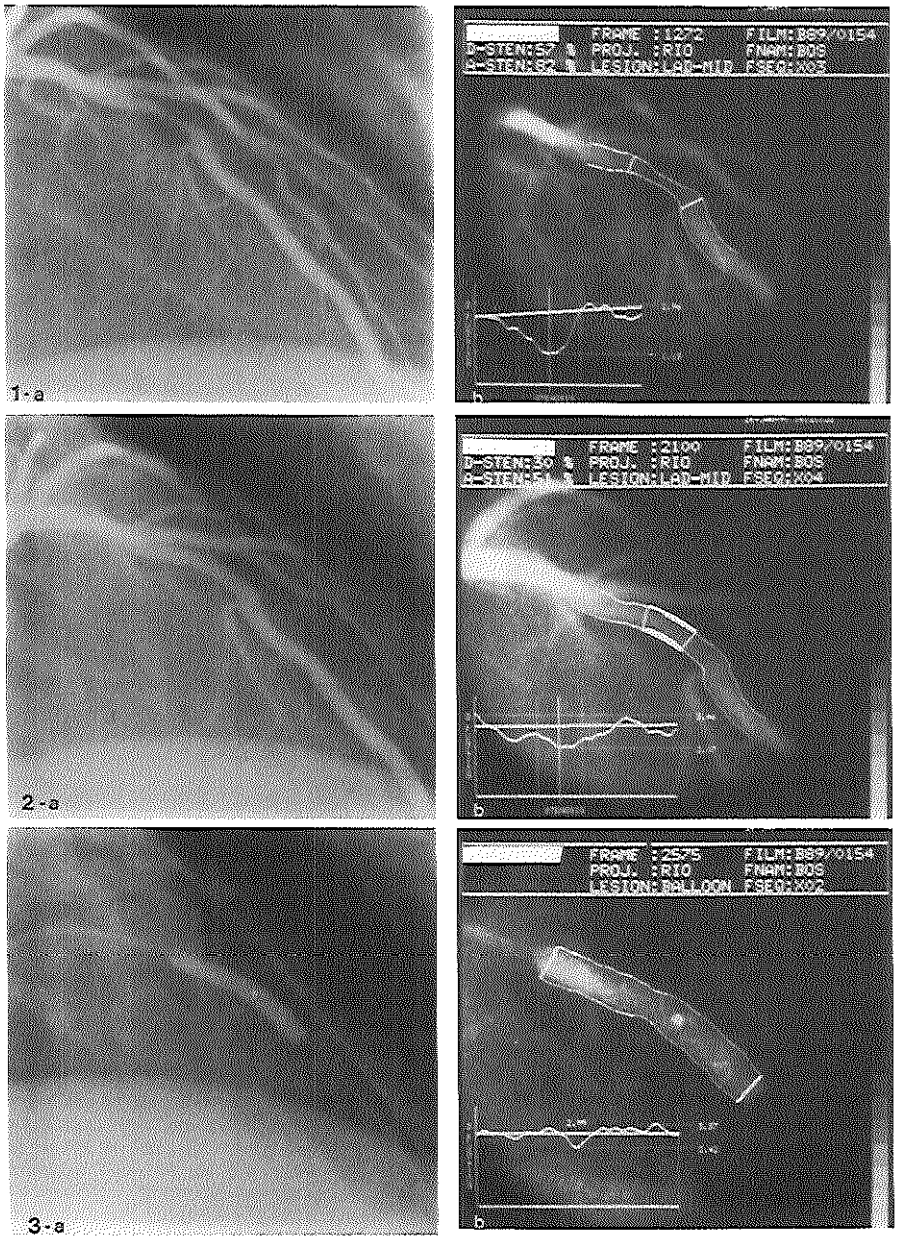
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Fig. 2, 1a–3b.

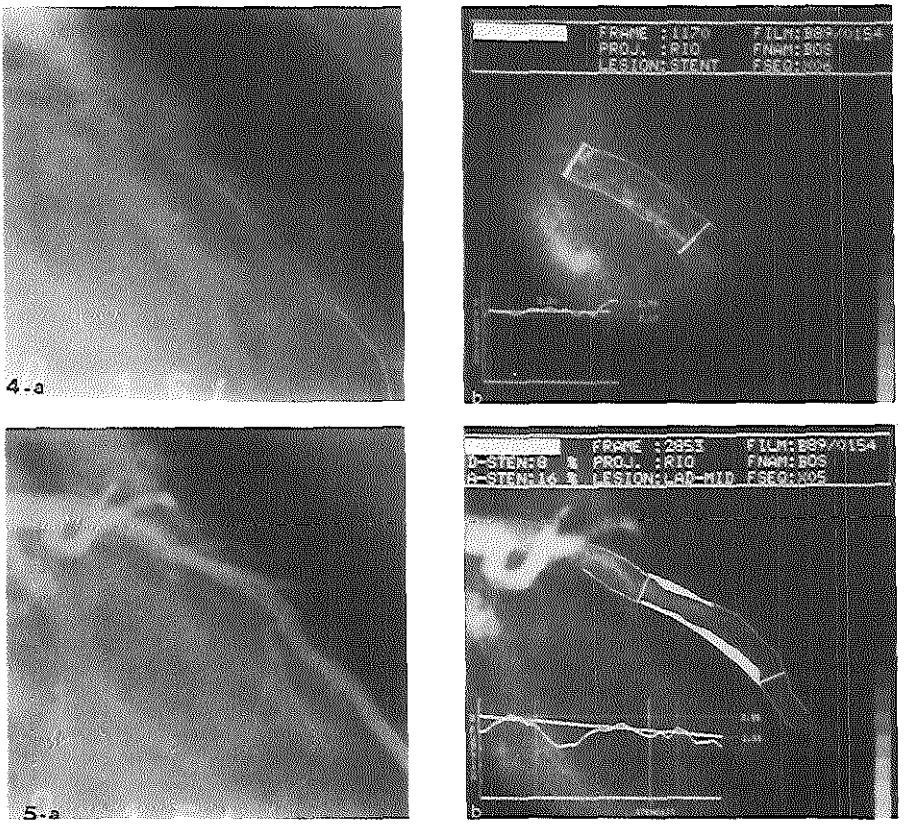

Fig. 2. Illustration of a quantitative analysis of a coronary artery. Single plane angiograms of the proximal left anterior descending before and after balloon angioplasty and immediately after stent implantation with superimposition of the automated contours of the region of interest. Below each angiogram is shown the diameter function of the detected contours of the artery. The minimal luminal diameter (vertical line) and the interpolated diameter function (horizontal line) from which the reference diameter is derived are shown. For further explanation, see text.

In most patients, the measured diameter of the balloon when fully inflated exceeded the measured diameter of the stent (Fig. 3). During maximum inflation the mean diameter of the balloon for the total study group was 2.98 ± 0.44 and the mean diameter of the stented segment immediately following implantation was 2.88 ± 0.43 mm (Table IV). This implies a recoil of 0.10 ± 0.36 mm or 3% ($P < 0.03$).

DISCUSSION

Coronary artery stenting has been introduced as an adjunct to PTCA in obstructive coronary artery disease [6–10,19,32]. The implantation of vascular endoprostheses may provide a useful approach to prevent occlusion and restenosis [6]. As for every therapeutic procedure, an objective and reproducible technique evaluating efficacy is needed. Computer based automated

TABLE I. Morphologic Changes Immediately After Balloon Angioplasty and Subsequent Stent Implantation

	Pre-PTCA	Post-PTCA	Post-stent	P_1	P_2
Extent obstruction (mm)	7.24 ± 2.48	6.63 ± 2.63	5.35 ± 1.86	NS	0.001
Reference diameter (mm)	2.81 ± 0.47	2.78 ± 0.48	2.91 ± 0.43	NS	0.001
MLD (mm)	1.09 ± 0.26	1.80 ± 0.32	2.45 ± 0.36	0.00001	0.00001
Diameter stenosis (%)	61.00 ± 9.19	34.00 ± 10.76	17.00 ± 7.18	0.00001	0.00001
Reference area (mm^2)	6.38 ± 2.15	6.26 ± 2.18	6.83 ± 2.07	NS	0.003
MLCA (mm^2)	0.99 ± 0.44	2.63 ± 0.92	4.83 ± 1.42	0.00001	0.00001
Area stenosis (%)	84.00 ± 7.58	56.00 ± 13.94	31.00 ± 11.57	0.00001	0.00001
		P_1	P_2		

MLCA, minimal luminal cross-sectional area; MLD, minimal luminal diameter. All parameters are expressed in mean ± SD.

TABLE II. Morphologic Changes Immediately After Balloon Angioplasty and Subsequent Stent Implantation

	Pre-PTCA	Post-PTCA	Post-stent	P_1	P_2
Curvature	21.00 ± 8.90	21.00 ± 8.65	20.00 ± 9.49	NS	NS
Plaque area (mm^2)	8.53 ± 4.33	5.13 ± 3.48	3.33 ± 2.29	0.00001	0.0004
Inflow angle	23.00 ± 6.28	15.00 ± 5.25	7.00 ± 15.64	NS	0.00001
Outflow angle	23.00 ± 10.39	19.00 ± 19.74	5.00 ± 15.17	NS	0.00001
		P_1	P_2		

All parameters are expressed in mean ± SD.

TABLE III. Hemodynamic Results Immediately After Balloon Angioplasty and Subsequent Stent Implantation

	Pre-PTCA	Post-PTCA	Post-stent	P_1	P_2
Rpois	18.00 ± 38.44	1.22 ± 1.72	0.47 ± 0.28	0.002	0.003
Rturb	11.00 ± 28.91	0.32 ± 0.72	0.02 ± 0.02	0.01	0.005
Pgrad (0.5 ml/sec)	29.00 ± 67.00	1.52 ± 2.42	0.49 ± 0.29	0.004	0.004
Pgrad (1 ml/sec)	48.00 ± 65.57	3.66 ± 6.26	1.00 ± 0.61	0.00001	0.004
Pgrad (3 ml/sec)	92.00 ± 126.75	6.45 ± 11.53	1.53 ± 0.99	0.00001	0.004
		P_1	P_2		

Rpois, Poiseuille resistance; Rturb, turbulent resistance; Pgrad, pressure drop. All parameters are expressed in mean ± SD.

edge detection angiographic analysis systems have reduced the variability resulting from visual and caliper-determined contour detection of coronary cineangiograms [20–22].

The optimal method to quantitatively analyze the immediate angiographic results of coronary stenting in native coronary arteries is still a matter of debate. At present, two techniques are available: automated edge detection and videodensitometry. The technique of automated edge detection is limited in eccentric lesions and in particular following balloon angioplasty when acute tears and dissections distort the anatomy. Videodensitometric measurements of cross-sectional area are independent of geometric assumptions regarding the shape of the stenosis and should, in theory, be more reliable than edge detection, especially after the disruptive action of balloon angioplasty, which is known to cause asymmetric enlargement of the lumen [23,24]. However, a recent study has shown that edge detection and videodensitometry are equally acceptable methods of analysis after coronary stenting [25]. This may be explained by the more regular and smooth vessel contours after stenting, with tacking back of the intimal flaps by the scaffolding property of the stent in some cases and by the remodeling of the stented segment into a more circular geometry. Moreover, it has been shown that videodensitometry overestimates the minimal luminal cross-sectional area, particularly in smaller vessels with the Wiktor® stent [26]. This may be due to the radiographic characteristics of the stent itself.

X-ray energy dispersion spectrometry studies from our laboratory have shown that the structure of the Wiktor® stent has only one element, tantalum, which has a higher atomic number than the elements contained in the Palmaz-Schatz® stent and the Wallstent®. Consequently, more X-ray energy is absorbed by the Wiktor® stent

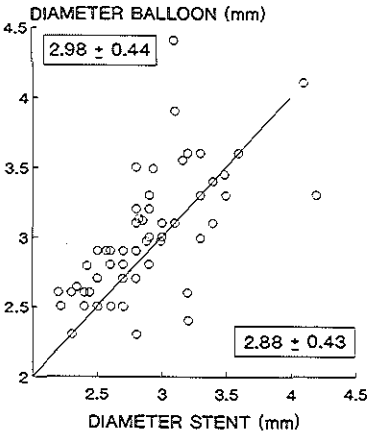

Fig. 3. Correlation between the measured diameter of the balloon when fully inflated and of the stent immediately after implantation.

wire. Furthermore, the Wiktor® stent has a greater wire cross-sectional area than the other two stents. These physical characteristics result in a higher radiopacity in comparison with the stainless steel stents. As a result, the intraluminal brightness profile generated by the Wiktor® stent makes automated edge detection the appropriate technique for quantification of the stented segment. Conversely, videodensitometry may be the technique of choice for the assessment of restenosis. Intimal hyperplasia developing within the stent may not be detected by edge detection technique, which is unable to distinguish between the radiopaque structure of the wire embedded in the vessel wall and the actual boundaries of the lumen radiopacified by the contrast medium. For these reasons, automated edge detection was used for the immediate angiographic assessment in this study.

The increase in minimal luminal diameter after balloon angioplasty (1.09 ± 0.26 mm to 1.80 ± 0.32 mm), is what has been observed in other series [27,28]. This emphasizes that prior to stenting the stenotic lesion has been dilated to the extent normally expected. The additional improvement after the implantation of the Wiktor® stent is comparable to what has been observed with either self expanding or balloon expandable stents [7,28,29]. The same holds for the minimal luminal cross-sectional area. There is a fivefold increase in the minimal luminal cross-sectional area after stenting (0.99 ± 0.44 mm^2 to 4.83 ± 1.42 mm^2). As previously demonstrated, a normalization of the coronary flow reserve

TABLE IV. Nominal Diameter of the Balloon, Measured Diameter of Balloon at Maximal Inflation Pressure, and of Stented Segment by Edge Detection

Nominal diameter balloon	Measured diameter balloon	Measured diameter stented segment	P_1	P_2
3.35 ± 0.36 mm	2.98 ± 0.44 mm	2.88 ± 0.43 mm	0.0001	0.03
	P_1	P_2		

All parameters are expressed in mean ± SD.

may be expected with such an increase [30]. As indirect confirmation of the above findings, the pressure drop across the stenosis remains virtually zero even with a theoretical flow of 3 ml/sec and a normalization of the calculated resistances. In addition to the increase in the minimal luminal cross-sectional area, there is a significant change in plaque area, in the inflow and outflow angles, and in the extent of obstruction, while the natural curvature of the artery is respected.

However, the smaller mean diameter of the stented segment (2.88 ± 0.43 mm) in comparison with the measured diameter of the fully expanded balloon (2.98 ± 0.44 mm) suggests some recoil of the stented segment. This minimal recoil appears to be a true phenomenon since the accuracy and the precision of the CAAS system is −30 μ and 90 μ, respectively [13–15]. Furthermore, the recoil phenomenon has also been observed, although to a larger extent, after Wiktor® stent implantation in Yorkshire pigs [11]. The more pronounced recoil (10%) in the animal model compared to the 3% recoil in this study may be explained by the fact that in the former study the stent was implanted in normal animal coronary arteries. These angiographic data indicate that in contrast to balloon angioplasty, where recoil amounting to 50% has been documented [31], the Wiktor® stent appropriately scaffolds the vessel.

The measured diameter of the inflated balloon at an average inflation pressure of 6–8 atm (2.98 ± 0.44 mm) did not achieve the nominal size of the balloon (3.35 ± 0.36 mm) as specified by the manufacturer. The inflation pressure needed to obtain the nominal size of the balloon has been tested in air. It may be that a higher inflation pressure should be applied to achieve full expansion of the balloon to overcome the opposing forces exerted by the arterial wall and possibly by the stent itself.

CONCLUSIONS

Implantation of the Wiktor® stent results in a further improvement in stenosis geometry after balloon angioplasty. A fivefold increase in the minimal luminal cross-sectional area with a significant reduction of the inflow and outflow angles is observed without changing the curvature of the stenosis. This is associated with a nor-

malization of the resistances to flow. With the recommended inflation pressure of 6–8 atm, there is no full expansion of the balloon on which the stent is mounted. Furthermore, some recoil (0.10 ± 0.36 mm) is observed after stent implantation. This may be explained by the rather loose interdigitating coil structure of this particular stent.

Whether these observations will result in a reduced restenosis rate in comparison with balloon angioplasty and to an improved long-term clinical success rate remains to be determined.

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CHAPTER 3

IMMEDIATE CHANGES IN STENOSIS GEOMETRY FOLLOWING STENT IMPLANTATION: COMPARISON BETWEEN A SELF-EXPANDING AND A BALLOON-EXPANDABLE STENT

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Immediate Changes in Stenosis Geometry Following Stent Implantation: Comparison Between a Self-Expanding and a Balloon-Expandable Stent

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The immediate changes in stenosis geometry following Wallstent and Wiktor stent implantation in native coronary arteries were compared in 92 patients (46 in each group) using automated edge detection. Patients with comparable baseline stenosis characteristics were selected. Lesions were matched for lesion site, reference diameter, and minimal luminal diameter. In both groups, the stented coronary artery was the left anterior descending artery in 27 patients (59%), the left circumflex artery in four patients (9%), and the right coronary artery in 15 patients (33%). The baseline reference diameter was 2.86 ± 0.39 mm and 2.87 ± 0.42 mm in the Wallstent and Wiktor stent study group, respectively (NS). The baseline minimal luminal diameter was identical in both groups (1.13 ± 0.24 mm). The nominal size (mean ± SD) of the unconstrained Wallstent was 3.5 ± 0.3 mm and 3.3 ± 0.3 mm for the Wiktor stent ($P < 0.05$). Both types of stents resulted in a similar increase in minimal luminal diameter immediately following implantation (Wallstent: 2.34 ± 0.38 mm, Wiktor stent: 2.43 ± 0.27 mm, NS). Furthermore, there was a similar decrease in diameter stenosis and increase in minimal luminal cross-section area following implantation of both stents. These morphological changes were associated with a normalization of the hemodynamic parameters in both groups. It is concluded that, although the Wallstent and Wiktor stent are different in design and mechanical characteristics, there is a similar immediate improvement in stenosis geometry following implantation of both devices. (J Interven Cardiol 1992; 5:71–78)

Introduction

Treating obstructive coronary artery disease by means of intravascular catheters is an old dream that came true in the late 1970s.[1,2] Percutaneous coronary artery balloon angioplasty has been plagued by restenosis since its introduction. To circumvent this limiting factor, intracoronary stenting has been proposed as an adjunct to balloon angioplasty.[3] Although the exact pathophysiological mechanism(s) responsible for restenosis are largely unknown, intracoronary stenting may result in a lower incidence of restenosis by optimizing the balloon dilatation process. Indeed, it has been shown that stent implantation does not only provide scaffolding for the vessel and thereby prevents recoil but also results in a larger vessel lumen and cross-sectional area compared to balloon angioplasty and thus may compensate for late neointimal hyperplasia.[4–7]

At present, several stents are available, each with its own specific design and physico-chemical characteristics.[6,8–10] Distinction can be made be-

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tween self-expanding and balloon-expandable devices. The self-expanding stent, in contrast to the balloon-expandable devices, exerts active radial force on the vessel wall after deployment.[3,5,11,12] This may result in differences in vessel lumen geometry following stenting. Therefore, the aim of this study is to compare the morphological changes in stenosis geometry immediately following the implantation of a self-expanding stent (Wallstent, Medinvent, Lausanne, Switzerland) and a balloon-expandable stent (Wiktor stent, Medtronic, Inc., Minneapolis, MN, USA).

Methods

Patients. At present, our database contains the angiographic data of 257 patients in whom a Wallstent (162 patients) or Wiktor stent (95 patients) were successfully implanted in a native coronary artery. Two groups of patients with comparable baseline stenosis characteristics were selected according to the matching principle. Only patients in whom a Wallstent or Wiktor stent was successfully implanted as elective procedure in a native coronary artery were eligible. Lesions were matched for lesion site, reference diameter, and minimal luminal diameter. The coronary artery tree was subdivided into 15 segments according to the American Heart Association guidelines.[13] Since the variability of repeat measurement of the reference diameter and minimal luminal diameter from the same cineangiogram is 0.10 mm, matching was performed such that the difference of this parameter between two patients of each group did not exceed 0.20 mm (twice the variability or 95% confidence interval).[14]

A total of 92 patients (46 in each group) met the matching criteria and formed the study population. Matching was considered adequate since there was an equal number of different stenosis locations in both groups (left anterior descending coronary artery, 27 patients; left circumflex artery, 4 patients; and right coronary artery, 15 patients), the reference diameter was 2.86 ± 0.39 mm and 2.87 ± 0.42 mm for the Wallstent group and Wiktor stent group, respectively (NS). The minimal luminal diameter was identical in both groups (1.13 ± 0.24).

Description of the Stents. The Wallstent (Fig. 1) is a geometrically stable, pliable, and self-expanding prosthesis, woven from a surgical grade stainless steel alloy. The stent consists of 16 wire filaments, each 0.08 mm in diameter. Its elastic and pliable properties are such that its diameter can be substantially reduced by moderate elongation. It can be constrained on a small diameter delivery catheter, but spontaneously returns to its original (unconstrained) larger diameter when the constraining membrane is removed. The outer diameter of the stent-catheter system mounted on this delivery device is 1.57 mm, using prostheses that expand to a diameter of 6.5 mm.

The Wiktor stent (Fig. 2) is a radiopaque balloon-expandable stent constructed of a single loose interdigitating tantalum wire (0.125 mm in diameter) formed into a sinusoidal wave and configured as a helix. The prosthesis is crimped onto the deflated polyethylene balloon of a standard angioplasty catheter. The crimped stent profile is approximately 1.5 mm. Upon inflation of the balloon, the sinusoidal waves expand to that extent that the stent conforms to the vessel wall. The features of the prosthesis are such that by inflating the balloon, the diameter of the stent increases without alteration of its length (14–16 mm). The maximal diameter of the balloon during inflation determines the ultimate size of the prosthesis.

Selection of Stent Size. Selection of the stent size was based on the visual assessment of the vessel size. The size of the Wallstent was selected to obtain an unconstrained diameter of 0.5 mm larger than the vessel. For the Wiktor stent, a balloon on which the Wiktor stent is mounted with a nominal size, which is 0.5 mm larger than the vessel, was selected. The size (mean ± SD) of the unconstrained Wallstent proved to be 3.5 ± 0.3 mm and was 3.3 ± 0.3 mm for the Wiktor stent ($P < 0.05$). In case of incomplete expansion of either stent, a repeat balloon dilatation within the stent was performed.

Quantitative Coronary Angiography. To assess the immediate and long-term changes in stenosis geometry, all coronary cineangiograms were analyzed at the core laboratory in Rotterdam by means of the computer-assisted Cardiovascular Angiography Analysis System (CAAS), described in detail elsewhere.[15] This system allows

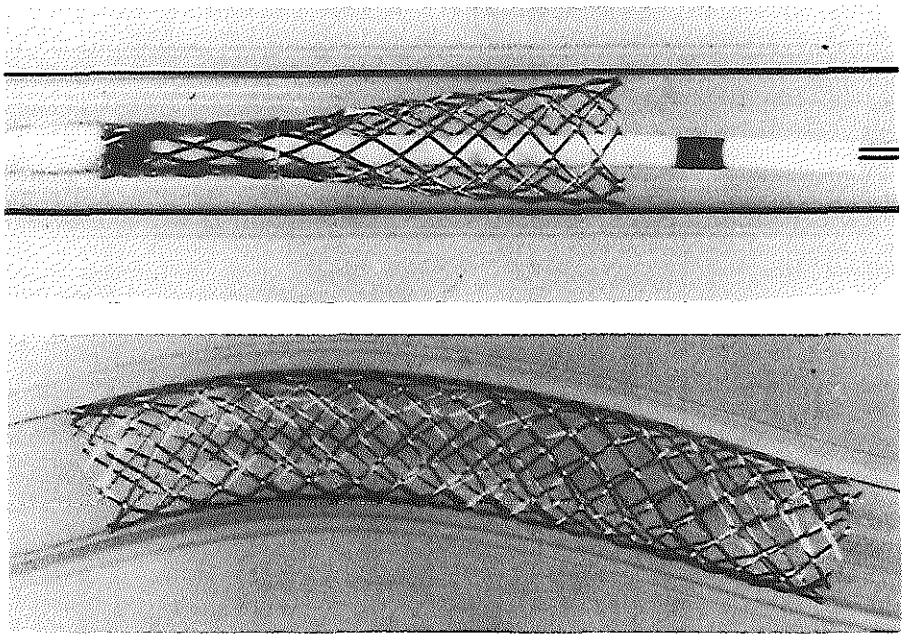

Figure 1. Self-expanding stent (Wallstent) with membrane partially pulled back and expanding stent (top); and stent in position illustrating longitudinal flexibility (bottom).

an objective and reproducible quantification of a coronary artery stenosis. Briefly, a 35-mm cineframe selected for analysis is digitized with a charge coupled device (CCD) camera at high resolution (1330 × 1770 pixels) in a matrix size of 512 × 512 pixels with eight bits of brightness resolution. The segment to be analyzed is determined by selecting a number of centerline points that are connected by interpolation. An automated edge detection program determines the arterial contour by assessing the brightness profile along scanlines perpendicular to the centerline. After correction for pincushion distortion and calibration using the guiding catheter as scaling device, a diameter function curve can be determined from the contour analysis by computing the distances between the left and right edges. From this diameter function curve, several parameters can be computed such as the minimal luminal diameter, reference diameter, and diameter stenosis. The variability, precision, and accuracy of the system has been reported previously.[14,16]

All angiograms for subsequent analysis were performed after intracoronary injection of 2-mg isosorbide dinitrate.

The hemodynamic significance of the obstruction and its changes after stent implantation were evaluated by calculating the theoretic pressure drop using the arteriogram and digital computation, according to the formulae described in the literature: Pgrad = Q. (Rp + Rt), where Pgrad = the theoretic transstenotic pressure decrease (mmHg) over the stenosis, Q = the mean coronary blood flow (mL/sec), Rp = the Poiseuille resistance, and Rt = the turbulent resistance.[17,18]

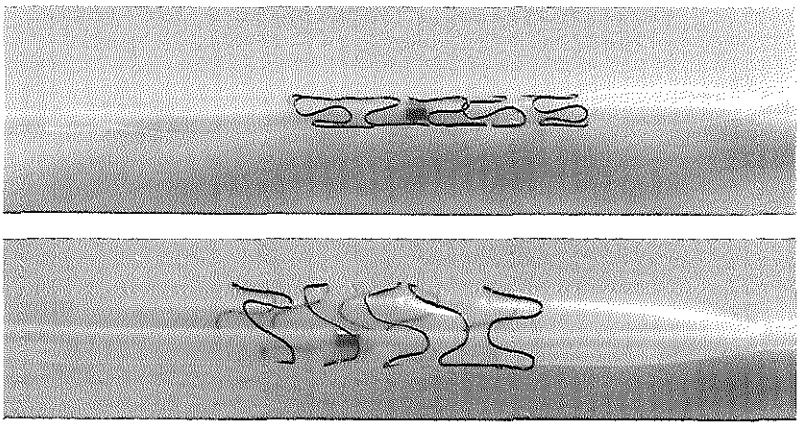

Figure 2. Balloon-expandable stent (Wiktor stent) mounted on a conventional polyethylene balloon when de- and inflated.

These resistances have been defined as follows: Rp = C1. (length obstruction)/(minimal cross-sectional area)^2, where C1 = 8.π. (blood viscosity) with blood viscosity = 0.03 g/cm·sec. Rt = C2. (1/minimal cross-sectional area − 1/normal distal area)^2, where C2 = (blood density)/0.266 with blood density = 1.0 g/cm^3.

The theoretic transstenotic pressure drop was calculated for theoretic coronary blood flow of 0.5, 1, and 3 mL/sec. The Poiseuille and turbulent contributions to the flow resistance were determined from stenotic geometry assessed by quantitative coronary angiography.

Statistics. Values obtained by quantitative angiographic analysis are expressed as means ± SD. The changes of each angiographic variable before and immediately after stent implantation were compared by analysis of variance. If significant differences were found, two-tailed Student's *t*-tests were applied to paired data. A statistical probability of < 0.05 was considered to indicate significance.

Results

The morphological and hemodynamic changes in stenosis geometry are presented in Tables 1 and 2. There was no difference in any baseline angiographic parameter between the two study groups. Predilatation with a balloon catheter resulted in a significant increase in minimal luminal diameter from 1.13 ± 0.24 mm to 1.86 ± 0.31 mm and 1.78 ± 0.28 mm in the Wallstent group and Wiktor stent group, respectively. There was no difference in the minimal luminal diameter post-PTCA (percutaneous transluminal coronary angioplasty) between the two groups. Stent implantation resulted in a further significant increase in minimal luminal diameter from 1.86 ± 0.31 mm to 2.34 ± 0.38 mm following Wallstent implantation and from 1.78 ± 0.28 mm to 2.43 ± 0.27 mm following Wiktor stent implantation. Although the mean change in minimal luminal diameter was 1.21 ± 0.40 mm following Wallstent implantation and 1.30 ± 0.30 mm following Wiktor stent implantation, there was no statistical difference in the minimal luminal diameter poststent implantation between the two study groups. The cumulative distribution of the minimal luminal diameter and its changes is depicted in Figure 3. It shows a wider range in minimal luminal diameter immediately following Wallstent implantation compared to Wiktor stent implantation. Statistical analysis performed between the two study

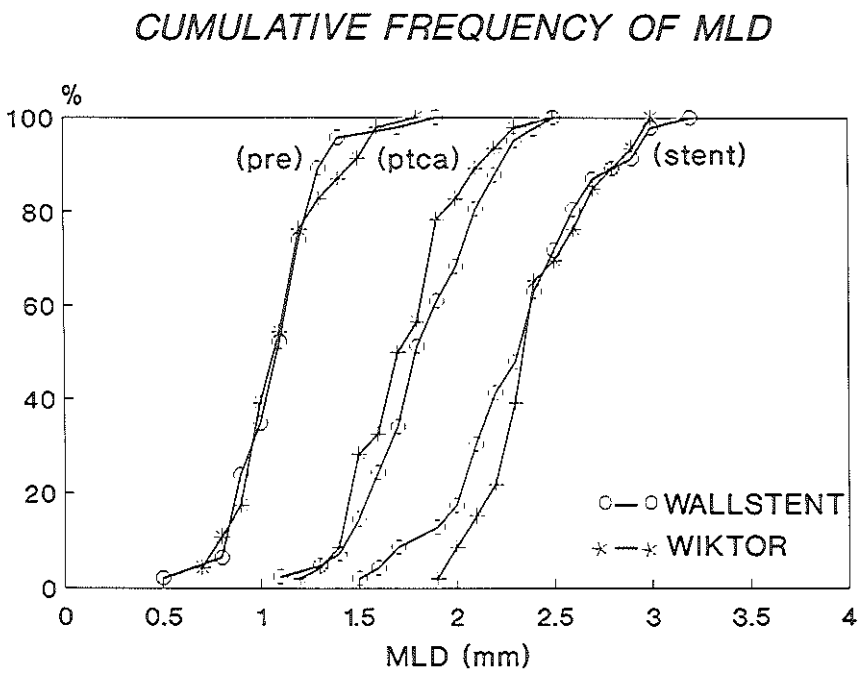

Figure 3. Cumulative distribution of the minimal luminal diameter pre-PTCA, post-PTCA, and immediately following stent implantation.

groups, revealed no difference between any angiographic parameter after PTCA and immediately following stent implantation. These morphological changes were associated with a significant decrease in the calculated turbulent and Poiseuille resistance and a virtual disappearance of the pressure drop for a theoretical blood flow of 0.5, 1, and 3 mL/sec (Table 2).

Discussion

PTCA, by means of balloon catheters, has gained widespread acceptance as a nonsurgical method of treating obstructive coronary heart disease. Despite its high initial success rate, its efficacy is limited by the occurrence of restenosis.[19–22] Pharmacological efforts to reduce or eliminate this proliferative process have largely been unsuccessful.[23–28] This is due partly to the lack of knowledge and understanding of the pathophysiological mechanism(s) responsible for restenosis. Therefore, it is not surprising that along with the pharmacological interventions, new devices have entered clinical testing to circumvent restenosis. In this respect, intracoronary stenting may be a logical approach. It is obvious that implantation of an endovascular prosthesis by itself cannot eliminate the triggers for the proliferative response of the vessel wall following injury. On the contrary, stents could promote intimal proliferation by stretching medial smooth muscle cells, stimulating mural thrombus, or attracting inflammatory cells.[29,30] How-

Table 1. Immediate Morphological Changes in Coronary Artery Stenosis Following Wallstent and Wiktor Stent Implantation

	Wallstent				
	pre-PTCA	post-PTCA	post-STENT	P_1	P_2
Ref. Diam. (mm)	2.86 ± 0.39	2.95 ± 0.49	2.98 ± 0.35	NS	NS
MLD (mm)	1.13 ± 0.24	1.86 ± 0.31	2.34 ± 0.38	0.00001	0.00001
DS (%)	60 ± 8	36 ± 10	22 ± 9	0.00001	0.00001
RA (mm^2)	6.52 ± 1.78	7.04 ± 2.39	7.09 ± 1.68	NS	NS
MLCA (mm^2)	1.04 ± 0.45	2.81 ± 0.89	4.40 ± 1.38	0.00001	0.00001
AS (%)	83 ± 6	58 ± 13	38 ± 14	0.00001	0.00001
		P_1	P_2		

Ref. Diam. = reference diameter; MLD = minimal luminal diameter; DS = diameter stenosis; RA = reference area; MLCA = minimal luminal cross sectional area; AS = area stenosis.

Comparison between the Wallstent and Wiktor Stent study group revealed no statistical difference between any angiographic parameter.

All parameters are expressed in mean ± SD.

ever, by optimizing the luminal geometry and minimizing the residual stenosis, a stent may compensate for the proliferative process.

Randomized studies comparing new coronary angioplasty techniques are not available. To compare the angiographic effect of different interventions, patients with identical baseline stenosis characteristics have to be selected.[31,32] For this purpose, the method of matching was used in this study. At present, this may be the best surrogate for a randomized study, which would be very time-consuming. The baseline stenosis characteristics of the patients herein reported are representative for the angioplasty population, encountered in general practice.[6,8,11,28,33]

Quantitative coronary angiography was used to assess the difference in the immediate modifications in stenosis geometry following Wallstent and Wiktor stent implantation. This is not only of pure academic importance, but may hold important clinical consequences. As stated previously, a high initial gain after stent implantation may compensate for late neointimal hyperplasia. A residual diameter stenosis larger than 20% following stenting is an angiographic predictor for restenosis.[34] However, the gain is a double-edged sword. Mechanical medial injury is a known factor in generating a proliferative vessel wall response. Experimental animal and angiographic studies indicate a relation between

Table 2. Immediate Hemodynamic Changes Following Wallstent and Wiktor Stent Implantation

	Wallstent				
	pre-PTCA	post-PTCA	post-STENT	P_1	P_2
Rpois	22.55 ± 61.76	2.34 ± 7.76	1.92 ± 6.58	0.02	NS
Rturb	7.98 ± 23.72	0.39 ± 0.54	0.04 ± 0.10	0.05	0.0002
Pgrad (0.5 mL/sec)	30.53 ± 78.73	2.67 ± 7.08	1.95 ± 7.47	0.02	0.03
Pgrad (1 mL/sec)	56.98 ± 109.73	5.97 ± 14.71	4.05 ± 15.10	0.002	0.007
Pgrad (3 mL/sec)	82.51 ± 148.09	9.88 ± 22.95	6.14 ± 22.88	0.002	0.002
		P_1	P_2		

Rpois = Poiseuille resistance; Rturb = turbulent resistance; Pgrad = pressure drop.

Comparison between the Wallstent and Wiktor Stent study group revealed no statistical difference between any angiographic parameter.

All parameters are expressed in mean ± SD.

Table 1. (*continued*)

Wiktor Stent				
pre-PTCA	post-PTCA	post-STENT	P_1	P_2
2.87 ± 0.42	2.79 ± 0.48	2.99 ± 0.38	0.03	0.00001
1.13 ± 0.24	1.78 ± 0.28	2.43 ± 0.27	0.00001	0.00001
60 ± 7	35 ± 10	18 ± 7	0.00001	0.00001
6.62 ± 1.93	6.29 ± 2.16	7.11 ± 1.88	0.05	0.0001
1.06 ± 0.46	2.55 ± 0.83	4.72 ± 1.08	0.00001	0.00001
83 ± 6	57 ± 14	33 ± 12	0.00001	0.00001
P_1		P_2		

vessel oversizing and neointimal proliferation.[29-34]

Both devices resulted in a more than twofold increase in minimal luminal diameter and a more than fourfold increase in the minimal luminal cross-sectional area. Despite the lesser increase in minimal luminal diameter post-PTCA in the Wiktor group and despite the smaller nominal size of the Wiktor stent used in this study, there was a larger, although statistically not different, increase in minimal luminal diameter following Wiktor stent implantation. However, there are several unknown factors limiting a comprehensive comparison. First, the number of repeat balloon inflations and balloon size within the Wiktor stent is not known. Second, this difference may be temporary since the dilatation process of the Wallstent continues until an equilibrium is attained between the circumferential elastic resistance of the vessel wall and the dilating force of the prosthesis. Moreover, previous and recent angiographic studies indicate that both stents dilate the vessel to the same extent.[6,8,33] Third, although our experience is that edge detection is the appropriate technique for quantification of stenosis geometry following Wiktor stent implantation, validation studies with phantom models are warranted to verify this.[35] Furthermore, a selection bias entered in the matching technique cannot be excluded.

Conclusions

These data indicate that although the Wallstent and Wiktor stent are different in design and mechanical characteristics, there is a similar immediate improvement in stenosis geometry following implantation of both devices.

Table 2. (*continued*)

Wiktor Stent				
pre-PTCA	post-PTCA	post-STENT	P_1	P_2
8.71 ± 7.98	1.06 ± 0.77	0.47 ± 0.20	0.00001	0.00001
4.47 ± 4.97	0.26 ± 0.36	0.02 ± 0.02	0.00001	0.00001
13.19 ± 12.54	1.33 ± 1.05	5.77 ± 35.77	0.00001	NS
34.90 ± 34.46	3.19 ± 2.32	1.01 ± 0.44	0.00001	0.00001
66.44 ± 66.60	5.59 ± 5.10	1.53 ± 0.74	0.00001	0.00001
P_1		P_2		

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CHAPTER 4

COMPARATIVE ANGIOGRAPHIC QUANTITATIVE ANALYSIS OF THE IMMEDIATE EFFICACY OF CORONARY ATHERECTOMY WITH BALLOON ANGIOPLASTY, STENTING AND ROTATIONAL ABLATION

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Comparative angiographic quantitative analysis of the immediate efficacy of coronary atherectomy with balloon angioplasty, stenting, and rotational ablation

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Directional atherectomy has recently been introduced as an alternative to conventional balloon dilatation.[1] It has been shown to be safe and effective when applied in human coronary arteries.[2, 3] It was initially hypothesized that removal of the atherosclerotic plaque would result in a better immediate result with fewer acute complications and a reduced restenosis rate compared with conventional balloon angioplasty.[4] However, at the present time it is difficult to compare the respective merits of various mechanical interventions, since no randomized studies have been attempted. While awaiting these trials we used information from our quantitative angiography data base to compare patients treated with various coronary interventions. Coronary lesions from 51 patients who underwent directional atherectomy were analyzed with the computer-based coronary angiography system and matched with similar lesions treated by means of balloon angioplasty, intracoronary stenting, and rotational ablation. The immediate results from geometric assessment of the stenotic lesion by edge detection before and after atherectomy are presented and compared with the results of conventional balloon angioplasty, intracoronary stenting, and rotational ablation.

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METHODOLOGY

Patient group. From September 1989 through September 1990, a total of 51 patients (43 men and 8 women) underwent an atherectomy procedure for symptomatic coronary artery disease. Three patients underwent two procedures and one patient had three procedures. The atherectomy procedure was successful in 54 of the 56 procedures (postprocedural diameter of stenosis <50%). The mean age (±SD) was 58.2 (±10.1) years. At the time of atherectomy 21 patients were in New York Heart Association functional class IV, 11 were in class III and 19 were in class II. Coronary angiography showed one-vessel disease in 39 patients, two-vessel disease in eight, and three-vessel disease in four. The site of obstruction was located in the left anterior descending coronary artery in 31 patients, in the right coronary artery in 13, in the circumflex artery in nine, and in the venous bypass graft in three.

Atherectomy procedure. After administration of local anesthesia, an 11F sheath was inserted into the femoral artery. All patients received 250 mg acetylsalicylic acid and 10,000 U heparin intravenously. Intracoronary injection of isosorbide dinitrate was given to minimize any possible spasm. After initial angiograms in multiple views were obtained, a special 11F guiding catheter was placed into the ostium of the coronary artery. Under fluoroscopy the guide wire was advanced into the distal part of the artery. Then the atherectomy device was directed over the guide wire and positioned across the stenosis. The support balloon was then inflated up to 0.5 atm, the cutter was retracted, and the balloon inflation pressure was increased to 2 to 3 atm. The driving motor was activated, and the rotating cutter was slowly advanced to cut and collect the protruding atheroscle-

rotic lesion in the collecting chamber located at the tip of the catheter. After every pass the balloon was deflated and either removed or repositioned. On average 6.1 ± 2.9 passes in multiple directions were performed across a stenosis. Atherectomy was considered successful when the residual stenosis was less than 50% after tissue retrieval. After atherectomy the arterial and venous sheaths were usually left in place for 6 hours. Patients were monitored for 24 hours, and ECGs and cardiac enzyme levels were obtained twice a day. Nifedipine was given every 2 hours after the procedure, and patients continued to receive aspirin medication for 1 year.

Quantitative coronary angiography. Quantitative analysis of the coronary segments was performed with the computer-based Coronary Angiography Analysis System, which was previously described in detail.[5, 6] In essence boundaries of a selected coronary artery segment (Fig. 1) are detected automatically from optically magnified and video-digitized regions of interest (512 × 512 pixels) of a cineframe. The absolute diameter of the stenosis (in millimeters) is determined with the use of the guiding catheter as a scaling device. Calibration of the catheter in absolute values (in millimeters) is achieved by comparing the mean diameter of the guiding catheter in pixels with the measured size in millimeters. Each individual catheter is measured by a micrometer. To correct the detected contour of the arterial and catheter segments for pincushion distortion, a correction vector is computed for each pixel based on a computer-processed cineframe with a centimeter grid placed against the input screen of the image intensifier. Because the functional significance of a stenosis is related to the expected normal cross-sectional area of a vessel at the point of obstruction, we use a computer estimation of the original dimension of the artery at the site of the obstruction to define the interpolated reference area. The percentage diameter and area stenosis, as well as the cross-sectional area (in millimeters squared), are then calculated. The length of the lesion (in millimeters) is determined from the diameter function on the basis of a curvature analysis. By use of the reconstructed borders of the vessel, the computer calculates the symmetry coefficient for the stenosis. The symmetry index ranges from zero (totally eccentric stenosis) to one (symmetric). The degree of coronary bend is assessed by the curvature value at the site of the obstruction. This parameter is computed as the average value of all the individual curvature values along the center line of the coronary segment, with the curvature defined as the first derivative of the tangent as it moves along the center line, which for a circle is equal to the reciprocal of the radius.

Hemodynamic assessment. The hemodynamic results were determined as described earlier.[7-10] Briefly the theoretical pressure decrease was calculated by means of the arteriogram and digital computation according to the formula: Pgrad = Q. (Rp + Q. Rt), where Pgrad is the theoretical transstenotic pressure decrease (mm Hg) over the stenosis, Q is the mean coronary flow (ml/sec), Rp is the Poiseuille resistance, and Rt is the turbulence resistance. The theoretical transstenotic pressure decrease was calculated for a theoretical blood flow of 1, 2 and 3 ml/sec. The Poiseuille and turbulence contributions to flow resistance were determined from stenosis geometry assessed by quantitative coronary angiography.

Matching process. To avoid patient selection bias we selected populations with comparable baseline stenosis characteristics. The coronary artery tree was subdivided into 15 segments according to the American Heart Association guidelines. The lesions were individually matched according to the location of the stenosis and the reference diameter. Matching was considered adequate if the mean difference of the reference diameter between the groups was identical. Three patients who were treated for bypass graft stenosis and two patients with an unsuccessful procedure were excluded from the matching process. Thus 51 lesions treated with intracoronary atherectomy were individually matched with "twin" lesions treated with balloon angioplasty or self-expandable stent. The group treated with the Rotablator (Heart Technology Inc., Bellevue, Wash.) was not individually matched, since only seven patients were included. Their results are represented as a group. Currently the Thoraxcenter angiographic registry contains quantitatively assessed stenosis data for 2300 patients treated either by angioplasty (n = 1847), intracoronary stenting (n = 406), directional atherectomy (n = 56), or rotational ablation (n = 7).

Device profiles

Atherectomy devices. In 50 of 51 patients undergoing atherectomy a 6F catheter was used, whereas in one patient a 7F atherectomy device was employed. The mean diameter of the atherectomy device was 2.1 mm by quantitative angiographic assessment.

Balloon angioplasty. The transverse diameter of the deflated balloon is an important determinant as to whether a stenosis can be crossed. Currently used balloons have favorable profile characteristics as expressed by their small diameter (1.0 mm: ranging from 0.8 to 1.1 mm). The balloon sizes were matched to the reference diameter with the goal of achieving

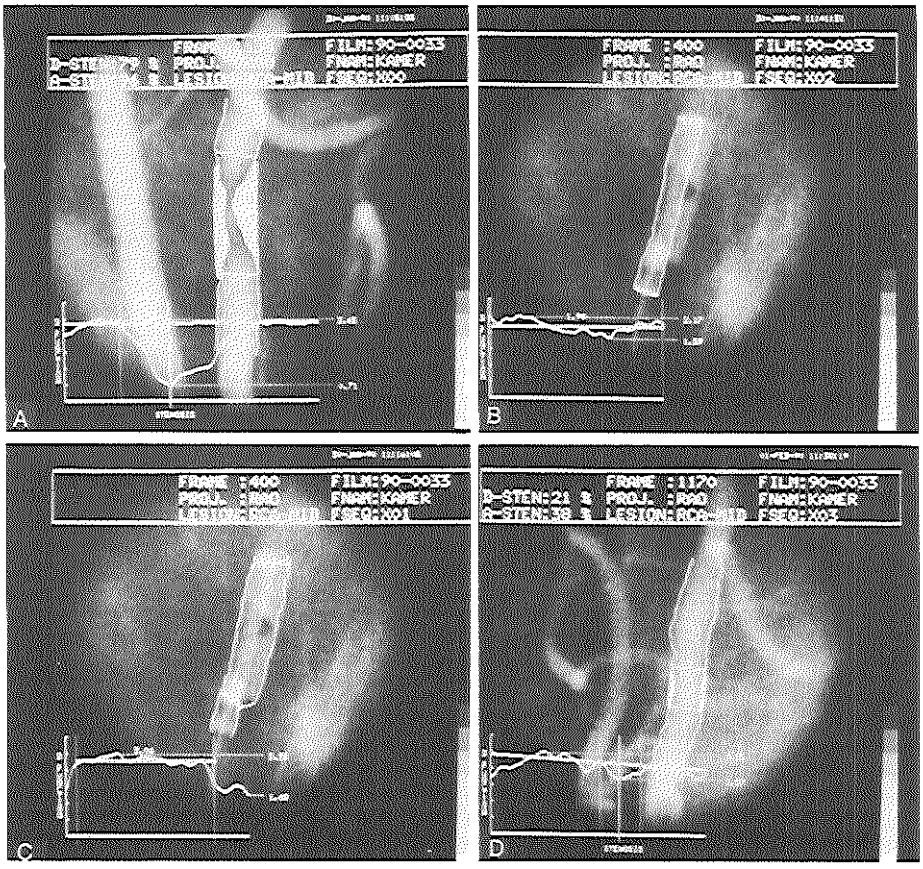

Fig. 1. A, Detected contours superimposed on original video image for a representative right coronary artery stenosis filmed in right anterior oblique projection before directional atherectomy. Diameter function is shown at bottom. *White area* is measure for "atherosclerotic plaque." Minimum luminal diameter *(verticle line)* is 0.71 mm, corresponding to diameter stenosis of 79% and area stenosis of 96%. **B,** Contour analysis of intracoronary atherectomy device without inflated support balloon. This represents first or "prefunctional" stage of intracoronary intervention characterized by intrinsic diameter of device. **C,** Contour analysis of intracoronary filmed atherectomy device with inflated support balloon. Beneath this is shown diameter function. Mean diameter is 3.06 mm. This analysis represents second or "operational" stage in which atherectomy device exhibits its mode of action. **D,** Single-frame angiogram of right coronary artery filmed in right anterior oblique projection after directional atherectomy. Minimum luminal diameter increased to 2.27 mm, corresponding to diameter stenosis of 21% and area stenosis of 38%.

a ratio of 1:1 (inflated balloon diameter:artery diameter). The following balloon diameters were used in this study population: 2.0 mm (n = 1), 2.5 mm (n = 12), 3.0 mm (n = 27), 3.4 mm (n = 1), 3.5 (n = 9), and 4.0 mm (n = 1).

Stenting. The self-expanding stent is constrained on a small-diameter delivery catheter but assumes its unconstrained larger diameter up to 6 mm when the constraining membrane is removed. The stent catheter profile mounted on its delivery device is 1.57

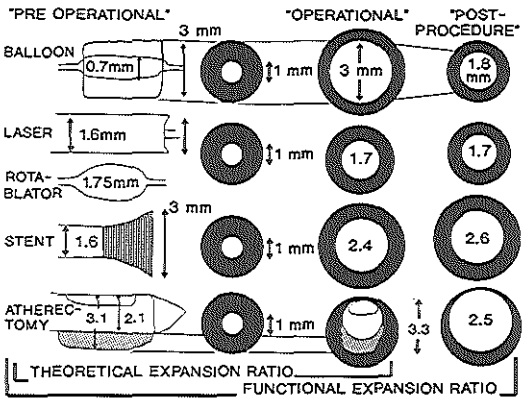

Fig. 2. Schematic representation of concept of functional and theoretical expansion ratio of various intracoronary intervention techniques. First or "prefunctional" stage is characterized by introduction of device. In becoming operational some devices get expanded *(atherectomy, balloon, stent)*, whereas others maintain their original dimensions *(laser, Rotablator)*. End result is determined by recoil phenomenon and vascular reactivity. After device is removed maximum acute effect may be partially lost because of elastic recoil vessel. Expansion ratio is subdivided into theoretical expansion ratio, which is determined by operational device, and functional expansion ratio, which takes into account elastic recoil phenomenon and describes net result.

mm.[11] In the 51 study patients the unconstrained diameters were 3.0 mm (n = 5), 3.5 mm (n = 29), 4.0 mm (n = 9), 4.5 mm (n = 1), and 5.0 mm (n = 3); the diameter was unknown in four. The stent sizes were selected on the basis of the size of the arterial segment, taking into account that the stent in its unconstrained form must have a diameter 0.5 mm larger than the reference diameter of the stented vessel.[11]

Rotational ablation. With rotational ablation the device consists of a rotating abrasive burr of variable profile characteristics (from 1.5 to 3.5 mm). In this series the largest burr size used was 2.25 mm. Choice of burr size was selected according to the reference diameter.

Quantitative assessment of the expansion ratio of the various devices. Recently the concept of the expansion ratio has been addressed.[12] Briefly the mechanism of all intracoronary interventions may be divided into three stages. The first or "prefunctional" stage is characterized by the introduction of the device. The device is not yet operational, and its intrinsic dimensions determine to what extent the device may be introduced into the coronary tree. During the introduction of a bulky device across a stenotic lesion, some degree of dilatation occurs as a direct result of a Dotter effect. The second or "operational" stage starts when the device becomes operational and exhibits its specific mode of action (dilatation, cutting, ablation, vaporization). In becoming operational the diameter of the device may expand (atherectomy, balloon, stent) or maintain its original dimensions (laser, rotational ablation). During this stage the maximum effect of the device is achieved. The final result after removal of the device is then determined by the recoil phenomenon and vascular reactivity. Consequently the net luminal gain will be less than the initial gain when the device is operational (Fig. 2).

To distinguish the acute effect of the various devices from the vascular reactivity and recoil phenomenon, we subdivided the expansion ratio into the theoretical expansion ratio, which occurs during the "operational" stage, and the functional expansion ratio, which takes into account the elastic recoil phenomenon and describes the net result.[13] Both the theoretical and functional ratios were assessed for all interventional devices used in our study. The maximum achievable diameter of the vessel is calculated according to the diameter of the operational device while it is active. In the case of balloon angioplasty and self-expandable stent, this corresponds to the diameter of the inflated balloon and to the unconstrained diameter of the self-expandable stent. For atherectomy this was assessed by intracoronary quan-

Table I. Effect of directional coronary atherectomy on 55 obstructive lesions

	Extent (mm)	*MLD (mm)*	*Reference (mm)*	*DS (%)*	*MLCA (mm^2)*	*Plaque area (mm^2)*	*Symmetry index*
Mean ± SD							
Before atherectomy	6.4 ± 2.5	1.1 ± 0.4	3.0 ± 0.6	63 ± 11	1.1 ± 0.8	8.8 ± 5.6	0.6 ± 0.3
After atherectomy	4.7 ± 2.1	2.5 ± 0.5	3.2 ± 0.4	22 ± 15	5.2 ± 1.8	2.6 ± 2.1	0.7 ± 0.2
p Value	<0.00001	<0.00001	0.03	<0.00001	<0.00001	<0.00001	NS

MLD, Minimal luminal diameter; DS, diameter stenosis; MLCA, minimal cross-sectional area; SD, standard deviation; NS, not significant.

Table II. Hemodynamic results immediately after directional coronary atherectomy

			Pressure gradient (mm Hg)		
	Poiseuille resistance (dynes/sec/cm^{-5})	*Turbulent resistance (dynes/sec/cm^{-5})*	*Flow (1 ml/sec)*	*Flow (2 ml/sec)*	*Flow (3 ml/sec)*
Mean ± SD					
Before atherectomy	39.2 ± 124.8	20.6 ± 59.7	48.0 ± 154.5	105.5 ± 380.9	197.5 ± 697.0
After atherectomy	0.3 ± 0.4	0.05 ± 0.17	0.4 ± 0.1	0.6 ± 1.0	1.0 ± 1.6
p Value	0.025	0.013	0.026	<0.01	0.042

SD, Standard deviation.

titative analysis during inflation of the support balloon. The Rotablator does not alter its diameter while operational. The postprocedure diameter has been measured immediately after withdrawal of the device. For example, when the diameter of an intracoronary atherectomy device increases from 2.1 mm to 3.5 mm on inflation of the balloon, the maximum achievable vessel diameter becomes 3.5 mm. However, the final luminal diameter at the end of the procedure measures 2.6 mm. Thus the theoretical and functional expansion ratios are 1.7 (3.5/2.1) and 1.2 (2.6/2.1), respectively.

Statistical analysis. All values are expressed as mean values ± 1 standard deviation. Morphologic and hemodynamic variables before and after atherectomy were compared by the paired Student's *t* test. Comparisons of the severity of minimum luminal diameter, area of plaque, and diameter of stenosis among the groups were performed by means of analysis of variance. If significant differences were found, the unpaired Student's *t* test was applied. Differences were considered statistically significant at $p < 0.05$.

OBSERVATIONS

Directional atherectomy. Fifty-six lesions in 51 patients were studied, and a mean of 1.4 angiographic projections per lesion were analyzed. The morphologic and hemodynamic data are presented in Tables I and II, respectively. The mean values for the minimum luminal diameter before and after atherectomy were 1.1 ± 0.4 mm and 2.5 ± 0.4 mm, respectively. This morphologic improvement was associated with a significant decrease in the calculated Poiseuille and turbulent resistance, as well as a theoretical transstenotic gradient decrease for a theoretical flow of 1 ml/sec.

Atherectomy versus angioplasty and stenting. Matching according to lesion distribution and reference diameter was considered adequate since the reference diameter was equal in all groups (3.0 ± 0.6 mm), whereas the mean difference for this parameter between the groups was 0.0 ± 0.1 mm. No preprocedural differences were found among patients undergoing atherectomy, balloon angioplasty, and stenting with regard to minimum luminal diameter (1.2 ± 0.4 mm vs 1.2 ± 0.3 mm vs 1.2 ± 0.5 mm), diameter stenosis (63 ± 10% vs 62 ± 10% vs 60 ± 12%), area plaque (8.8 ± 5.8 mm^2 vs 8.2 ± 4.5 mm^2 vs 8.4 ± 4.5 mm^2), and symmetry value (0.5 ± 0.3 vs 0.6 ± 0.3 vs 0.5 ± 0.2). Curvature value was less in the atherectomy group compared with the angioplasty group (15.9 ± 7.0 vs 22.2 ± 13.1). Table III represents the changes in minimum luminal diameter, diameter of stenosis, and area plaque induced by presently available intracoronary interventional devices as assessed by quantitative angiography in our institution. A significantly larger gain in lumen diameter was achieved by directional atherectomy and stenting compared with balloon angioplasty (1.4 mm and 1.3 mm vs 0.7 mm; $p < 0.00001$). Rotational ablation resulted in the smallest luminal increment (1.2 ± 0.4 mm to 1.6 ± 0.1 mm).

Table III. Comparative quantitative analysis of the immediate results of atherectomy, angioplasty, and stenting

	Atherectomy		*PTCA*		*Stenting*	
	Before	*After*	*Before*	*After*	*Before*	*After*
MLD (mm)	1.2 ± 0.4	2.6 ± 0.4	1.2 ± 0.3	1.9 ± 0.4*	1.2 ± 0.5	2.5 ± 0.4†
AP (mm^2)	8.8 ± 5.8	2.6 ± 2.1	8.2 ± 4.5	5.3 ± 4.0*	8.4 ± 4.5	3.5 ± 2.4†
DS (%)	63 ± 10	20 ± 11	62 ± 10	36 ± 11*	60 ± 12	20 ± 9†

PTCA, Percutaneous transluminal coronary angioplasty; MLD, minimal luminal diameter; AP, area plaque; DS, diameter stenosis.
*$p < 0.00001$ atherectomy versus PTCA and stenting versus PTCA.
†p Value not significant for atherectomy versus stenting.

Table IV. Quantitative assessment of the theoretical and functional expansion ratio of intracoronary devices

Intervention	*Device profile (mm)*	*Maximum diameter achieved (mm)**	*Postinterventional diameter (mm)**	*Expansion ratio*	
				Theoretical	*Functional*
Balloon angioplasty	1.0 (0.8-1.1)	2.8 ± 0.5	1.9 ± 0.4	2.9	1.9
Self-expandable stents	1.6	3.3 ± 0.3†	2.5 ± 0.4	2.5	1.6
Directional atherectomy	2.1 (2.0-2.4)	3.3 ± 0.5	2.6 ± 0.4	1.6	1.2
Rotational ablation	2.0 (1.5-2.3)	1.9 ± 0.4	1.6 ± 0.2	1.0	0.8

*Assessed by quantitative coronary analysis.
†Unconstrained stent diameter.

Quantitative analysis of the theoretical and functional expansion ratio. Quantitative analysis of the intracoronary atherectomy device shows a mean diameter of 2.1 mm, which increases to 3.3 mm after inflation of the support balloon. Compared with the other devices atherectomy has a larger catheter delivery system, which limits the theoretical and effective expansion ratio (1.6 and 1.2, respectively). Balloon angioplasty and stenting give superior expansion ratios, since they are introduced on smaller delivery systems. Rotational ablation had the lowest expansion ratio, since the Rotablator does not change in size while in operation (Table IV).

COMMENTS

Over the past 5 years there has been a rapid increase in the development of new interventional devices aimed at supplementing conventional balloon dilatation. This progress in technology has resulted in the introduction of directional coronary atherectomy, intracoronary stenting, rotational coronary ablation, and laser-assisted angioplasty. Clinical studies have demonstrated the feasibility and safety of these interventions; however, the relative efficacy of each technique remains to be assessed.

Edge detection versus videodensitometry. The immediate efficacy of the various coronary interventions should be assessed by reproducible quantitative angiographic measurements.[14] Visual estimation of the severity of stenosis alone results in unacceptable variation in the assessment of changes in coronary artery lesions. To obtain values that are objective and reproducible, a computer-assisted technique that uses automated edge detection or videodensitometry should be applied.[15] Whether edge-detection techniques are inferior to videodensitometry remains an unresolved issue. Results of a previous study[5] demonstrated that the edge-detection method correlates well with densitometric analysis of the severity of stenosis before angioplasty. However, after angioplasty discrepancies between these types of measurements may be observed when a single-plane view is used.[16] Recently we have shown that a linear relationship exists between edge detection and videodensitometry both before and after atherectomy, although the strength of this relationship deteriorates slightly after atherectomy.[17] Therefore we felt justified in assessing the immediate efficacy of coronary atherectomy by edge-detection analysis.

Atherectomy versus angioplasty and stenting. With the increasing number of interventional modalities, current indications and patient selection become difficult. This study demonstrates the important finding that atherectomy and stenting result in a larger increase in minimum luminal diameter when compared with results of balloon angioplasty (1.4 and 1.3 mm vs 0.7 mm, $p < 0.00001$). In addition, no differences in the postinterventional angiographic results were observed between groups undergoing atherectomy and stenting. Results of this study con-

firm the findings of Muller et al.[18]; however, with our more refined matching technique individual atherectomy lesions were directly compared with angiographically similar lesions treated by angioplasty or stenting. Although a randomized trial is the optimum method for comparing the short- and long-term results of new interventional techniques, matching based on quantitative analysis might become an acceptable alternative while patients are awaiting these trials. With the use of this matching program we selected populations with comparable baseline stenosis parameters. The lesions were adequately matched, since no differences were found in reference diameter, minimal luminal diameter, area plaque, and symmetry index among the three groups. Whether the superior immediate results after atherectomy and stenting will be associated with a reduction in restenosis remains to be assessed in random trials.

Intracoronary devices. The expansion ratio is an important concept that relates the final effect of the intracoronary device on the arterial diameter to the size of the catheter required to deliver this effect.[12] The maximum effect of the device may be partially lost because of the elastic recoil of the vessel. The expansion ratio has been subdivided into two components, theoretical and functional, to separate these influences.[13] Balloon angioplasty and stenting give extremely favorable theoretical and functional expansion ratios (2.9 and 1.9 vs 2.5 and 1.6, respectively), since they may be delivered on low-profile catheters. The directional atherectomy device is more limited by the size of the housing and collecting chamber. The dimensions of the rotational atherectomy device do not change during the operation and therefore this procedure exhibits the lowest theoretical expansion ratio.

Although balloon angioplasty has the most favorable expansion ratio, the final result is profoundly influenced by the elastic recoil of the vessel.[19,20] Stenting and atherectomy appear to be more effective in resisting elastic recoil, although the mechanisms are likely different. Stenting effectively prevents this recoil phenomenon presumably because of its scaffolding function and its intrinsic dilating effect.[10,13] By physically removing tissue atherectomy appears to diminish the potential elastic recoil effect. However, the actual diameter of the atherectomy device limits its suitability in smaller coronary arteries.

Limitations. There are several limitations of this study. First, it is an uncontrolled retrospective observational study limited to a subset of patients who underwent successful coronary intervention. Although matching for angiographic variables is a promising technique to assess the efficacy of intracoronary interventions, patient- and procedure-related variables should also be included in the analysis. Second, this study is based on early experiences with atherectomy and stenting. Future design changes and improved operator experience may further improve the immediate and long-term results. Finally, the efficacy of all intracoronary interventions will be limited by the problem of restenosis, which necessitates careful and complete angiographic follow-up. Thus controlled clinical trials are imperative in the future to determine the immediate angiographic results and the long-term efficacy of these interventions and whether any benefit can be shown in particular patient subgroups.

Conclusions. Quantitative angiographic assessment of the immediate results after directional atherectomy shows significant improvement in the geometry and hemodynamics of stenosis. While patients are awaiting randomized trials, matching on the basis of quantitative analysis might become an acceptable alternative for objective and comparative assessment of various interventional techniques. In matched populations directional atherectomy and stenting appear to be more effective intracoronary interventional devices than balloon angioplasty based on the immediate result; however, atherectomy is limited in smaller coronary vessels by its larger size. Theoretically stenting has the most favorable characteristics as a dilating device, although its clinical use is limited by its more complicated patient management.

SUMMARY

Interventional cardiology has branched in two directions: devices that primarily dilate coronary stenoses and those that debulk coronary tissue. Presently the optimum coronary intervention has not been found. While patients are awaiting randomized trials, a comparison based on matched quantitative coronary analysis may be useful to evaluate results of new interventional techniques. Therefore we compared 51 patients undergoing atherectomy with individually matched patients who were undergoing balloon angioplasty and stenting. The lesions were matched according to location of stenosis and reference diameter. Atherectomy and stenting resulted in larger gains in minimal luminal diameter compared with conventional balloon angioplasty. The minimal luminal diameter was increased from 1.2 ± 0.4 mm to 2.6 ± 0.4 mm in the atherectomy group and from 1.2 ± 0.3 mm to 1.9 ± 0.4 mm in the angioplasty group ($p < 0.00001$). Atherectomy and stenting resulted in similar gains in minimum luminal diameter (1.4 mm vs 1.3 mm, p = NS). In addition, atherec-

tomy and stenting appear to be more effective in resisting elastic recoil because of tissue removal and an intrinsic dilating effect, respectively. In matched populations directional atherectomy and stenting appear to be more effective intracoronary interventional devices than balloon angioplasty based on the immediate results. However, atherectomy is limited in smaller coronary vessels because of its larger size.

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CHAPTER 5

RECOIL FOLLOWING WIKTOR STENT IMPLANTATION IN NATIVE CORONARY ARTERIES

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INTRODUCTION

The exact mechanisms by which balloon angioplasty leads to luminal enlargement and clinical improvement remain unclear [1]. Several mechanims have been proposed but principally rely on histopathological examination of experimentally induced atherosclerosis in animals or postmortem examination of human coronary arteries and therefore preclude any firm conclusions [2-7]. In vivo serial analysis of the vascular wall during balloon angioplasty with intravascular ultrasound has shown that in addition to plastic changes such as plaque fracture and compression, elastic changes occur which contribute to luminal enlargement [1,8,9,10]. As a response to these elastic changes, recoil may occur and constitute a mechanical reason for loss of gain achieved during balloon angioplasty [11]. It has been reported that elastic recoil accounts for an average 32% to 47% loss of the maximal achievable vessel diameter or vessel cross-sectional area [12-16]. To improve the immediate and long-term results of balloon angioplasty, intracoronary stent implantation has been advocated [17]. At present, the stent is the only catheter technology which scaffolds the vessel and therefore may prevent recoil. A number of stents are currently available [17-21]. They differ in geometry, wire thickness and physico-chemical characteristics. It has been hypothesized that the Wiktor stent, which is constructed of a single loose interdigitating tantalum wire, may have less scaffolding properties compared to the other stents with a more rigid and stiff mesh architecture. Therefore, the purpose of this study was to determine elastic recoil immediately after Wiktor stent implantation in native coronary arteries and to assess whether there is compression or "late recoil" of the stent itself at follow-up.

METHODS

Patients

The study population consisted of 77 consecutive patients (88% male, age 58 ± 9 years) in whom a single Wiktor stent (Figure 1) was successfully implanted and in whom repeat angiography was performed at (mean ± sd) 5.7 ± 1.3 months. In all patients, a stent was implanted because of recurrence of angina with objective evidence of ischemie due to restenosis of a lesion in a native coronary artery. A first restenosis was documented in 44 patients (57%), a second in 27 patients (35%) and a third in 6 patients (8%). The target vessel was the left anterior descending artery in 42 patients (54%), the circumflex artery in 9 patients (12%) and the right coronary artery in 26 patients (34%). The nominal size of the stent used was (mean ± SD) 3.40 ± 0.37 mm (3.0 mm device in 30 patients (39%), 3.5 mm device in 33 patients (43%) and a 4.0 mm device in 14 patients (19%)). The baseline angiographic characteristics of the study population are shown in Table 1. Written informed consent was required for every patient. The study protocol was approved by the

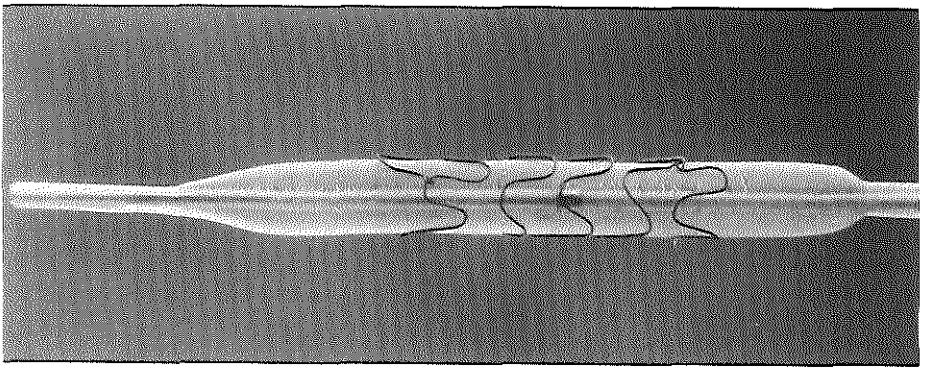

Fig. 1. The Wiktor stent is a radiopaque balloon expandable device, constructed of a single loose interdigitating tantalum wire (0.125 mm in diameter), formed into a sinusoidal wave and wrapped into a helical coil structure. The stent is crimped onto the deflated polyethylene balloon of a standard angioplasty catheter. The features are such that by inflating the balloon the diameter of the stent increases without any alteration in length (14 - 16 mm). The crimped stent profile is approximately 1.5 mm.

Table I. Baseline angiographic data of the 77 study patients.

Reference diameter (mm)	2.88 ± 0.55
Minimal luminal diameter (mm)	1.14 ± 0.37
Diameter stenosis (%)	60 ± 10
Reference area (mm^2)	6.68 ± 2.36
Minimal luminal cross-sectional area (mm^2)	1.13 ± 0.85
Area stenosis (%)	82 ± 11
Lesion length (mm)	12.6 ± 2.33
Plaque area (mm^2)	13.8 ± 5.00
Symmetry	0.50 ± 0.30

All parameters are expressed as mean ± SD.

ethics committee of the individual hospitals. The procedure of stent implantation and anticoagulation protocol have been described in depth elsewhere [22].

Assessment of recoil

All coronary angiograms were analyzed by the computer assisted Cardiovascular Angiography Analysis System (CAAS) using automated edge detection as previously described [23]. Single identical views before and after stent implantation and during complete expansion of the balloon on which the stent was mounted were chosen for quantitative analysis. The same X-ray setting in terms of kilovoltage and milli-amperes were used during the cine recordings. Vessel segments were analyzed in the least foreshortened projection that is, perpendicular to the incoming X-ray beam. To maximally dilate the vessel and to control vasomotion, the same amount of intracoronary nitrates - either nitroglycerin, 0.1 to 0.3 mg, or isosorbide dinitrate, 1 to 3 mg - was administered before and after stent implantation [24].

Definition of recoil

Elastic recoil immediately after stent implantation was defined by the difference between the mean diameter of the fully expanded balloon on which the stent was mounted and the mean diameter of the stented segment immediately after stent deployment (Figure 2). The time interval between balloon inflation and post stent cine recordings was usually less than 1 min. Advantage was taken of the unique radiopaque properties of the Wiktor stent to analyze whether there was compression or "late recoil" of the stent itself at follow-up. The mean diameter of the stent itself was measured without opacification of the vessel. Compression was calculated by comparing the mean stent diameter immediately after implantation and at follow-up (Figure 3).

A number of clinical (gender and age), angiographic (target vessel, vessel size, minimal luminal diameter before and after intervention, percent diameter stenosis, lesion length, plaque area, symmetry, curvature) and procedural variables (stent/artery ratio defined as the ratio of the mean diameter of the fully expanded balloon on which the stent was mounted and the interpolated reference diameter) were selected to study their relation with acute and chronic recoil.

Furthermore, the relation between acute recoil and late restenosis was analyzed. For this purpose recoil was not only defined by the definition described above, but also as the difference between the mean diameter of the final balloon diameter and the minimal luminal diameter post stenting. This was done because restenosis is clasically described by the loss in minimal luminal diameter (difference between the minimal luminal diameter post intervention and the minimal luminal diameter at follow-up). In addition, the incidence of restenosis was defined according to the categorical approach using the 0.72 mm and the 50% diameter stenosis criteria [19].

Statistical Analysis

Data are presented as mean ± standard deviation. The 95% confidence intervals were calculated with the statistical package CIA [25]. When using an univariate analysis, continuous variables were divided in three subgroups. Subgroups from categorical or discrete variables, or obtained from continuous variables were compared by means of the estimated differences and their 95% confidence interval.

To obtain independent predictors of recoil, variables were entered in a multiple linear regression analysis in which recoil was the dependent variable. Multiple linear regression analysis was performed to assess the relationship between the variables that were statistically significant at an 0.05 level in the univariate analysis (independent variables X_1) and recoil (dependent variable Y): $Y = \beta_0 + \beta_1 X_1$, were β_0 is the intercept and β_1 the regression coefficient. The standard criteria of the F statistic being or not being significant at a 0.10 level were used for inclusion and elimination in the model, respectively. Continuous variables were entered as such in the multivariate analysis, except for variables with two of three tertiles showing

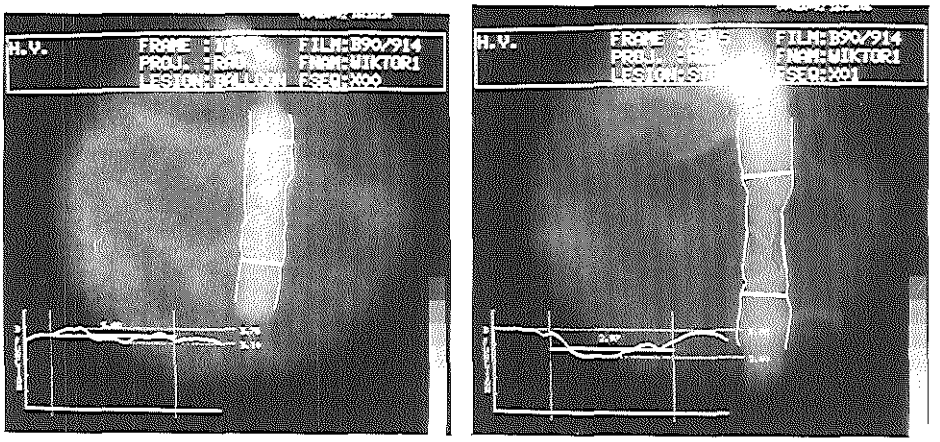

Fig. 2. Quantitative analysis with the computer-assisted Cardiovascular Angiography Analysis System using automated edge detection of the fully expanded balloon on which a Wiktor stent is mounted (left panel) and of the stented segment immediately after stent deployment (right panel). Superimposed on the videoimage is the diameter function curve. The mean diameter of the fully expanded balloon and of the stented segment amounts to 3.40 and 2.97 mm, respectively. This corresponds to an acute recoil of 0.43 mm or 12.6%, in this case.

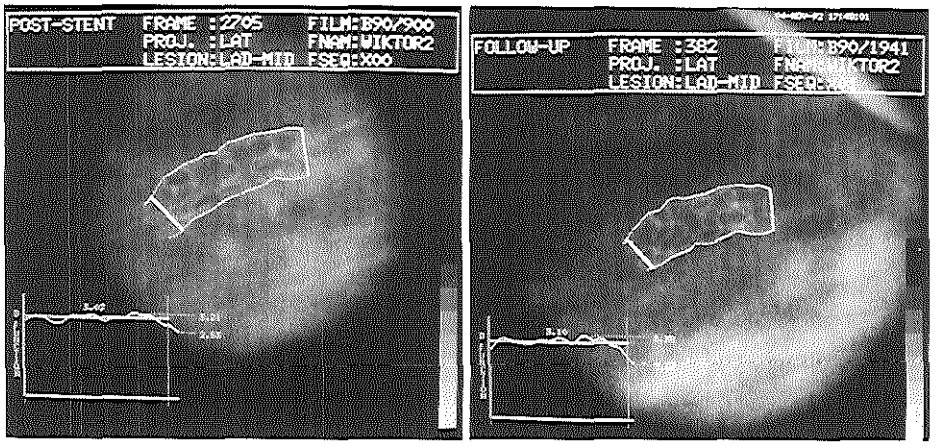

Fig. 3. Advantage was taken of the radiopaque properties of the stent for automated detection of its boundaries with the same system and methods illustrated in Figure 2 in order to define late compression or "late recoil" of the stent itself. In this case, the mean diameter of the stent immediately after implantation and at follow-up was 3.02 mm (left panel) and 3.10 mm (right panel), respectively. This suggests some increase in the diameter of the stent itself or negative "late recoil" of 0.08 mm or 2.6%.

approximately the same amount of recoil. These were entered as discrete variables [26]. Statistical analysis was carried out with a commercial statistical package (SAS - release 6.03).

RESULTS

Acute recoil

The mean diameter of the fully expanded balloon and stented segment was 3.05 ± 0.37 mm and 2.80 ± 0.44 mm, respectively (Table 2). Therefore acute recoil amounted to 0.25 ± 0.32 mm or 8.2%.

Table 2. Acute recoil following Wiktor stent implantation in native coronary arteries.

Mean diameter fully expanded balloon	Mean diameter stented segment	Δ	95% CI
3.05 ± 0.37 mm	2.80 ± 0.44 mm	0.25 ± 0.32 mm	(0.18; 0.33 mm)

All variables are expressed as mean ± SD; Δ difference; CI = confidence interval.

Univariate analysis identified sex, reference diameter, lesion length and stent/artery ratio as potential predictors of acute recoil (Table 3). After multivariate analysis, only sex and stent/artery ratio prevailed as the two independent predictors of acute recoil (Figure 4).

Table 3. Relation between clinical and angiographic variables and acute recoil. Results of the univariate analysis.

	n	Acute recoil (mm)	Δ	95% CI
Sex				
Male	68	0.29 ± 0.32	-	
Female	9	−0.01 ± 0.21	0.30	(0.08; 0.51)
Reference diameter (mm)*				
< 2.5	23	0.36 ± 0.30	-	
2.5 - 3.0	26	0.25 ± 0.28	0.11	(−0.05; 0.28)
≥ 3.0	26	0.15 ± 0.35	0.21	(0.03; 0.40)
Lesion length (mm)*				
< 11.5	25	0.35 ± 0.22	-	
11.5-13.5	25	0.19 ± 0.23	0.16	(0.04;0.29)
≥ 13.5	25	0.21 ± 0.45	0.14	(−0.05; 0.34)
Stent/artery ratio*				
< 1.00	23	0.07 ± 0.27	-	
1.00-1.13	25	0.24 ± 0.21	−0.17	(−0.31;0.03)
≥ 1.13	27	0.43 ± 0.36	−0.36	(−0.51;−0.12)

All parameters are expressed as mean ± SD; Δ difference
* of 2 patients the reference diameter, lesion length and stent/artery ratio was not known.

"Late recoil"

Late compression of the stent itself was not observed. On the contrary, the overall difference of the mean diameter of the stent itself immediately after implantation and at follow-up was −0.15 ± 0.33 mm, suggesting an overall increase in diameter of

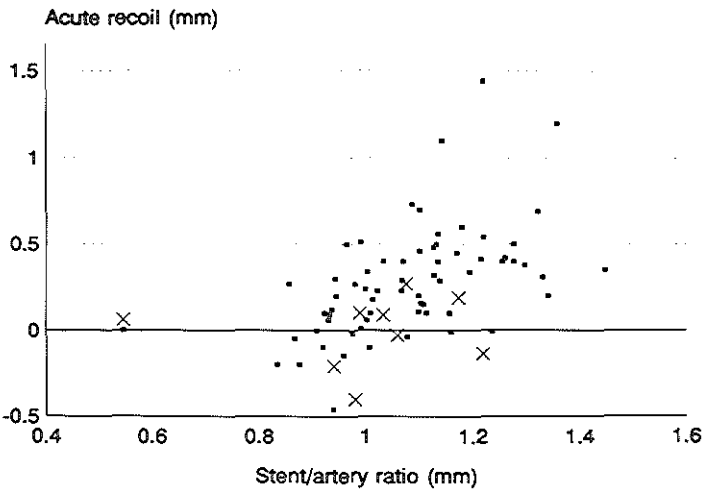

Fig. 4. Graphic display of the linear regression analysis studying the relation between acute recoil (Y-axis) and stent/artery ratio (X-axis). Stent oversizing is associated with significant more recoil. Dots denotes data of male patients, crosses denotes data of female patients.

5.0% (Table 4). Lesion length and mean diameter of the stent immediately after implantation were identified as predictors of late (negative) recoil in the univariate analysis. They were both retained as independent predictors in the multivariate analysis.

Table 4. "Late recoil" following Wiktor stent implantation in native coronary arteries.

Mean stent diameter immediately after implantation	Mean stent diameter at follow-up	Δ	95% CI
2.99 ± 0.41 mm	3.13 ± 0.37 mm	−0.15 ± 0.33 mm	−0.23; −0.07

All variables are expressed as mean ± SD; Δ difference; CI = confidence interval.

Relation between acute recoil and late restenosis

The incidence of restenosis was 43% and 27% according to the 0.72 mm and 50% diameter stenosis criteria, respectively (Table 5). Irrespective of the definition of acute recoil described above, there was no difference in the degree of recoil between patients with restenosis and those without angiographic restenosis (Table 5). When defining recoil as the difference between the mean final balloon diameter and the minimal luminal diameter post stenting, there was a trend towards a greater degree of recoil in patients without restenosis compared to those with restenosis according to the 0.72 mm criterion (0.70 ± 0.30 mm versus 0.58 ± 0.27 mm, respectively). Moreover, linear regression analysis disclosed a weak but *negative* correlation between acute recoil and loss in minimal luminal diameter ($r = 0.25$, slope: −0.55, $p = 0.04$). This trend towards an inverse relationship indicates that patients with more

Table 5. Relation between acute recoil (mm) and late restenosis

	Restenosis criterion					
	0.72 mm			50% Diameter Stenosis		
	Yes n = 33	No n = 44	Δ	Yes n = 21	No n = 54	Δ
Acute recoil 1	0.26 ± 0.26	0.25 ± 0.29	-0.02 ± 0.30	0.28 ± 0.42	0.24 ± 0.28	0.04 ± 0.32
95% CI	0.13 ; 0.39	0.16 ; 0.34	-0.14 ; 0.16	0.09 ; 0.47	0.16 ; 0.31	-0.12 ; 0.21
Acute recoil 2	0.58 ± 0.27	0.70 ± 0.30	-0.12 ± 0.29	0.63 ± 0.28	0.64 ± 0.31	-0.01 ± 0.30
95% CI	0.48 ; 0.67	0.61 ; 0.79	-0.25 ; 0.01	0.51 ; 0.76	0.56 ; 0.73	-0.16 ; 0.14

All values are expressed as mean ± SD. Acute recoil 1 = difference between mean final balloon diameter and mean diameter stented segment. Acute recoil 2 = difference between mean final balloon diameter and minimal luminal diameter post stent implantation. CI = confidence interval.

acute recoil tended to have a smaller loss in minimal luminal diameter. There was no relation between acute recoil and minimal luminal diameter at follow-up ($r = 0.0$, slope: -0.004, $p = 0.99$).

DISCUSSION

Although the precise mechanisms by which balloon angioplasty lead to luminal enlargement are still incompletely understood, there is now substantial evidence that in addition to plastic changes (e.g. plaque fracture, plaque compression, dissection), elastic changes (arterial wall stretching) occur which contribute to the dilatation process [1,8,9,11]. As a response to these elastic changes, elastic recoil after balloon angioplasty has been reported to be responsible for 32% to 47% loss of the theoretically achievable result which in turn may affect the long-term angiographic outcome [12-16]. Since it has been hypothesized that the Wiktor stent may offer less scaffolding properties in comparison with other stents, the behaviour of the vessel wall after Wiktor stent implantation and of the stent itself at follow-up were studied using quantitative coronary angiography.

In comparison with historical data on balloon angioplasty, only a limited amount of recoil (0.25 mm or 8.2%) was found [12-16]. This is in accordance with the degree of recoil observed after Wiktor stent implantation in non-atherogenic porcine coronary arteries [27]. These data, furthermore, compare favorably with those of other investigators assessing recoil after stent implantation in human coronary arteries [28-30]. In these studies recoil is reported to vary between 3.5 and 17.7% following Palmaz-Schatz stent implantation and between 20 and 22% following Gianturco-Roubin and Wiktor stent implantation [28-30]. The difference in recoil after Wiktor stent implantation between the study reported by Popma et al. (22%) and this study (8.2%) is most likely related to the difference in definitions used [29]. In the former, recoil was defined as the difference between the mean final balloon diameter and the minimal luminal diameter post stent implantation, while in this study recoil was

defined as the difference in the mean final balloon diameter and the mean diameter of the stented segment. This definition was chosen because we were interested in the behaviour of the vessel wall of the entire stented segment. Studies using either quantitative coronary angiography or a combination of a balloon catheter which houses a ultrasound transducer clearly demonstrated that balloon expansion is not uniform [11,16]. This has recently been observed in balloons on which a stent was mounted resulting in asymmetric stent expansion [31]. This suggets that one part of the dilated or stented segment may yield more easily to the mechanical force of the balloon than the other. Therefore, one segment may experience more stretch than the other and consequently more recoil [11,16,31]. It is noteworthy that, if recoil is defined according to the definitions proposed by other investigators, it amounts to 0.65 ± 0.30 mm or 21% which is strikingly similar to the degree of recoil after Wiktor stent implantation reported by Popma et al. [29].

In accordance with data on balloon angioplasty, stent oversizing was found to be the strongest independent predictor of acute recoil after Wiktor stent implantation [12,13,15]. Such a relation was also found by Leon et al. in patients who received a Palmaz-Schatz stent, but is at variance with the data of Haude et al. [28,30]. The discrepancy between the herein reported results and those of Leon et al., on one hand, and the results of Haude et al.on the other, is unclear. It may be related to differences in matching the stent size to the vessel size. In this study, most patients (52%) received a stent which was larger than the target vessel. The mean stent/artery ratio was 1.08 ± 0.15 (median 1.0, range 0.5 – 1.5). Haude et al. reported a mean stent/artery ratio of 0.96 [30].

In this study, female gender was found to predict acute recoil and contrasts with data on balloon angioplasty [12]. One should realize that this conclusion, although statistically significant, was based on data of only nine female patients. Its biological significance is unclear. It is unlikely that the response of the coronary artery to mechanical energy is different between males and females.

Another interesting observation is that there was no late compression of the Wiktor stent itself at follow-up. On the contrary, overall there was an negative "late recoil". Although the principle of balloon-expandable stent implantation is based on the plastic deformation of the stent beyond its elastic properties, it can be speculated that chronic damage to the vessel wall, as observed after Wiktor stent implantation in porcine coronary arteries, may offset opposing forces of the vessel wall permitting further stent expansion [32]. Whether this damage is due to movement of the rigid implant within the vessel wall or due to local weakening of the media underneath the stent wires reflecting reparative processess remains to be elucidated.

The absence of late recoil in addition to the evidence that acute recoil does not contribute to late luminal renarrowing or restenosis (Table 5) indicate that late loss in minimal luminal diameter is due to tissue ingrowth into the lumen of the stented segment. This is in accordance with pathologic observations disclosing that the predominant cause of restenosis following balloon angioplasty or stent implantation is extensive neointimal thickening due to smooth muscle cell proliferation at the dilated or stented site [27,32,33-37].

Contrast angiography to assess recoil

Elastic recoil implies an active component of the vessel wall which, for obvious reasons, cannot be directly studied with contrast angiography. This technique, which was used in almost all other studies on recoil after balloon angioplasty and intracoronary stenting, at best describes the luminal changes but does not provide any insight into the underlying pathological mechanisms [12-16,26-28]. In addition to recoil, other mechanisms such as vasoconstriction, platelet deposition, nonocclusive mural thrombus formation and subintimal hemorrhage have been proposed to cause early luminal narrowing [12]. Although attractive from a theoretical point of view, they are unlikely to explain these changes. Vasomotion was controlled by intracoronary injection of nitrates before each cine run which effectively reverses vasoconstriction [24]. Given the intrinsic thrombogenicity of the intracoronary stent, platelet deposition and mural thrombus formation cannot be ruled out. It is nevertheless unlikely to be the cause of the reduced luminal diameter taking into account the time interval between stent implantation and control angiography. The same holds for intramural hemorrhage. Stents have been shown to effectively prevent vessel collapse in such circumstances [38].

Obviously, the ideal method to study the nature of vessel wall behaviour during coronary intervention is the use of intravascular ultrasound and preferably the use of a combination of a balloon-ultrasound imaging catheter described by Isner et al. [11]. This method offers the unique opportunity to continuously assess vessel wall changes before, after and above all during balloon inflation. The preliminary results of Görge et al. who used conventional intravascular ultrasound techniques suggests that recoil indeed exists after stent implantation [39].

Automated edge detection to quantify recoil

To quantify recoil, one has to rely on cardiac imaging techniques with known precision, accurracy, inter- and intraobserver variablity. The computer-assisted Cardiovascular Angiography Analysis System used in this study has been extensively validated in both the clinical as well as in the experimental setting following balloon angioplasty and stent implantation [40-43]. Despite the radiopacity of the Wiktor stent, it is our experience that in case of adequate filling of the balloon or coronary artery with contrast medium at a concentration of 100%, the radiopaque stent wires do not interfere with the automated contour detection [19,22,43]. This is explained by the high iodine content in the coronary artery in such circumstances which absorps most of the incoming X-rays. This is, furthermore, in accordance with phantom studies from our laboratory which disclosed that automated contour detection, in contrast to videodensitometry, adequately identified luminal contours of a Wiktor stent-containing plexiglass phantom [43]. With respect to intravascular ultrasound, one should acknowlegde that notwithstanding its value and importance, the delineation of the arterial boundaries is subjective and therefore may not always be precise.

CONCLUSIONS

The Wiktor stent effectively scaffolds the instrumented vessel. Although statistically significant, only a minimal amount of acute recoil was noted which did not contribute to late luminal renarrowing or restenosis. In addition, no late compression of the stent itself was observed. Therefore, tissue ingrowth into the lumen of the stented segment is the main cause of late luminal renarrowing after stent implantation.

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Part 2

Clinical aspects

CHAPTER 6

WIKTOR STENT IMPLANTATION IN PATIENTS WITH RESTENOSIS FOLLOWING BALLOON ANGIOPLASTY OF A NATIVE CORONARY ARTERY

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Wiktor Stent Implantation in Patients with Restenosis Following Balloon Angioplasty of a Native Coronary Artery

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Intracoronary stenting has been introduced as an adjunct to balloon angioplasty aimed at overcoming its limitations, namely acute vessel closure and late restenosis. This study reports the first experience with the Wiktor™ stent implanted in the first 50 consecutive patients. All patients had restenosis of a native coronary artery lesion after prior balloon angioplasty. The target coronary artery was the left anterior descending artery in 26 patients, the circumflex artery in 7 patients and the right coronary artery in 17 patients. The implantation success rate was 98% (49 of 50 patients). There were no procedural deaths. Acute or subacute thrombotic stent occlusion occurred in 5 patients (10%). All 5 patients sustained a nonfatal acute myocardial infarction. Four of these patients underwent recanalization by means of balloon angioplasty; the remaining patient was referred for bypass surgery. A major bleeding complication occurred in 11 patients (22%): groin bleeding necessitating blood transfusion in 6, gastrointestinal bleeding in 3 and hematuria in 2. Repeat angiography was performed at a mean of 5.6 ± 1.1 months in all but 1 patient undergoing implantation. Restenosis, defined by a reduction of ≥0.72 mm in the minimal luminal diameter or a change in diameter stenosis from < to ≥50%, occurred in 20 (45%) and 13 (29%) patients, respectively. In this first experience, the easiness and high technical success rate of Wiktor stent implantation are overshadowed by a high incidence of subacute stent occlusion and bleeding complications. Although direct comparison with balloon angioplasty regarding the incidence of subsequent restenosis rate is not possible, the experience reported in this study compares favorably with data reported in other published reports.

(Am J Cardiol 1992;69:598–602)

Percutaneous transluminal coronary balloon angioplasty (PTCA) has established its role as a nonsurgical revascularization procedure in selected patients with obstructive coronary artery disease. Gained operator experience and improved catheter technology has resulted in a high immediate success rate and a low incidence of complications.[1] These favorable initial results are compromised by the unpredictable problem of late restenosis, occurring in 20 to 40% of the patients after successful PTCA.[2–5] Furthermore, there is some evidence that the recurrence of subsequent restenosis after repeat PTCA increases with the number of repeat interventions.[6–9] Intracoronary stents are one of the new technologies that (along with pharmacologic interventions, atherectomy and laser techniques) have entered clinical testing to address this problem.[10] Recently, the first experience with the self-expandable Wallstent® and the balloon expandable Palmaz-Schatz® stent have been reported.[11,12] The stent used in this study is the Medtronic Wiktor™ stent which, in contrast to the Wallstent and the Palmaz-Schatz stent, is not a mesh-made stainless steel device but a coil-like prosthesis made of a single loose interdigitating tantalum wire formed into a sinusoidal wave and configured as a helix. This loose configuration may offer less scaffolding properties compared with the other 2 stents. Therefore, the purpose of this study was to assess the immediate and long-term clinical and angiographic results following Wiktor stent implantation in the first 50 consecutive patients with restenosis following balloon angioplasty of a native coronary artery lesion.

METHODS

Patients: The study group consisted of the first 50 consecutive patients in whom a single Wiktor stent implantation was attempted (Table I). All patients had recurrence of angina with objective evidence of ischemia due to restenosis of a native coronary artery lesion following PTCA. A first restenosis was documented in 33 patients, a second restenosis in 13 patients and a third in 4 patients. The dilated and stented coronary artery was the left anterior descending artery in 26 patients (52%),

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the circumflex artery in 7 patients (14%) and the right coronary artery in 17 patients (34%). A written informed consent was required for every patient. The study protocol was approved by the ethics committee of the individual hospitals. The stents used in this study are shown in Figures 1 and 2. They are described in detail elsewhere as well as the drug protocol associated with stent implantation.[11,13] The angiograms were analyzed using automated edge-detection as previously described.[14,15]

End points: Primary clinical end points were death, myocardial infarction, bypass surgery or repeat intervention and bleeding complications. All deaths were considered cardiac, unless an unequivocal noncardiac cause could be established. The primary angiographic end point was the change in minimal luminal diameter at the dilated and stented segment at 6 months relative to the baseline. If a revascularization procedure involving the stented segment had been performed before 6 months repeat angiography, the last angiogram before this intervention was used to obtain follow-up values, irrespective of the timing of repeat PTCA (hours, days or weeks). The secondary angiographic end point was the incidence of restenosis defined according to the following criteria: First, a continuous approach was used in which restenosis was defined by a reduction of ≥0.72 mm in the minimal luminal diameter at follow-up. This change in minimal luminal diameter has been found to be a reliable indicator of angiographic progression of vessel narrowing. This value takes into account the limitations of coronary angiographic measurements and represents twice the long-term variability of repeat measurements of a coronary artery obstruction with the Cardiovascular Angiographic Analysis System.[15] Second, a categorical approach was used in which an increase in diameter stenosis of <50% immediately after stent implantation to ≥50% at follow-up was used as a cutoff point to define restenosis. This criterion was selected since common clinical practice has continued to express lesion severity as a percentage of stenosis.

Statistics: Values obtained by quantitative angiographic analysis are expressed as mean ± SD. The means for each angiographic variable before PTCA, after PTCA, immediately after stent implantation and at follow-up were compared by analysis of variance. If significant differences were found, 2-tailed *t* tests were applied to paired data. A statistical probability of <0.05 was considered significant. In the patient with the missing follow-up angiogram and no clinical evidence of restenosis, imputation of the minimal luminal diameter at follow-up was performed: the minimal luminal diameter at follow-up of this patient was calculated by subtracting the mean change of the minimal luminal diameter of the entire study population from the value of the minimal luminal diameter immediately after stent implantation of this particular patient.

TABLE 1 Clinical Characteristics

No. of patients	50
Age (mean ± SD, yrs)	55 ± 9
Men	44
Functional class*	
I	10
II	6
III	14
IV	20
Systemic hypertension	7
Cholesterol > 200 mg %	7
Cigarette smokers	17
Diabetes mellitus†	6

*According to Canadian Cardiovascular Society.
†All non-insulin-dependent.

RESULTS

Clinical results: The implantation success rate was 98% (49 of 50 attempted implants). In 1 patient, the stent could not be delivered at the target site due to the inability to cross a tortuous proximal right coronary artery. There were no procedural related deaths. However, subacute thrombotic stent occlusion occurred in 5 patients (10%) while still in the hospital. The occurrence to this thrombotic event with respect to the implantation was as follows: day 0 = 1 patient, day 1 = 1

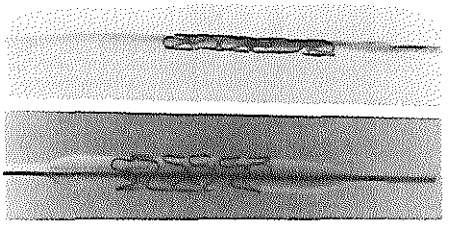

FIGURE 1. Medtronic Wiktor stent mounted on a conventional polyethylene balloon when deflated *(top panel)* and inflated *(bottom panel).*

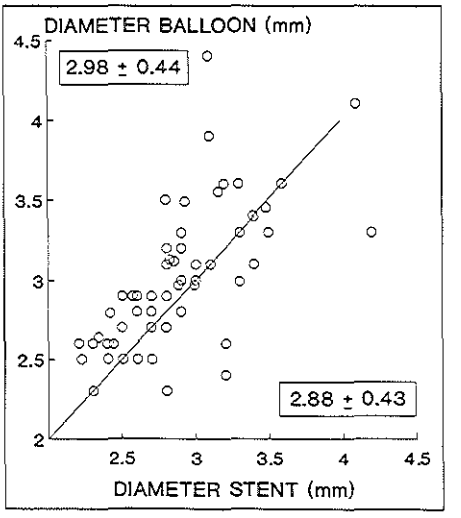

FIGURE 2. Difference between the mean diameter of the balloon when fully inflated and stented segment immediately after implantation.

TABLE II Changes in Minimal Luminal Diameter After Wiktor Stent Implantation

	Before PTCA	After PTCA	After Stent Implantation	At Follow-Up: All Pts. (n = 49)	At Follow-Up: Pts. Without Subacute Occlusion (n = 44)
Minimal luminal diameter (mm)	1.09 ± 0.26	1.80 ± 0.32	2.45 ± 0.35	1.59 ± 0.79	1.78 ± 0.60
Diameter stenosis (%)	61 ± 9	34 ± 11	18 ± 7	45 ± 25	39 ± 18
	p < 0.00001	p < 0.001	p < 0.00001		
			p < 0.00001		

All parameters are expressed as mean ± SD.
PTCA = percutaneous transluminal coronary angioplasty.

patient, day 4 = 1 patient, and day 5 = 2 patients. Four patients underwent recanalization by means of conventional balloon angioplasty. In 1 of these patients adjunctive thrombolytic therapy was used. In the remaining patient, repeat PTCA was not attempted because retrospective analysis of the implantation angiogram revealed incomplete stent expansion. This patient was referred for emergency bypass surgery. All 5 patients sustained a nonfatal acute myocardial infarction (mean ± SD, creatine phosphokinase 1,797 ± 1,849 U/liter). A major bleeding complication occurred in 11 patients (22%): 6 patients sustained a groin hematoma necessitating blood transfusion, 3 patients had a gastrointestinal bleeding (2 duodenal ulcers, 1 intestinal polyps) and 2 patients had hematuria. One patient had an infected pharyngeal hematoma caused by acenocoumarol therapy at 3 months after implant.

During follow-up, 1 patient died 3 months after stent implantation following prostate surgery. This patient had a history of bypass surgery, mitral valve replacement and multiple PTCA's. Because of severe disabling heart failure, he was screened for heart transplantation. During this period, a prostate adenoma was found and surgically removed. The second day after surgery, he died because of heart failure. Although necropsy was not performed, death was not considered stent-related because there was no clinical evidence of restenosis. No patient sustained an acute myocardial infarction. Three patients (6%) underwent bypass surgery (2 patients 3.5 months and 1 patient 6 months after the stent implantation). There was a significant improvement in functional class at 6-month follow-up. Before stent implantation, 10 patients were in class I, 6 in class II, 14 in class III and 20 in class IV, according to the Canadian Cardiovascular Society. At follow-up, 34 patients were in class I, 9 in class II, 4 in class III and 3 in class IV.

Angiographic results: Wiktor stent implantation resulted in a further significant increase in minimal luminal diameter, from 1.80 ± 0.32 mm immediately following balloon angioplasty to 2.45 ± 0.35 mm immediately after stent implantation. This was associated with a reduction in diameter stenosis from 34 ± 11 to 18 ± 7% (Table II). There was no change in the reference diameter before and after PTCA (2.81 ± 0.48 and 2.80 ± 0.48 mm, respectively, p = not significant). However, there was a significant increase after stent implantation (2.98 ± 0.42 mm, p <0.00001), which was confirmed at follow-up (2.91 ± 0.55 mm). In most patients the measured diameter of the balloon when fully inflated was higher than the measured diameter of the stent (Figure 2). During maximal inflation the mean diameter of the balloon for the total study group was 2.98 ± 0.44 mm. The mean diameter of the stented segment immediately after implantation was 2.88 ± 0.43 mm. This implies a recoil of 0.10 ± 0.36 mm (p <0.03).

Repeat angiography was performed in all patients with successful stent implantation (49 patients), except in 1, who died 3 months after stent implantation follow-

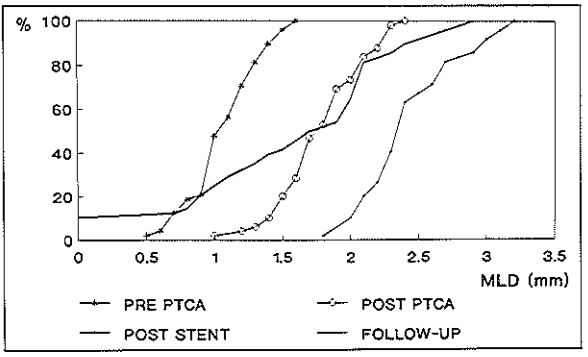

FIGURE 3. Cumulative distribution of the minimal luminal diameter (MLD) of the entire study population and its changes immediately after balloon angioplasty, stent implantation and at follow-up. PTCA = percutaneous transluminal coronary angioplasty.

ing prostate surgery. There was no clinical evidence of restenosis in this patient. The mean time interval between stent implantation and control study was 5.6 ± 1.1 months. Overall, the minimal luminal diameter was found to have decreased from 2.45 ± 0.35 to 1.59 ± 0.79 mm ($p < 0.00001$). The percentage of stenosis had increased from 18 ± 7 to 45 ± 25% ($p < 0.0001$, Table II). When only patients without clinical evidence of subacute vessel closure during hospital stay (44 patients) were included, the minimal luminal diameter and percentage of stenosis were 1.78 ± 0.60 mm and 39 ± 18%, respectively (Table II). Figure 3 displays the cumulative distribution of the minimal luminal diameter and its changes (immediately after balloon angioplasty and stent implantation and at follow-up). The additional increase in minimal luminal diameter immediately after stent implantation is lost at follow-up.

The incidence of restenosis depended on the definition used. When a change of ≥0.72 mm in minimal luminal diameter was used as the criterion, restenosis was observed within the stent in 19 patients (43%) and in the segment immediately distal to the stent in 1 (2%) of the 44 patients without clinical evidence of subacute stent occlusion during hospital stay. Of these 44 patients, the percentage of stenosis at follow-up had increased to ≥50% within the stent in 12 (27%) and in the segment distal to the stent in 1 (2%). Therefore, the total restenosis rate was 45% according to the 0.72 mm criterion and 29% according to the 50% diameter stenosis criterion (Figure 4).

DISCUSSION

Clinical results: Intracoronary stents are currently being tested in clinical practice to reduce the incidence of acute vessel occlusion and restenosis following balloon angioplasty. Several stents are available, each with its own specific design, composition and physicochemical behavior once implanted. Implanting foreign body material implies an increased risk for acute thrombosis. Therefore, a stringent anticoagulation protocol is mandatory. Despite the protocol previously described, a thrombotic subacute stent occlusion occurred in 5 patients (10%). Three of these patients did not receive dextran and 1 patient was not properly treated with acenocoumarol. Of the 44 patients without clinical evidence of subacute stent occlusion during hospital stay, only 6 (14%) did not receive dextran. Unfortunately, since central assessment of anticoagulation was not performed, the exact role of the failure of anticoagulation with respect to subacute thrombotic stent occlusion cannot be elucidated. Although it is tempting to speculate that suboptimal anticoagulation may be the main cause of stent occlusion, other pathophysiologic mechanisms also may be involved. Before stent implantation, balloon angioplasty is performed to facilitate stent delivery. The disruptive action of the balloon may cause intimal dissection, which in turn may be the primary cause of an ensuing thrombotic event. Furthermore, patients' related factors such as acute ischemic syndromes, procedure-related factors such as technical difficult stent implantation and angiographic related factors such as small vessel size and total occlusion may predispose to thrombotic stent occlusion. In this study group, no difference in vessel size was seen in patients with and without subacute stent occlusion (reference diameter 2.8 ± 0.4 and 2.8 ± 0.5 mm, respectively (p = not significant). The reported subacute stent occlusion rate compares very favorably with the initial Wallstent experience (20% in 105 patients), but is similar to the subacute occlusion rate following the extended Wallstent experience (12% in an additional 160 patients).[11,16] However, it contrasts sharply with the incidence of 0.6% following Palmaz-Schatz stent implantation.[12] True comparison is not possible because the studies differ in methods for patient selection, indication for stent implantation and type of vessel stented. Furthermore, the very low incidence of 0.6% reported by Schatz, has not been confirmed by a recent study, using the same device.[17] In this latter study, an incidence of 16% is reported. Probably, the incidence of subacute stent occlusion may be reduced by a more detailed coagulation monitoring. Indeed, recent work indicates that measurement of prothrombin fragment 1 + 2 and its changes after stent implantation may be predictive for subacute thrombotic stent occlusion.[18]

Another matter of concern is the risk of bleeding, inherently associated with aggressive anticoagulation. The incidence of bleeding is negligible after PTCA but is substantial when a combination of intravenous and

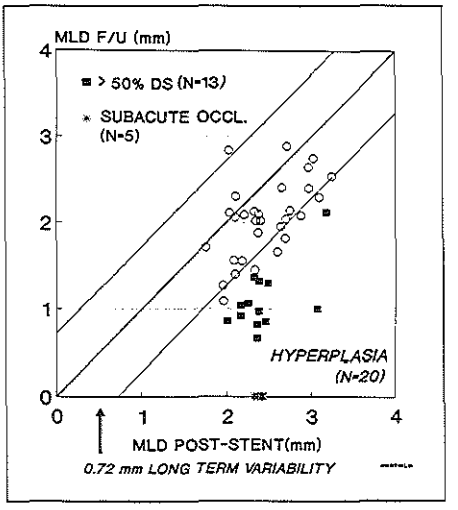

FIGURE 4. Changes in the minimal luminal diameter (MLD) at follow-up (F/U) after Wiktor stent implantation in native coronary arteries. The diameter of each segment immediately after stent implantation is plotted against the diameter at follow-up. The lines on each side of the line of identity *(diagonal)* represent twice the variability (95% confidence interval) of duplicate measurements (a change of ≥0.72 mm). Of the 49 patients, 5 (10%) sustained a subacute stent occlusion (OCCL.) (X-axis). In the remaining 44 patients, restenosis was observed in 20 patients (45%) according to the 0.72 mm criterion and in 13 patients (29%) according to the 50% diameter stenosis (DS) criterion.

oral anticoagulant drugs are administered.[12] The most serious bleeding complication is intracranial hemorrhage, which occurred in 1 of 174 patients following Palmaz-Schatz stent implantation and in 3 of 265 patients following Wallstent implantation.[12,16] Another aspect to be considered regarding anticoagulation is the longer period of hospitalization, which in turn increases the overall costs of the procedure.[19] In this study, the hospital stay was (mean ± SD) 11.8 ± 7.4 days for the entire study population.

Angiographic results: The smaller mean diameter of the stented segment (2.88 ± 0.43 mm) compared with the measured diameter of the fully expanded balloon (2.98 ± 0.44 mm) suggests some recoil of the stented segment. This minimal recoil appears to be a true phenomenon since the accuracy and the precision of the quantitative coronary angiography system used in this study is −30 and 90 μ, respectively.[15] Furthermore, recoil has also been observed, although to a larger extent, after Wiktor stent implantation in Yorkshire pigs.[20] The more pronounced recoil (10%) observed in the animal model compared with recoil observed in this study (3%) may be explained by the fact that in the former animal study the stent was implanted in normal coronary arteries. All these angiographic data indicate that in contrast to balloon angioplasty, where recoil amounting to 50% has been documented, the Wiktor stent appropriately scaffolds the vessel.[21]

Restenosis and recurrence of restenosis remains the major limitation of (repeat) PTCA. Whether intracoronary stents can address this issue appropriately is still unknown. There are some encouraging data from preliminary reports.[22,23] However, firm conclusions cannot be drawn, since these data stem from nonrandomized studies in which single and multiple stent implantations have been performed in both native coronary arteries and venous bypass grafts have been performed in patients with either acute ischemic syndromes or stable angina for a variety of indications (primary stent implantation, restenosis, bail out). Patients undergoing repeat PTCA appear to be at a higher risk for recurrence of restenosis after repeat intervention. The angiographic documented restenosis rate increases from 34% after a second dilatation to 40% after a fourth dilatation.[6,9] This is probably an underestimation of the actual incidence owing to incomplete angiographic follow-up. Repeat angiography is mandatory in all patients, even in patients free of angina at follow-up since approximately 25% of the patients with restenosis are asymptomatic.[24] Taking into account the limitations of these nonrandomized observational studies, as is done in this study, the incidence of 29% restenosis using the 50% diameter stenosis criterion compares favorably with data from those former studies. Indeed, randomized studies are needed to define the exact role of intracoronary stenting in the prevention of (recurrent) restenosis.

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CHAPTER 7

ANGIOGRAPHIC PREDICTORS OF RECURRENCE OF RESTENOSIS FOLLOWING WIKTOR STENT IMPLANTATION IN NATIVE CORONARY ARTERIES

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INTRODUCTION

Percutaneous transluminal coronary balloon angioplasty is now widely accepted as a safe and effective treatment in selected patients with obstructive coronary artery disease [1]. However, acute vessel closure and late restenosis are inherent to balloon angioplasty and continue to compromise its efficacy [2,3]. Although the exact pathophysiologic mechanism(s) and factors responsible for restenosis are largely unknown, some clinical and angiographic variables have been identified as potential risk factors [4]. There is, furthermore, some evidence that repeat angioplasty of a previously dilated lesion in a native coronary artery is associated with a higher incidence of restenosis [5–9]. The Wiktor stent has been used to treat such patients. The incidence of recurrence of restenosis following Wiktor stent implantation in the first 50 consecutive patients has recently been published [10]. The subject of this paper is to try to identify angiographic predictors of recurrence of restenosis following Wiktor stent implantation. This may not only have important clinical consequences but may also broaden our understanding of the pathophysiology of restenosis.

METHODS

Patients

Between January 1990 and May 1992, Wiktor stent implantation was attempted in 193 patients because of recurrence of angina due to restenosis of a native coronary artery lesion following prior balloon angioplasty. The study population herein reported consists of the 91 out of the 109 consecutive patients with successful stent implantation without clinical evidence of thrombotic stent occlusion during hospital stay and in whom the scheduled follow-up angiography was completed at (mean ±

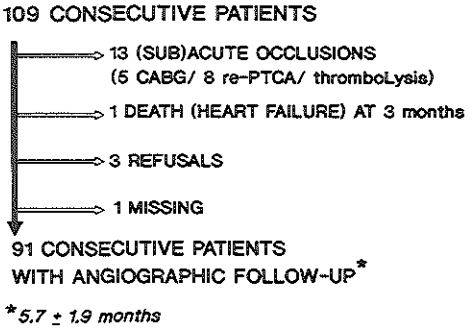

Fig. 1. Flow diagram showing angiographic follow-up in the first 109 consecutive patients. In hospital acute or subacute occlusion occurred in 13 patients (12%). Of the remaining 96 patients who were discharged without clinical evidence of (sub)acute occlusion, 91 underwent repeat angiography at (mean ± sd) 5.7 ± 1.9 months after stent implantation.

sd) 5.7 ± 1.9 months (Figure 1).

Eighty-one patients were male (89%), the age (mean ± sd) was 58 ± 11 years. A first restenosis was documented in 50 patients (55%), a second in 32 patients (35%), a third in 8 patients (9%) and a fourth in one other patient (1%). In all patients, a single Wiktor stent was implanted except in one, in whom a single stent was implanted in both the left anterior descending and the right coronary artery. The target vessel was the left anterior descending artery in 48 patients (52%), the right coronary artery in 31 patients (34%), the left circumflex in 12 patients (13%). In another patient (1%), a single Wiktor stent was implanted in the left main stem. The size of the stent used (mean ± sd) was 3.4 ± 0.4 mm; 3.0 mm device in 38 patients (41%), 3.5 mm device in 40 patients (44%) and a 4.0 mm device in 14 patients (15%). The stent is described in detail elsewhere as well as the associated drug protocol [11].

Angiographic variables and definition of restenosis

Based on the quantitative angiographic data, multiple variables were identified and recorded for each lesion. These variables were of a priori clinical interest on the basis of previously published reports on balloon angioplasty and intracoronary stenting and of a more fundamental scientific interest based on experimental studies on stent implantation in animals [4,12-16]. The following continuous variables were selected: obstruction diameter before and immediately after stent implantation, baseline reference diameter and diameter stenosis, length of target lesion, plaque area and the relative gain defined by the increase in minimal luminal diameter immediately following stent implantation normalized to the vessel size. In addition to these continuous variables, one discrete variable (Left anterior descending artery) was selected. All coronary angiograms were analyzed with the computer assisted Cardiovascular Angiography Analysis System. Its principles and definitions of angiographic variables have been described in a previous study on Wiktor stent implantation [11]. Since the primary objective of this study was to identify angiographic variables predicting restenosis, the process of restenosis was dichotomized and defined according to the 0.72 mm and 50% diameter stenosis criteria [17].

Statistics

A relative risk analysis was performed for the aforementioned angiographic variables. To avoid an arbitrary subdivision of data in the continuous variables, the median value was chosen as cut off point. The selection of this value as cut off point has the advantage of being consistent for all values and thus avoids any bias in the selection of subgroups that might be undertaken to emphasize a particular point. All values are expressed as means ± SD. The risk for restenosis for each parameter according to the 0.72 mm and 50% diameter stenosis criteria was determined by using an univariate analysis and is expressed as odds ratio with corresponding 95% confidence interval. An odds ratio of 1.0 for a particular variable implies that the presence of that variable poses no additional risk for restenosis, an odds ratio greater than 1.0 or less

than 1.0 implies additional or reduction in risk. Furthermore, since experimental animal data indicate that there is a relation between the severity of vessel wall injury and the extent of subsequent neointimal thickening, the relation between relative gain (as index of vessel wall injury) and relative loss (as index of neointimal thickening) was studied using a regression analysis. The relative gain is defined above. The relative loss is the difference between the minimal luminal diameter immediately after stent implantation and at follow-up normalized to the vessel size.

RESULTS

Incidence of restenosis

The changes in stenosis geometry are summarized in Table 1. The incidence of restenosis was 44% (40/91 patients) according to the 0.72 mm criterion and 30% (27/91 patients) according to the 50% diameter stenosis criterion. When the stent is used as a unit, the incidence of restenosis was 45% (41 out of the 92 stents) and 29% (27 out of the 92 stents), respectively (Figure 2).

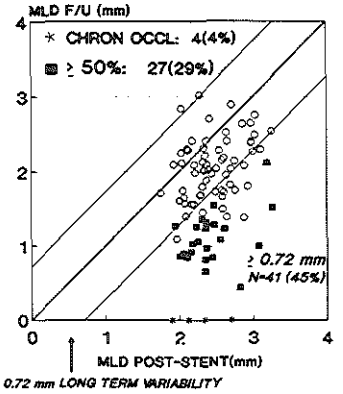

Fig. 2. Changes in the minimal luminal diameter at follow-up following Wiktor stent implantation. The diameter of each segment immediately after stent implantation is plotted against the diameter at follow-up. The lines on each side of the line of identity (diagonal) represent twice the variability (95% confidence interval) of duplicate measurements (a change ≥ 0.72 mm). A significant decrease in minimal luminal diameter according to the 0.72 mm criterion was found in 41 out of the 92 stents implanted (45%). The incidence of restenosis according to the 50% diameter stenosis criterion was 29% (27 out of the 92 stents). Of these, 4 stents were completely occluded at follow-up, as shown on the X-axis.

Angiographic predictors

The relative risk and 95% confidence intervals for each variable using either of the two criteria are shown in Table 2. The only statistically significant predictor of

Table 1. Findings at quantitative angiography following wiktor stent implantation (n = 91 patients).

	Before PTCA	After PTCA	After Stent Implantation	At follow-up
Reference diameter (mm)	2.85 ± 0.49	2.80 ± 0.48	3.02 ± 0.42	2.98 ± 0.47
Minimal luminal diameter (mm)	1.13 ± 0.36	1.77 ± 0.36	2.45 ± 0.34	1.73 ± 0.67
Diameter stenosis (%)	60 ± 10	35 ± 11	19 ± 7	42 ± 21

All parameters are expressed as mean ± SD. PTCA = percutaneous transluminal coronary angioplasty. All changes were higly significant ($p < 0.00001$), except for the reference diameter; only the difference in reference diameter after stent implantation and after PTCA was statistically significant ($p < 0.001$).

Table 2. Angiographic predictors of restenosis following Wiktor stent implantation.

Angiographic variable		Restenosis criteria	
		0.72 mm criterion	50% diameter stenosis criterion
Relative gain (mm)	≥ 0.48	2.7 (1.1 - 6.4)	1.1 (0.4 - 2.7)
Minimal Luminal Diameter post (mm)	≥ 2.38	1.8 (0.8 - 4.2)	0.5 (0.2 - 1.4)
Minimal Luminal Diameter pre (mm)	≤ 1.08	1.6 (0.7 - 3.7)	2.7 (1.0 - 7.2)
Lesion length (mm)	≥ 6.48	1.4 (0.6 - 3.2)	1.8 (0.7 - 4.6)
Reference Diameter pre (mm)	≤ 2.77	1.3 (0.6 - 2.9)	1.4 (0.5 - 3.4)
Plaque area (mm^2)	≥ 7.47	1.3 (0.6 - 2.9)	1.1 (0.4 - 2.7)
Diameter stenosis pre (%)	≥ 61	1.0 (0.4 - 2.3)	1.3 (0.5 - 3.2)
Left anterior descending artery		0.7 (0.3 - 1.7)	1.1 (0.5 - 2.8)

recurrence of restenosis according to the 0.72 mm criterion was the relative gain when it exceeded 0.48 (odds ratio 2.7, 95% confidence interval 1.1 - 6.4). Related to the relative gain is the obstruction diameter before and after stent implantation. Although their odds ratio exceeds 1.0, their corresponding 95% confidence interval precludes any firm conclusion. The same holds for lesion length, reference diameter and plaque area. The left anterior descending artery was not identified as a risk factor for recurrence of restenosis. When using the 50% diameter stenosis criterion, no angiographic predictor of restenosis was evident.

The number of balloon angioplasty performed before stent implantation did not influence the risk for subsequent restenosis after stenting. The odds for restenosis in case of stent implantation for a second, third or fourth restenosis compared with stent implantation for a first restenosis was 0.8 (95% confidence interval 0.4 - 1.8) according to the 0.72 mm criterion and was 1.5 (95% confidence 0.6 - 3.7) according to the 50% diameter stenosis criterion.

Regression analysis

The relation between relative gain, as index of vessel wall injury, and relative loss, as index of late neo-intimal hyperplasia as vessel wall response to injury, is shown in Figure 3. A Pearson product-moment correlation coefficient of 0.38 was found ($p < 0.001$, slope 0.61, intercept −0.06).

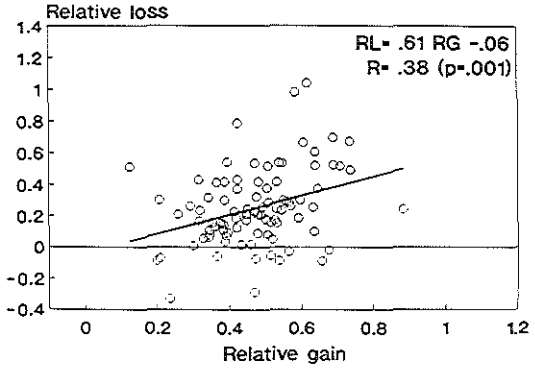

Fig. 3. Graphic display of the relation between the relative gain (RG = increase in minimal luminal diameter immediately after stent implantation normalized to the vessel wall) and relative loss (RL = decrease in minimal luminal diameter at follow-up normalized to the vessel wall). A positive linear relation was found with a correlation coefficient of 0.38 ($p < 0.001$) with a slope of 0.61 and an intercept on the Y-axis of −0.06.

DISCUSSION

The primary objective of this study was not the determination of the incidence of recurrent restenosis following Wiktor stent implantation in patients with restenosis after previous balloon angioplasty. However, it is noteworthy that the incidence of post-stent restenosis reported here in the 91 patients is identical to the incidence of recurrent restenosis in the first 50 consecutive patients [10]. Detailed analysis of a subgroup of 74 patients revealed that there was no late compression of the stent itself. Therefore, late loss or restenosis was due to ingrowth of tissue into the lumen of the stented segment [18].

The lack of randomized studies precludes any conclusion as to whether stent implantation in this subset of patients will reduce the incidence of subsequent restenosis. Moreover, the exact incidence of recurrent restenosis after repeat balloon angioplasty is not known. There is some evidence that it increases with the number of repeat angioplasty. A second restenosis has been reported to occur in 25 and 34%, but amounts to 39 and 40% following a third or fourth angioplasty, respectively [5-9]. These data should be interpreted with caution considering the difference between the study populations, the difference in definition of restenosis and in the time and completeness of follow-up angiography. In the present study in which stents were implanted because of restenosis, the risk for recurrent restenosis after stenting did not differ between patients with a first restenosis and patients with a second, third or fourth restenosis. Two other studies failed to show a statistically siginificant difference in the restenosis rate for primary or de novo lesions compared with lesions who had undergone previous balloon angioplasty [12,13]. However, subgroup analysis of those patients in whom a single Palmaz-Schatz stent was implanted showed a restenosis rate of 13% compared with 36% for patients with previous restenosis [13].

The pathogenesis of restenosis remains incompletely understood. Histologic data have shown that any injury to the vessel wall, whatever its nature, will invariably be associated with neointimal hyperplasia as a non-specific tissue response leading to restenosis when excessive [14,19-23]. It is both of scientific and utmost clinical importance to know and understand its pathogenesis but also to know the factors controlling the extent of the vessel wall response following injury. Experimental animal studies, postmortem pathologic observations in humans and angiographic studies have shown that the extent of neointimal hyperplasia is proportional to the degree of injury applied to the vessel wall (Figure 4) [14-16,24]. This is in accord with earlier work in the porcine model, describing a relation between the degree of injury and early platelet deposition [25,26]. In the present study, the relative gain was used as angiographic correlate of vessel wall injury. This parameter was found to be the only statistically significant predictor of recurrence of restenosis when using the 0.72 mm criterion. The drawback of the latter is, first, that the process of restenosis is dichotomized (present/not present) and secondly, that although statistically justifiable, cutoff points are used for the angiographic variables under investigation. However, the continuous approach underscores these findings by indicating a positive linear relation between the relative gain and relative loss. These observations were still valid when using absolute measurements. However, the correlation between the absolute gain and absolute loss was somewhat weaker ($r = 0.21$, $p = 0.05$). This is explained by the fact that the use of absolute values does not relate these changes to

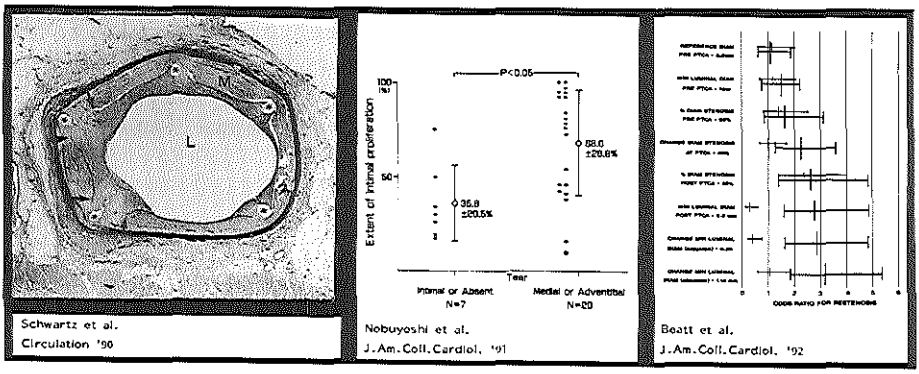

Fig. 4. Experimental animal data, postmortem pathologic observations in hunans and angiographic studies independently from each other indicate a proportional relationship between the degree of vessel wall injury and the extent of late neointimal thickening. Left panel: coil stent implantation in domistic pigs results in a more extensive smooth muscle cell proliferation in case of rupture of the internal elastic lamina and consequent medial injury (reproduced with permission from Schwarz et al. Circulation 1990;82: 2190-2200), middle panel: pathologic observations in human indicate that deep arterial injury is associated with more extensive intimal proliferation (reproduced with permission from Nobuyoshi et al. J Am Coll Cardiol 1991;17:433-439), right panel: an angiographic study assessing the immediate and long-term changes in stenosis geometry following balloon angioplasty, shows that restenosis defined as ≥ 0.72 mm decrease in minimal luminal diameter (MLD, bold line), was found to be signifanctly correlated with both a larger increase in MLD and larger absolute dimension after balloon angioplasty (reproduced with permission from Beatt et al, J Am Coll Cardiol 1992;19:258-266).

the vessel size. Although we found no difference in absolute loss between small and large vessels, an identical loss in minimal luminal diameter represents a larger relative loss in a small vessel than in a large vessel and vice versa. This confirms other studies using a categorical approach to define restenosis after stenting, that small vessels are not per se more prone to restenosis than large vessels [12,13,27].

This concept, describing a proportional relationhip between vessel wall injury and neointimal thickening, has been reported in other studies using quantitative coronary angiography. Beatt et al. found that restenosis (0.72 mm criterion) was significantly correlated with both a greater improvement in obstruction diameter and a larger absolute dimension after balloon angioplasty [16]. Furthermore, in a recent study the absolute change in minimal luminal diameter was reported to be the greatest single determinant of late luminal narrowing after balloon angioplasty [28]. In another report, it was found that interventions achieving a "bigger" lumen provoke a concomitantly larger relative loss, so that the ultimate end point of various treatment modalities is similar [29].

All these findings carry potential far-reaching clinical implications. Clearly, the greater the improvement in minimal luminal diameter achieved by intervention, the greater the magnitude of subsequent luminal narrowing will be. Unfortunately, what can not be drawn from the data is how much damage the clinician may inflict on the vessel wall. On one hand, a suboptimal angiographic result is associated with a higher risk of subacute occlusion due to rheologic factors and platelet deposition and a higher need for repeat balloon angioplasty but, on the other hand, improvement of the initial result may be at the price of more extensive late neo-intimal thickening [14-16,30,31]. This indistinctness can be circumvented by proper matching the balloon size or device with the vessel wall using on line quantitative coronary angiography. This is underscored by the data displayed in Figure 5 indicating that the more the stent is oversized, the greater the loss in minimal luminal diameter will be.

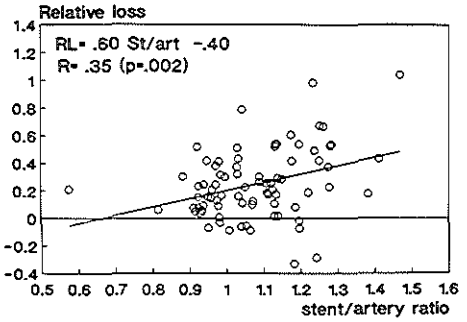

Fig. 5. Graphic display of the relation between the stent/artery ratio (X-axis) and relative loss (Y-axis). A positive linear relation was found with a correlation coefficient of 0.35 ($p < 0.002$) with a slope of 0.60 and an intercept of −0.40.

So far, there are two other angiographic studies which have attempted to identify risk factors for restenosis or recurrence of restenosis and found, as in the present

study, that the vessel size, severity of stenosis expressed as diameter stenosis and length of the lesion not to be associated with an increased risk for restenosis [12,13]. As mentioned above, the indication (primary or secondary stenting) was not associated with an increased risk for restenosis [12,13]. In accordance with these two studies on stenting and one other study on balloon angioplasty, the target vessel was not associated with an increased risk for (recurrent) restenosis [12,13,32].

Study limitations: The study limitations are essentialy two fold. First, the precision of relative gain as an angiographic index of vessel wall injury and relative loss as an index of neointimal hyperplasia has not been studied. The coronary angiogram is a two dimensional lumenogram describing the changes in stenosis geometry but not the nature and/or extent of the pathology explaining these angiographic changes. Therefore, the measurement of the minimal luminal diameter, and consequently the relative gain and loss, are subject to potential imprecision. Secondly, the effect of other clinical, procedural and lesion-related characteristics on the development of late neointimal hyperplasia, has not been considered. It is conceivable that, if they play a role in the pathogenesis of neointimal thickening, they were unequally distributed over the study population.

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CHAPTER 8

BALLOON ANGIOPLASTY FOR THE TREATMENT OF LESIONS IN SAPHENOUS VENOUS BYPASS GRAFTS

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INTRODUCTION

The management of recurrent ischemia in patients who have had previous saphenous venous bypass surgery poses a serious, difficult problem. Recurrent ischemia occurs not only due to attrition of the saphenous vein grafts but also to progression of coronary artery disease in the native coronary arteries. The attrition rate during the first year after surgery is 15 to 20%; between 1 to 6 years after surgery it is 1 to 2% per year and between 6 to 10 years after surgery the rate is 4% per year [1-8]. By five years, about 45% of the grafts are occluded [3,7]. Progression of native coronary artery disease occurs in approximately 5% of the patients per year after operation [8-11]. Symptoms recur or progress in about 5% of patients per year and it has been estimated that 10% to 15% of the patients will require repeat surgery within 10 years after initial surgery [11-15]. However, currently improved surgically techniques in combination with administration of aspirin and risk factor modification have improved early graft attrition rate and may improve longterm attrition [16]. Despite improved surgical results it may be expected that the number of patients with recurrence of ischemia will increase, because the pool of operated patients continues to accumulate.

Reoperation is technically more difficult to perform and is associated with a rather high mortality (3% to 6.5%) and high peri-operative myocardial infarction rate (3.4% to 11.5%) and the likelihood on complete relief of symptoms is less compared to a first operation [11-16]. This has stimulated the search for an alternative treatment.

Gruentzig reported already in 1979 that vein graft angioplasty was successful in 5 of 7 attempts [17]. However, three out of five demonstrated restenosis during follow-up and Gruentzig suggested that the "different kind of disease" in the bypass graft may have explained the high recurrence rate in graft stenosis. Since then many studies concerning angioplasty of lesions in saphenous vein grafts have been reported.

In this article we review the literature and we will discuss the indications, the initial and late results of angioplasty of saphenous venous bypasses and we will briefly discuss the role of new techniques including stents, directional and extractional atherectomy, and laser angioplasty.

Patho-anatomy of saphenous venous grafts

The pathophysiological mechanisms underlying graft failure can, arbitrarily, be distinguished into those occurring early, within 1 year, and late after surgery. In each period one assumes a specific predominant pathogenetic mechanism, although one must bear in mind that the different pathological processes may occur in a continuous fashion and overlap in time [18,19].

Graft occlusion early after surgery is usually associated with acute thrombosis [18,19]. This is possibly attributable to harvesting and handling of the vein, or to failure of surgical techniques at anastomosis sites [20].

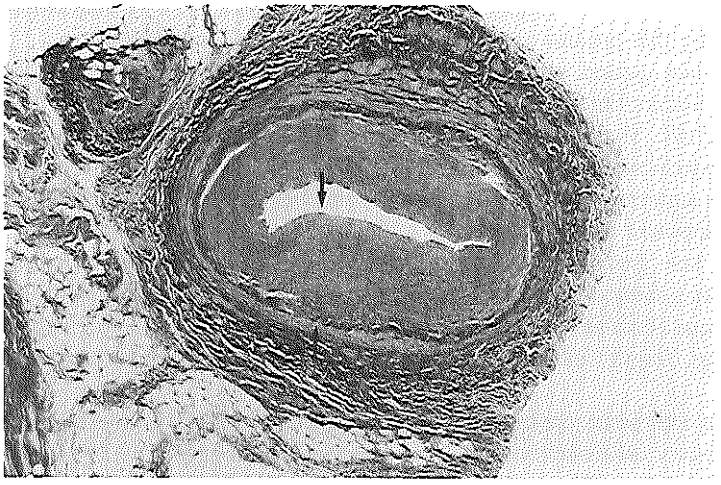

Fig. 1. Histological cross-section of a two year old saphenous vein graft showing a severe luminal narrowing due to concentric intimal thickening (arrows) consisting of fibro-collagenous tissue.
(Elastic van Giesson stain × 25 magnification).

Fig. 2. Saphenous vein (v) - coronary artery (a) anastomosis, 9 months after bypass surgery, showing intimal thickening (I) and occlusive thrombus
(Elastic van Giesson stain × 25 magnification).

Fibro-intimal hyperplasia is the dominant feature 1 to 12 months following surgery [20-22]. The cells of fibro-intimal hyperplasia resemble smooth muscle cells and some cells may have a "foamy" cytoplasmic appearance [21]. Focally stenotic lesions produced by this process appear particularly amenable to dilatation.

In the late period after surgery fibro-intimal hyperplasia at first remains the dominant feature but gradually atherosclerotic lesions become more frequent (Figure 1 and 2) [19]. The fibro-intimal lesion gradually diminishes its cellularity and the smooth muscle cells are replaced by fibrous tissue and the matrix is increased. With time there appears to be an increase in the number of "foam cells" within the intima. The development of atherosclerosis in the aortocoronary vein grafts is an important factor in late graft stenosis and occlusion [23-32]. The atherosclerotic process proceeds to a fully developed complex atherosclerotic plaque (Figure 3) and rupture of the plaque leads to a superimposed thrombotic occlusion [23,24]. The plaques are often large, fragile and ulcerated and the graft may show aneurysmal dilatation [25,26].

There is still some controversy as to whether venous graft atherosclerosis differs from coronary atherosclerosis. Some investigators suggest [28,29] that vein graft lesions contain more foam cells, and that they exhibit an inflammatory reaction with foreign body giant cells. This process undermines the thickened intima so that the fibrous cap is weakened (Figure 4) [28]. One study demonstrated lack of a fibrous cap [29]. This thinning and weakening of the fibrous cap may explain the greater propensity of venous plaque rupture and thrombosis. The propensity of thrombus formation in vein grafts is enlarged because the lack of side branches, the large diameter of vessels and consequently low flow velocities may contribute to platelet aggregation and thrombus formation. These factors may explain the frequent occurrence of thrombotic complications or embolization of material during balloon angioplasty.

However, other investigators [18,19,26,30-32] favour the opinion that atherosclerosis vein graft disease is not different from arterial atherosclerosis.

Immediate results of angioplasty for saphenous venous bypass grafts.

Ford et al. [33] reported a small series of 7 patients of whom 6 patients were dilated successfully. Since then, many centers have reported their initial result of angioplasty of saphenous vein grafts. Only the upgraded latest reports per center are presented (Table 1).

The initial success rate varies from 75 to 94% with a combined overall success rate of 88%. The major complication rate is low with a procedural related death rate of less than 1%, a myocardial infarction rate of approximately 4% and a need for urgent surgery of less than 2%. Remarkable is the low tendency to abrupt occlusion and the relative high success rate, probably due to the absence of sidebranches and tortuosity. The risk of embolization of friable, thrombotic material into the native circulation is less than 3%. Emboli usually occur during attempts in older grafts, with long diseased segments containing friable, thrombotic lesions. The initial success rate

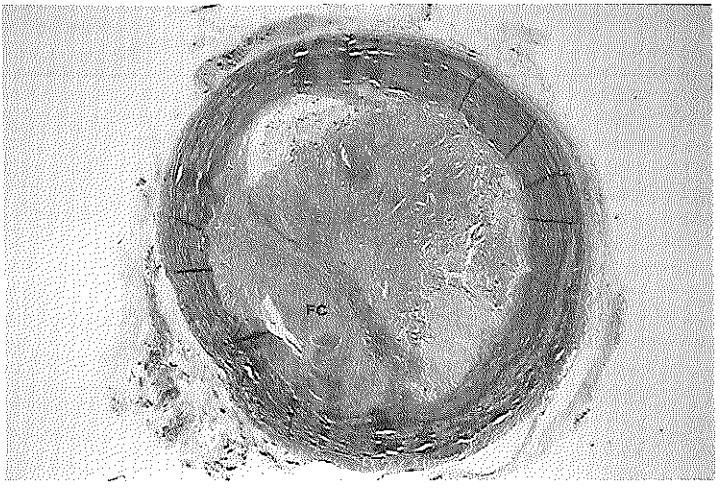

Fig. 3. Six year old vein graft showing severe luminal narrowing by a "classical" atherosclerotic plaque; fatty debris is covered by a fibrous cap (Fc) (lumen; arrow).
(Elastic van Giesson stain × 25 magnification).

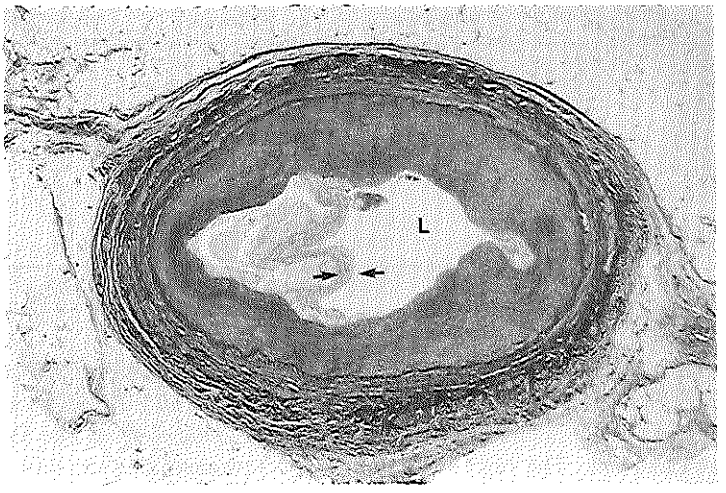

Fig. 4. Four year old saphenous bypass graft showing a concentric fibrous intimal thickening and an eccentric atherosclerotic plaque with fatty debris seperated from the lumen (2) by a very thin fibrous cap (arrows). (Elastic van Giesson stain × 25 magnification).

Table 1. Initial results of angioplasty of saphenous vein grafts

Authors	(year)	No. of pts	Clinical Success % (pts)	Procedural complications			
				Death (%)	MI (%)	Embolization (%)	Acute CABG (%)
Douglas [34]	1983	62	94 (58)	0	2	0	2
El Gamal [35]	1984	44	93 (41)	0	5	0	0
Block [36]	1984	40	78 (31)	0	0	0	2.5
Corbelli [37]	1985	35	89 (31)	0	0	0	3.0
Reeder [38]	1986	19	84 (16)	5	5	0	0
Douglas [39]	1986	235	92 (216)	0	7*	3	1.3
Cote [40]	1987	82	85 (70)	0	1	2	1
Ernst [41]	1987	33	97 (32)	0	3	n.r.	0
Dorros [42]	1988	53	83 (44)	2	2	6	2
Reed [43]	1989	54	90 (47)	0	0	0	2
Cooper [44]	1989	24	75 (18)	4	0	n.r.	0
Platko [45]	1989	101	90 (90)	2	6	3	2
Webb [46]	1990	140	85 (119)	0	4	n.r.	1
Meester [47]	1991	84	82 (69)	1	8	n.r.	2.5
Plokker [48]	1991	454	90 (408)	0.7	2.8	n.r.	1.3
Reeves [49]	1991	57	83 (47)	2	9	7	2
Total		1571	88 (1337)	<1%	<4%	<3%	<2%

* 15 of 16 patients had non-q-wave infarction; n.r.: not reported, MI = myocardial infarction; CABG = coronary artery bypass grafting.

Table 2. Initial success rate of dilatation of saphenous vein grafts at different sites.

Author	Year	Site of venous graft dilation					
		Proximal % (lesions)		Body % (lesions)		Distal % (lesions)	
Douglas [34]	1983	80	(5)	96	(23)	94	(34)
Dorros [50]	1984	84	(12)	88	(8)	69	(13)
Corbelli [37]	1985	88	(26)	100	(7)	93	(14)
Pinkerton [51]	1988	94	(36)	90	(29)	94	(35)
Cooper [44]	1989	56	(9)	67	(3)	92	(12)
Platko [45]	1989	89	(53)	100	(24)	93	(30)
Webb [46]	1990	80	(47)	86	(39)	89	(56)
Meester [47]	1991	86	(28)	97	(33)	81	(32)
Total		86	(216)	93	(162)	90	(226)

depends on the site of dilatation (Table 2). The overall combined initial results of dilatation of the proximal site is 87%, of the body 94% and of the distal site 90%. These rates appear to be similar, except for a slight lower success rate for dilatation at the proximal site. The high success rate and low complication rate reflects the careful selection of patients and probably difficult potentially risky lesions including long diffuse lesions, or ulcerated, thrombotic, friable lesions have been excluded from these series.

Restenosis after successful dilatation of saphenous vein grafts

The restenosis rate (defined as > 50% luminal diameter in the majority of the reported studies) after an initial successful angioplasty depends highly on the site of the dilation within the graft (Table 3). Ostial, or very proximal lesions of the graft tend to have a very high restenosis rate on average 58%; the restenosis rate of the body of the graft is 52% and the restenosis rate in the distal, anastomotic part of the graft is 28%. The overall combined restenosis rate is 42%. The restenosis figures probably overestimate the true incidence of restenosis because not all asymptomatic patients are restudied. The angiographic completeness of follow-up varied from 56% to 100% in the reported studies (Table 3).

Table 3. Restenosis after successful angioplasty of saphenous venous grafts

Author	Year	No. of Pts	Definition Restenosis	Completeness Angiographic F.U. (%)	Angiographic restenosis by site (lesions)			
					Prox.	Body	Distal	All sites (%)
Douglas [34]	1983	41	n.r.	n.r.	1/2	9/17	4/22	14/41 (34)
El Gamal [35]	1984	16	> 50%	61	1/2	5/12	2/3	7/17 (41)
Block [36]	1984	22	> 50%	71	n.r.	n.r.	n.r.	12/22 (55)
Dorros [50]	1984	26	n.r.	n.r.	8/10	2/7	2/9	12/26 (46)
Reeder [38]	1986	16	> 30%	100	2/3	3/5	3/8	8/16 (50)
Douglas [39]	1986	130	n.r.	n.r.	11/14	40/65	10/51	61/130 (47)
Cote [40]	1987	26	> 50%	70	3/9	5/21	2/13	10/43 (23)
Dorros [42]	1988	25	n.r.	57	3/5	3/7	4/13	10/25 (40)
Pinkerton [51]	1988	23	n.r.	92	1/3	3/5	6/15	10/23 (44)
Platko [45]	1989	49	> 50%	56	21/42	9/20	10/24	40/86 (47)
Meester [47]	1991	59	> 50%	n.r.	n.r.	n.r.	n.r.	13/59 (22)
Reeves [49]	1991	45	> 50%	93	7/11	20/32	5/14	32/57 (56)
Total		478			58/101 (58%)	99/191 (52%)	48/172 (28%)	229/545 (42%)

n.r.: not reported

In native coronary arteries the restenosis process takes place in the majority of the patients within 6 months after angioplasty. Whether this is similar in restenosis in venous bypass grafts is unknown. But data reported by Douglas et al. [52] suggest that this time window is longer. They followed 599 patients with successful angioplasty and found that restenosis occurred in 32% of lesions dilated within 6 months of surgery, 43% from 6 months to 1 year, 61% from 1 to 5 years, and 64% over 5 years.

Longterm follow-up after angioplasty of saphenous vein bypass grafts

The longterm outcome of patients selected for angioplasty of a saphenous venous bypass graft is not only influenced by the restenosis rate, and rate of progression of disease in the native arteries, but also by the extent of the left ventricular dys-

function. The frequency of late mortality, myocardial infarction and recurrence of angina is listed in Table 4. The wide range of rates reflects the differences in patient selection and duration of follow-up. It appears that the clinical event rate is significantly higher if the age of the graft is higher. The clinical event rate was 64% in grafts over 36 months of age, and 33% in grafts less than 36 months of age [45].

Table 4. Longterm results after immediate successful graft lesion angioplasty

Authors	Year	No of Patients	Mortality (%)	Myocardial Infarction (%)	Recurrence Angina (%)	Follow-up Months (mean ± SD)
Cote [40]	1987	82	2.5	0	29	21 ± 2
Reed [43]	1989	50	2	2	52	23 ± 11
Platko [45]	1989	87	11.5	20	47	17 ± 14
Webb [46]	1990	119	7.6	11	19*	33 ± 26
Reeves [49]	1991	50	4	4	54	32
Meester [47]	1991	69	11.5	10	42*	25
Plokker [48]	1991	454	22	n.r.	n.r.	60

* These patients underwent re-operation or re-angioplasty.

Plokker et al. [48] reported that after a follow-up period of 5 years, 74% of 454 patients were alive and only 26% of the patients were alive and event-free (no myocardial infarction, no repeat bypass surgery or repeat angioplasty) (Figure 5). The time interval between angioplasty and surgery was a significant predictor for 5-year-event-free survival. The event-free survival rates for patients who had bypass surgery 1 year before, between 1 and 5 years, and 5 years after bypass surgery were 45%, 25% and 19% respectively.

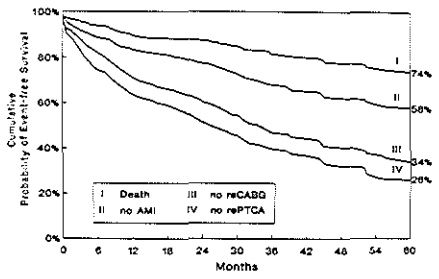

Fig. 5. Four hundred fifty-four patients were followed for 5 years. The cumulative probabilities of survival (I), of survival without AMI (II), without AMI and no re-CABG (III) and without any cardiac event (IV) (death, AMI, CABG and re-PTCA) are shown. AMI = acute myocardial infarction; re-CABG = repeat coronary artery bypass grafting; re-PTCA = repeat percutaneous transluminal coronary angioplasty. Reproduced with permission from Plokker et al. Am J Cardiol 1991; 67:361-366, Figure 2.

The late mortality and late myocardial infarction rate is expected to be high, because often these patients present as end-stage coronary artery disease patients. In these patients angioplasty should be considered a palliative treatment, and one should not expect a beneficial effect on late mortality.

Balloon Angioplasty of early (within 1 year) occlusion of saphenous venous bypass grafts

Graft occlusion occurring within 1 month after surgery is almost always associated with graft thrombosis [18-20,24,27]. Technical factors such as stenosis at surgical anastomotic-sites, or intra-operative vein trauma, or poor distal run-off due to severely diseased native arteries play a role and limit the possibilities of immediate and sustained beneficial effect of angioplasty.

Graft occlusion occurring between 1 month and 1 year after surgery is characterized by lesions consisting of fibro-intimal hyperplasia with superimposed occlusive thrombosis [18-21,24,27,28,30]. These occlusions are predominantly focal, not associated with diffuse vein graft disease, and usually the thrombotic component of the occlusion is not extensive. These occlusions appear to be amenable to successful perforation and dilatation.

Balloon Angioplasty of chronic totally saphenous venous bypass grafts more than 1 year after surgery

The underlying patho-anatomy plays an important role in the expected success rate of angioplasty of a chronic totally occluded graft. Late occlusions (1-3 years after surgery) are usually associated with focal atherosclerosis with occlusive thrombosis [18-21,24,27,28,30]. These lesions may be amenable to successful perforation and dilatation without increased risk of thrombotic embolization. Older occlusive obstructions are often composed of large, ulcerated plaques containing friable thrombotic material. The chronic total occlusions are often extended over a long segment of the graft and are often associated with diffuse graft disease. Obviously, perforation and dilatation of these chronic occlusions may be unsuccessful or even harmful due to dislodgement of material into the native coronary circulation with ensuing myocardial infarction.

The safety and results of angioplasty in occluded grafts is controversial. De Feyter et al. [53] reported in 13 patients with chronically totally occluded old degenerated grafts that attempts to recanalization of the graft expose the patient to a high risk of embolization and even if it is possible to re-open the graft it re-occludes frequently. In their study only 1 out of 13 patients had a longterm success and the procedure was complicated by a myocardial infarction in 5 patients (Table 5). Apparently the presence of large amounts of thrombotic material and the dislodgement of it are the main causes of low success and high complications with balloon angioplasty. These results contrast highly with a recent report of Kahn et al. [54]. They reported a 83% success rate, (64 out of 82 patients) with 1.5% in-hospital death, 3% myocardial infarction rate and no urgent bypass surgery. However, at 3 years follow-up only 33% of the patients were free of repeat PTCA or surgery. The difference in immediately results between the 2 reports may be explained by differences in patient selection. Results in short occlusions in angiographically reasonably normal appearing grafts are probably better than long occlusions in degenerated vein grafts.

Table 5. Coronary angioplasty of chronic totally occluded vein grafts

Author	Duration Occlusion	Age grafts	Number of Pts	Initial Clinical Success	Procedural Death	Procedural MI	Longterm Succes	Late Deaths	Late MI
	months	mean (yrs)		Pts	Pts	Pts	Pts	Pts	Pts
ANGIOPLASTY									
de Feyter [53]	3 - 6	6 ± 4	13	7	0	5	1	0	0
UROKINASE + ANGIOPLASTY									
Sievert [55]	0.5 - 4	0.2 - 3.6	7	6	0	0	4	0	0
Hartmann [56]	0.5 - 6	7 (1-13)	46*	36**	0	2	22	4	0
Levine [57]	n.r.	n.r.	10	6	2	2	0	0	1

n.r.: not reported
* 8 patients with acute non-q-wave infarction.
** 20 patients had repeat angiogram: 7 had an occluded graft.

Pre-treatment of chronic total occlusion with urokinase followed by angioplasty

Dissolving thrombus in a chronically occluded grafts with short infusion of urokinase dramatically improved the short and longterm results (Table 4). Sievert et al. [55] showed that after pretreatment with urokinase 6 out of 7 patients were successfully recanalized, with a longterm success in 4 patients. Hartmann et al. [56] also showed good results with longterm urokinase infusion (7.5 to 77h; mean 31h) followed by angioplasty. Recanalization could be achieved more easily in patients with a short estimated duration of occlusion. The price one must pay for this treatment is the occurrence of a significant haematoma in 22% of the patients and the long stay in a coronary care unit. Unfortunately, the reocclusion/restenosis rate is rather high and success was sustained in 48% (22 out of 46 patients) of the patients during 1 to 24 (mean 11) months follow-up period. Levine et al. [57] demonstrated that in 8 out of 10 patients patency was achieved (however, 2 patients died and 2 had embolic myocardial infarction) but during follow-up at an average of 13 ± 6 months no patient was free of reocclusion, myocardial infarction or death.

Identification of risk factors for unfavourable outcome

Variables predictive of unfavourable initial result include:

a) diffuseness of saphenous vein graft disease [40], b) attempts of angioplasty of stenoses in grafts older > 4-6 years [45,46], c) chronic totally occluded grafts [13] and d) the presence of intra vein graft thrombus [49]. The presence of one or more of these variables is associated with a high frequency of major complications (death, myocardial infarction and need for urgent bypass surgery) often due to embolization of friable material into the coronary circulation or the occurrence of abrupt occlusion with thrombosis formation.

Variables predictive of late restenosis include:

a) lesions in old (> 36 months) grafts (restenosis rate 83% vs 42%) [45], b) multiple lesions, diffuse graft disease and total occlusion (100% vs 38%) [49], c) small diameter (< 2.2 mm) grafted coronary artery (78% vs 27%) [58], d) length (> 10 mm) stenosis (62% vs 12%) [58] and e) dilatation of lesion at the proximal site and body of the graft (Table 3).

Limitations of surgical back-up

In many centers the availability of immediate surgical back-up is considered a pre-requisite for performing angioplasties. Although emergency operation for acute ischemia may not totally eliminate the development of a myocardial infarction, there is evidence that prompt revascularization does limit the damage [59]. Time between onset of ischemia and revascularization determines the outcome [60]. The ischemic period during reoperation is considerably prolonged because immediate access to the heart is hampered by the fibrosis of the previous operation, which may require considerable time to dissect free the heart. This inevitable delay limits the potential of revascularization to reduce myocardial damage. If possible, bail-out techniques for instance autoperfusion catheters, should always be used in these situations. Stent implantation for threatened closure has produced satisfactory results [61].

This expected time delay should be considered when counselling a patient. It would be prudent to refer a patient for reoperation, if for instance acute closure of a lesion would lead to acute heart failure due to the large area of myocardium at risk.

New interventional techniques for treatment of saphenous venous bypass grafts

Stent implantation

The intracoronary stent was the first of the new interventional techniques to be applied in bypass graft angioplasty. Shortly after the introduction into the native coronary artery system, stents were also implanted in bypass grafts (Figure 6) [62-64]. The immediate angiographic and implantation success rate is extremely high, 95% or higher (Table 6) [61-62,64-66]. However, early experience was associated with an unacceptable high incidence of subacute thrombosis and serious bleeding complications. Increased operator experience and meticulous anticoagulation resulted in a substantial decrease in complications [64-66]. Unfortunately, the incidence of restenosis does not seem to be reduced (Table 6). One detailed study on restenosis following Wall-stent implantation in venous bypass grafts reports an incidence of restenosis of 39% according to the 50% diameter stenosis criterion [67]. The restenosis rate after implantation of a flexible coil is 35% [61] and the restenosis rate after implantation of a Palmaz-Schatz stent was less: 28% [68]. It has been shown that restenosis after Wall-stent implantation in bypass grafts occurs more frequently than in stented native coronary arteries [69]. The rates were similar in

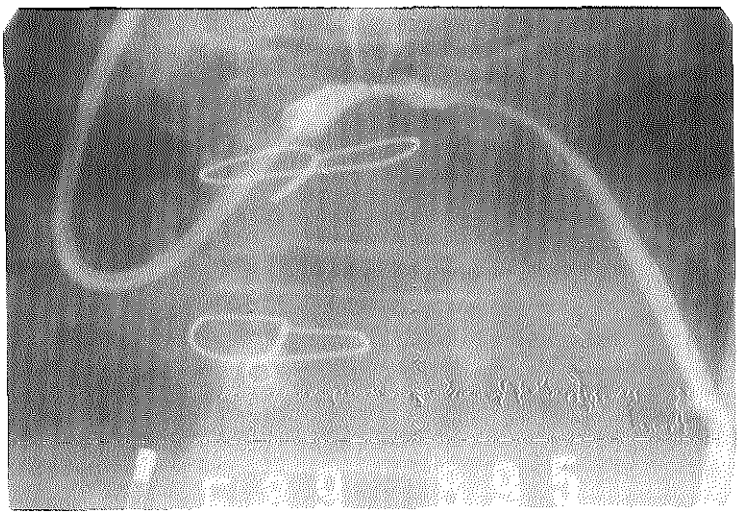

Fig. 6A. Diffuse disease in 7 years of bypass graft implanted on the left anterior descending artery.

Fig. 6B. Immediate result after implantation of 2 overlapping stents (Wall-stent).

grafts and native coronaries after Palmaz-Schatz stent implantation [68]. Whether the better results obtained with the Palmaz-Schatz are due to the more favorable features of this stent or improved peri-procedural pharmacological management or different patient selection is unknown.

Table 6. Stent implantation in venous bypass grafts

Author	Total No. of patients	Implantation success rate (%)	Clinical Success (%)	Death (%)	Inhospital complications MI (%)	Em/CABG (%)	Serious bleeding (%)	Restenosis (%)
			Wallstent					
Urban [62]	13	95	95	0	0	0	15	36
de Scheerder [64]	69	100	87	4*	7	6	33	47
			Palmaz Schatz					
Pomerantz [65]	54	100	100	0	0	0	n.r.	21
Leon [66]	192	98	97	1.6	1.0	1.6	n.r.	26
			Flexible coil					
Bilodeau [61]	37	100	86.5	0	13.5**	0	21.6	35

* Not mutual exclusive

** All acute events were seen in patients stented for dissection or threatened closure.

n.r. Not reported

The longterm clinical follow-up results of Wall-stent implantation in bypass grafts collected from 145 patients of 6 European centers is shown in Figure 7 [67]. The actuarial event-free survival (freedom from death, myocardial infarction, bypass surgery or angioplasty) for bypass graft patients was 37% at 20 months; with an

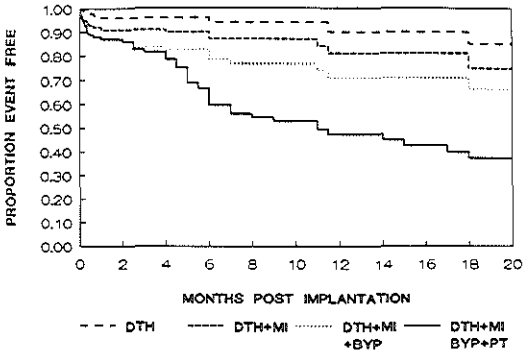

Fig. 7. Clinical follow-up in 145 patients with stent implantation in a bypass graft up to 20 months according to actuarial event-free survival. The curves (from upper to lower) represent freedom from death (DTH) alone; death plus myocardial infarction (MI); death, MI, plus bypass surgery (BYP); and death, MI, BYP plus angioplasty or atherectomy (AT). Reproduced with permission from Strauss et al. Am J Cardiol 1992; 69:475–481, Figure 4.

overall mortality rate of 9%. It is noteworthy that about 30% of the adverse events were unrelated to the stented lesion, but were due to worsening of a different lesions or development of new lesions [64,67].

Atherectomy: directional and extractional

The use of directional atherectomy in saphenous venous bypass grafts is feasible and successful in well above 90% of the patients (Table 7) [65,70,71]. The complication rate is acceptable, but one can imagine that the use of such a bulky device in case of friable, thrombotic lesions easily embolizes material. Preliminary data suggest that the restenosis rate is also high.

Table 7. Initial results of new devices for treatment of lesions of saphenous vein bypass grafts

Author	Year	Total No Patients	Clinical Success (%)	Complications Death (%)	MI (%)	Em/CABG (%)	Embolization (%)	Restenosis (%)
Directional atherectomy								
Kaufmann [70]	1990	14	93	7*	1	0	7	63
Pomerantz [65]	1991	29	93	0	0	0	7	31
Selmon [71]	1991	76	91	0	9.2	1.3	11.5	60
Extractional atherectomy								
Meany [72]	1992	278	89	0.3	0.3	0.7	3.5	53
Excimer laser								
Untereker [73]	1991	225	97	0.4	4.4	0.8	4.4	61

* Cross-over to PTCA: abrupt occlusion, Em/CABG: death; n.r. = not reported

Extractional atherectomy of venous graft lesions is successful in 89% of the patients (Table 7) [72]. The complication rate is low and the restenosis rate is 53%. It is conceivable that the use of this device in vein grafts, containing much material, is safe and is associated with a higher success rate and decreased risk of embolization due to the suction, extraction and removal of material with this device, although embolization occurred in 3.5% of the patients.

Excimer laser angioplasty

In an initial experience including 225 patients (Table 7) it has been shown that excimer laser angioplasty can be performed safely and effectively [73]. A success rate of 97% was achieved in lesions in older saphenous venous grafts; however, the preliminary reported restenosis rate of 61% is rather high.

CONCLUSION

Currently, sufficient data are lacking to establish the merits of reoperation and balloon angioplasty to treat obstructions in venous bypass grafts. The published results on reoperation and balloon angioplasty should not be compared because of differences in patient selection and firm conclusions about the superiority of one treatment above the other should not be drawn. After reviewing the litterature it appears that in selected patients balloon angioplasty may be the preferred strategy or in case of inoperability it is the only strategy.

Angioplasty of non-occlusive obstructions in venous bypass grafts is safe and the success rate is high. The high restenosis rate adversely affects the longterm results. The immediate and longterm results of angioplasty for chronic total occlusion in old grafts are poor.

Patients considered for saphenous vein graft angioplasty may be classified into 3 groups according to expected early and late outcome: A) those with an initial high success, low procedural risk and low restenosis; B) those with an initial high success, but high procedural risk and moderate too high restenosis rate; C) those with low success, high risk, and high restenosis rate (Table 8).

Table 8. Classification of patients with attempted saphenous vein graft angioplasty according to expected early and late outcome

A success > 90%; complication < 2%; restenosis: 30%	
- focal, short lesion	- lesion at distal site
- graft < 4-6 years	
- single graft	
- distal part sequential graft	
B success > 90%; complication < 5%; restenosis 45-50%	
- long lesion	- lesion at proximal site
- graft > 4-6 years	- lesion at body
- diffuse vein graft disease	
- intragraft thrombus	
- proximal part sequential graft	
C success < 50%; complication > 10%; restenosis > 60%	
- chronic totally occluded old vein graft	

New techniques have shown to be promising and in particular stent placement may be useful to "tack" friable material. However, definite conclusions concerning the merits of new techniques must await finalization of ongoing randomized trials.

Balloon angioplasty is a palliative procedure, not a longterm solution, in previously operated patients who often present with far stage coronary artery disease. The high restenosis rate is a serious limitation of balloon angioplasty.

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CHAPTER 9

MATCHING BASED ON QUANTITATIVE CORONARY ANGIOGRAPHY, A SURROGATE FOR RANDOMIZED STUDIES? COMPARISON BETWEEN STENT IMPLANTATION AND BALLOON ANGIOPLASTY OF A NATIVE CORONARY ARTERY LESION

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Matching based on quantitative coronary angiography as a surrogate for randomized studies: Comparison between stent implantation and balloon angioplasty of native coronary artery lesions

Although intracoronary stenting has been advocated as an adjunct to balloon angioplasty to circumvent late restenosis, its effectiveness has not yet been verified. Therefore the aim of this study was to determine the differences in the immediate and long-term changes in stenosis geometry between Wallstent implantation and balloon angioplasty in native coronary artery lesions. To obtain two study populations with identical baseline stenosis characteristics, patients were matched for lesion site, vessel size, and minimal luminal diameter. Only patients undergoing elective and successful coronary intervention of a native coronary artery, in whom a control angiographic study had been performed, were included. A total of 186 patients (93 in each group) were selected. The coronary angiograms were analyzed with the computer-assisted cardiovascular angiographic analysis system. Matching was considered adequate, since there was an equal number of lesion sites in each study population and there were no differences in baseline reference diameter and minimal luminal diameter. Wallstent implantation resulted in a significantly greater increase in minimal luminal diameter (from 1.22 ± 0.34 mm to 2.49 ± 0.40 mm, $p < 0.00001$) compared with balloon angioplasty (from 1.21 ± 0.29 mm to 1.92 ± 0.35 mm, $p < 0.00001$). Despite a greater decrease in minimal luminal diameter after Wallstent implantation (0.48 ± 0.74 mm) than after balloon angioplasty (0.20 ± 0.46 mm), the minimal luminal diameter at follow-up was significantly greater after stent implantation (2.01 ± 0.75 mm vs 1.72 ± 0.54, $p < 0.0001$). It was concluded that Wallstent implantation results in a superior immediate and long-term increase in minimal luminal diameter compared with balloon angioplasty. The larger initial gain after stent implantation compensates for the late loss, and thus an improved initial result and not lessened neointimal hyperplasia is responsible for a reduced incidence of restenosis. Studies based on matching of angiographic variables are a surrogate for randomized studies, forecasting their results and offering insight into the effects of different interventional techniques. Moreover, these studies yield statistical information that may be helpful for the proper design of a randomized study (sample size, type II error). (Am Heart J 1993;125:310.)

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Percutaneous transluminal coronary angioplasty by means of balloon catheters, which was introduced by Gruentzig et al.[1,2] in the late 1970s, has been a major breakthrough in the treatment of obstructive coronary artery disease. Gained operator experience and improved catheter technology have resulted in a high immediate success rate and a low incidence of complications, which in turn has resulted in an increasing number of patients with more advanced coronary artery disease now being considered candidates for balloon angioplasty.[3,4] Unfortunately these favorable results continue to be compromised by the unpredictable problem of late restenosis, which occurs in 20% to 40% of patients after successful balloon

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angioplasty.[5-8] Despite substantial basic and clinical research, the pathophysiologic mechanism(s) responsible for restenosis remain largely unknown and poorly understood. Pharmacologic efforts to reduce or eliminate restenosis have so far been unsuccessful.[9-14] Therefore it is not surprising that along with pharmacologic interventions, new technologies and devices are currently being developed and clinically tested to address the problem of restenosis. Directional rotational atherectomy devices and laser angioplasty do not seem to affect the restenosis rate.[15-18] The intracoronary stent may be an exception. There is some evidence to imply that suboptimal initial stenosis geometry after balloon angioplasty contributes to restenosis. The stent optimizes the dilatation process by effective scaffolding of the instrumented vessel, thereby preventing recoil, and by tacking back intimal flaps, thus covering underlying thrombogenic tissue.[19-21] Furthermore, it has been shown that stent implantation results in a larger and more homogeneous cross-sectional area resulting in normalization of the hemodynamic disturbances and flow across the dilated segment.[20, 22, 23] Consequently the vessel's response to balloon-induced intimal trauma is mitigated and the healing response modified. The aim of this study was to compare the immediate and long-term changes in stenosis geometry after stent implantation and balloon angioplasty in patients with identical baseline stenosis characteristics.

METHODS

Patients. At present the data base of the Thoraxcenter contains angiographic data from 411 patients in whom a Wallstent device (Schneider & Co. AG, K, Zürich, Switzerland) was implanted in a bypass graft or a native coronary artery and 3569 patients who underwent balloon angioplasty of a native coronary artery lesion. From this population a total of 186 patients (93 in each group) with identical baseline stenosis characteristics were selected according to the matching principle. Patients were eligible if they had undergone elective and successful coronary intervention of a native coronary artery and if a control angiographic study had been performed. Since we recently demonstrated that there is no difference in the restenosis rate after Wallstent implantation for restenosis or for a de novo lesion, patients with both types of indications were included in the stent population.[24] All patients who underwent balloon angioplasty were treated for a primary lesion.

Description of stent. The stent used in this study was the coronary Wallstent device (Fig. 1). It is constructed of a surgical grade stainless-steel alloy, braided in a tubular wire mesh design. The stent consists of 16 wire filaments, each 0.08 mm in diameter. The stent is collapsed down on a delivery catheter equipped with a restraining sheath and is deployed by pulling back the sheath. The outer diameter of the stent-catheter system is 1.57 mm. The device is radially self-expanding and longitudinally flexible. The selection of the stent size was based on visual assessment of the vessel size. The size of the Wallstent device was selected to obtain an unconstrained diameter that was 0.5 mm larger than the vessel. The size (mean ± SD) of the unconstrained Wallstent device proved to be 3.60 ± 0.48 mm. In case of incomplete expansion of either stent, repeat balloon dilatation within the stent was performed.

Quantitative coronary angiography. To assess the immediate and long-term changes in stenosis geometry, all coronary cineangiograms were analyzed by means of the computer-assisted cardiovascular angiography analysis system described in detail elsewhere.[25] This system allows an objective and reproducible quantification of coronary artery stenosis. Briefly, a region of interest (size 6.9 × 6.9 mm) in a selected cineframe (overall dimension 18 × 24 mm) encompassing the desired arterial segment is digitized by a high-resolution charge coupled device (CCD) camera with resolution of 512 × 512 pixels and eight bits of brightness resolution. The coronary segment to be analyzed is determined by selecting a number of center-line points, which are connected by linear interpolation. An automated edge-detection program determines the arterial contours by assessing the brightness profile along scan lines perpendicular to the center line. After correction for pincushion distortion and calibration with the use of the guiding catheter as a scaling device, a diameter function can be determined from the contour analysis by computing the distances between the left and right contours. From this diameter function several parameters can be computed, such as the minimal luminal diameter, reference diameter, and diameter stenosis. The variability, precision, and accuracy of the system have been reported previously.[26] All angiograms for subsequent analysis were obtained after intracoronary injection of 2 mg isosorbide dinitrate.

Matching. Lesions were matched for lesion site, minimal luminal diameter, and reference diameter. The coronary artery tree was subdivided into 15 segments according to the American Heart Association guidelines.[27] The variability of repeated measurement of the minimal luminal diameter and interpolated reference diameter from the same cineangiogram, by use of the computer-assisted coronary angiographic analysis system, has been shown to be 0.10 mm for both angiographic parameters.[26] Therefore patient pairs were selected in which the difference between those angiographic variables did not exceed 0.20 mm (twice the variability or 95% confidence interval).

End points. For each dilated or stented segment, the postangioplasty or poststent and follow-up minimal luminal diameters were taken as the mean values from multiple matched projections. The primary angiographic end point of the present study was the minimal luminal diameter at follow-up as determined by quantitative angiography. Furthermore, since data from experimental animals indicate that there is a correlation between the severity of vessel wall injury and subsequent neointimal thickening, the relationship between relative gain (as an index for ves-

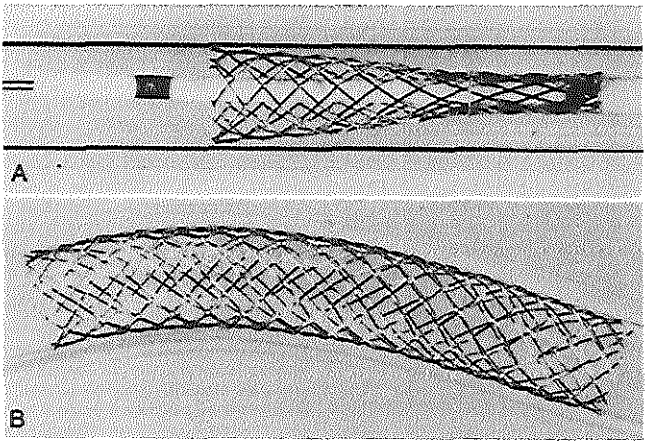

Fig. 1. Self-expanding stent (Wallstent). **A,** With membrane partially pulled back and expanding stent. **B,** Stent in position illustrating longitudinal flexibility.

Table I. Immediate and long-term changes in minimal luminal diameter after stent implantation and balloon angioplasty

	Wallstent			*Balloon angioplasty*		
	Pre	*Post*	*FU*	*Pre*	*Post*	*FU*
Minimal luminal diameter (mm)	1.22 ± 0.34	2.49 ± 0.40	2.01 ± 0.75	1.21 ± 0.29	1.92 ± 0.35*	1.72 ± 0.54†
Diameter stenosis (%)	59 ± 10	19 ± 7	35 ± 20	59 ± 8	36 ± 10*	42 ± 15‡
	$p < 0.00001$		$p < 0.00001$	$p < 0.00001$		$p < 0.00001$

All parameters are expressed as mean ± SD.
There was no statistical difference in baseline angiographic variables between the two study populations. Unpaired *t* tests between two study populations.
*$p < 0.00001$; †$p < 0.003$; ‡$p < 0.01$.

sel wall injury) and relative loss (as an index for neointimal thickening) was studied by means of regression analysis. Relative gain and relative loss are defined as follows: Relative gain = MLD post − MLD pre/RD, and Relative loss = MLD post − MLD fu/RD, where MLD is the minimal luminal diameter, RD is the reference diameter, pre and post refer to before and after the procedure, respectively, and fu is follow-up. The final outcome of the procedure was evaluated by calculating the net gain index. This index represents the ratio of the net gain in lumen improvement at follow-up and the reference diameter and is described by the following equation: MLD fu − MLD pre/RD.

Statistics. Values obtained by quantitative coronary angiography are expressed as means ± SD. The changes in each angiographic variable before and immediately after the intervention and at follow-up were compared by analysis of variance. If significant differences were found, two-tailed paired *t* tests were applied to comparisons within each treatment group and two-tailed unpaired *t* tests for comparisons between treatment groups. A statistical probability of less than 0.05 was considered significant.

RESULTS

Matching. Matching was considered adequate since the baseline interpolated reference diameter and minimal luminal diameter did not differ between groups (Wallstent: 2.99 ± 0.54 mm and 1.22 ± 0.34 mm, balloon angioplasty: 3.01 ± 0.53 mm and 1.21 ± 0.29 mm, respectively; unpaired *t* test $p > 0.05$; Table I). Furthermore, there was an equal number of patients with a lesion in the left anterior descending artery (47 patients), right coronary artery (36 patients), and left circumflex artery (10 patients) in both groups.

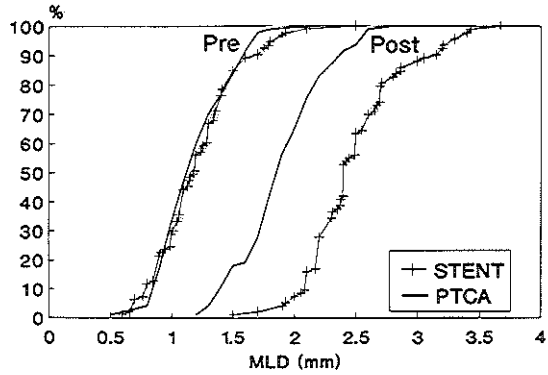

Fig. 2. Cumulative distribution of minimal luminal diameter *(MLD)* at baseline and immediately after stent implantation or balloon angioplasty.

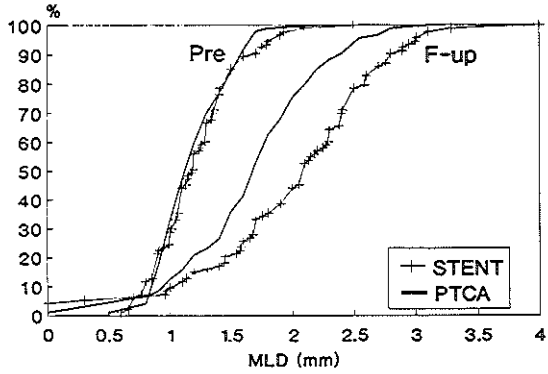

Fig. 3. Cumulative distribution of minimal luminal diameter *(MLD)* at baseline and at follow-up after stent implantation or balloon angioplasty.

Angiographic results. Table I and Figs. 2 and 3 summarize the results of quantitative coronary angiography. Both coronary interventions resulted in a significant immediate increase in minimal luminal diameter, although to a significantly greater extent after Wallstent implantation (from 1.22 ± 0.34 mm to 2.49 ± 0.40 mm) compared with balloon angioplasty (from 1.21 ± 0.29 mm to 1.92 ± 0.35 mm). This was associated with a significant reduction in diameter stenosis from 59 ± 10% to 19 ± 7% and 36 ± 10%, respectively. The reference diameter remained unchanged throughout the study period (2.99 ± 0.54 mm, 3.10 ± 0.49 mm, and 3.09 ± 0.62 mm at baseline, after stent implantation, and at follow-up, respectively, and 3.01 ± 0.53 mm, 3.03 ± 0.54 mm, and 2.97 ± 0.58 mm before and after balloon angioplasty and at follow-up, respectively).

Repeat angiography was performed in all patients at a mean interval of 6.3 ± 3.7 months (Wallstent population) and 5.1 ± 1.4 months (balloon angioplasty population). The minimal luminal diameter

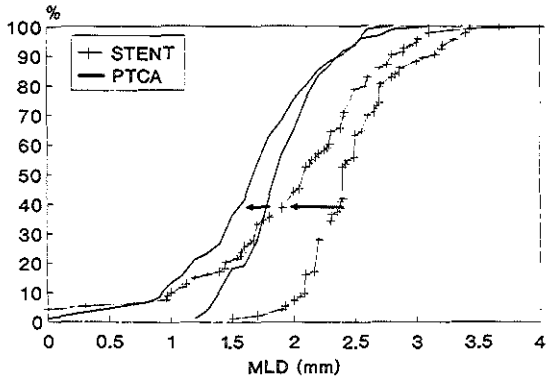

Fig. 4. Loss in minimal luminal diameter *(MLD)*. Cumulative distribution of minimal luminal diameter immediately after stent implantation and balloon angioplasty and at follow-up.

was found to have decreased from 2.49 ± 0.40 mm to 2.01 ± 0.75 mm ($p < 0.00001$) after Wallstent implantation and from 1.92 ± 0.35 mm to 1.72 ± 0.54 mm after balloon angioplasty (Table I, Fig. 3). The percentage of stenosis had increased from 19 ± 7% to 35 ± 20% and from 36 ± 10% to 42 ± 15%, respectively (Table I). To allow comparison with other interventional techniques potentially applied in vessels of different sizes, the final angiographic result was normalized for vessel size and expressed as the net gain index, as defined previously. Despite a greater loss in minimal luminal diameter after Wallstent implantation (0.48 ± 0.74 mm vs 0.20 ± 0.46 mm), the final outcome was superior in this group (2.01 ± 0.75 mm vs 1.72 ± 0.54 mm, $p < 0.003$; Fig. 4). As a result the net gain index after Wallstent implantation was superior to that after balloon angioplasty (0.27 vs 0.18, respectively; $p < 0.003$). Fig. 5 depicts the relationship between relative gain and relative loss. A weak but positive correlation was found after balloon angioplasty. No such relationship was observed in the Wallstent population.

DISCUSSION

Matching. The only method to compare short- and long-term clinical and angiographic results of different coronary interventions is a randomized study. It is beyond the scope of this report to outline the time, energy, and financial burden of such a study. Notwithstanding its utmost importance, other methods such as matching may be used as a surrogate for a randomized study. Subjects can be matched not only as they enter a study but also retrospectively, so that for each patient in one group there are one or more patients with the same characteristics in the comparison group. Therefore matching may not only forecast the results of a randomized study but may also offer insight into the effects of novel therapeutic coronary interventions.[28,29] Although it would be desirable to match subjects for both clinical and angiographic variables, this would require a substantial number of patients in the data base to obtain two study populations of sufficient size. The major disadvantage of such a study method is its retrospective design and the inevitable presence of selection bias. It controls for bias only for those variables taken into account. Matching for all variables is usually not possible because of practical difficulties in finding patients who meet all of the matching criteria. Moreover, if categories for matching are relatively crude, there may be room for substantial differences between matched groups. In this study matching was based on angiographic variables and was limited to lesion site, minimal luminal diameter, and reference diameter. The baseline stenosis characteristics of the patients reported herein are similar to those reported in other studies, and therefore the population of this study may be considered representative of the angioplasty population encountered in clinical practice.[8,14,30,31]

Angiographic parameters defining restenosis and results. Restenosis is the reparative response of the vessel wall after injury. The most accurate method to define and quantify restenosis is direct measurement of neointimal thickening after coronary intervention.[32,33] Obviously this is not possible in humans.

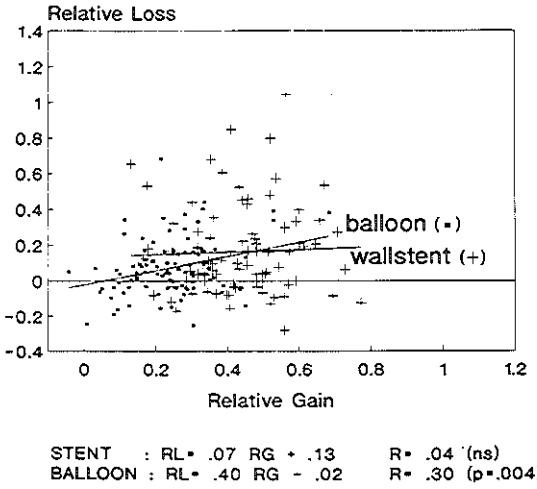

Fig. 5. Relationship between relative gain *(RG)* and relative loss *(RL)* after Wallstent implantation and balloon angioplasty.

Although quantitative coronary angiography indirectly measures the restenosis process without defining its nature (recoil, organized mural thrombus, or neointimal hyperplasia), it is the most objective and reproducible method to date to describe the changes in stenosis geometry after intervention and therefore has been accepted as the "gold standard" to define restenosis.[5, 8, 34-38] Whereas the clinician is best served by a "present/not present" assessment of restenosis, the process of restenosis itself is best analyzed by measuring an absolute angiographic dimension on a continuous scale.[14, 39-41] In this study the minimal luminal diameter was selected, because results of previous studies based on quantitative coronary angiography have demonstrated that this parameter provides more reliable and meaningful information than percentage diameter stenosis, with regard to the hemodynamic significance of a coronary artery lesion.[42-46] Furthermore, it has been shown that the minimal luminal diameter at follow-up correlates with recurrence of angina or exercise-induced myocardial ischemia.[47, 48] Although the process of restenosis can best be addressed by measuring the changes in the obstruction diameter, the final outcome can best be evaluated by measuring the minimal luminal diameter at follow-up, which describes the severity of the lesion at that particular moment. This is especially true when different interventional techniques with a different initial gain are compared. Figs. 2 and 3 elegantly illustrate how the use of this angiographic variable in a continuous approach may be applied to a comparative study of immediate and long-term outcome after balloon angioplasty and stent implantation. The advantage of ranking the minimal luminal diameter for the entire study population is that it depicts the process of restenosis independent of any definition without the application of an artificial threshold dichotomizing restenosis. Furthermore, it allows comparison of the immediate and long-term effects of different interventional techniques.

Inasmuch as lesions are matched not only for minimal luminal diameter but also for reference diameter, the initial gain and the late loss within and between each treatment group can easily be gleaned from the figure. It is easily appreciated that although stent implantation is associated with a significantly greater initial increase in minimal luminal diameter compared with balloon angioplasty (1.27 ± 0.39 mm vs 0.71 ± 0.35 mm), late loss is significantly greater (0.48 ± 0.74 mm vs 0.20 ± 0.46 mm). However, despite this greater loss, the minimal luminal diameter at follow-up after stent implantation is larger than that in patients who underwent balloon angioplasty (Table I, Fig. 4). This is in accordance with the angiographic observations of recent uncontrolled stud-

Table II. Changes in minimal luminal diameter after balloon angioplasty and stent implantation

Procedure	*Reference*	*No. of patients*	*Pre-PTCA*	*Post-PTCA*	*Post-stent*	*Follow-up*	
						All patients	*Patients with patent stent at discharge*
Balloon angioplasty							
	5	88	1.13 ± 0.41	2.10 ± 0.40	—	1.69 ± 0.55	—
	14	261	0.99 ± 0.35	1.77 ± 0.34	—	1.46 ± 0.59	—
	49	309	0.98 ± 0.35	1.77 ± 0.34	—	1.48 ± 0.54	—
	57	60	1.02 ± 0.20	1.80 ± 0.30	—	—	—
Stent implantation							
Wallstent	50	—	1.17 ± 0.52	—	2.53 ± 0.52	1.59 ± 1.08	1.99 ± 0.84
Wiktor	30	50	1.09 ± 0.26	—	2.45 ± 0.35	1.59 ± 0.79	1.78 ± 0.60
Palmaz-Schatz*	51	50	1.00 ± 0.57	—	3.26 ± 0.31	2.39 ± 1.15	—
Benestent	57	60	1.02 ± 0.20	—	2.40 ± 0.50	—	—

PTCA, Percutaneous transluminal coronary angioplasty.
*All coronary angiograms were analyzed with the computer-assisted cardiovascular angiographic analysis system except for the Palmaz-Schatz stent, in which the method of Brown et al.[56] was used.

ies.[8, 14, 30, 49-52] Overall a twofold increase in minimal luminal diameter is observed after stent implantation, whereas the increase in minimal luminal diameter after balloon angioplasty is <1.0 mm. However, a decrease in the minimal luminal diameter at follow-up of 1.0 mm may be expected after stent implantation, when all patients are analyzed including those with subacute stent occlusion, and 0.50 mm when only those patients with a patent stent at hospital discharge are considered. In contrast, balloon angioplasty is associated with a loss of 0.29 ± 0.49 mm to 0.31 ± 0.54 mm (Table II). This is nicely reflected when the process of restenosis is presented in a categorical approach. The incidence of restenosis is 25% after Wallstent implantation and 15% after balloon angioplasty according to the 0.72 mm criterion and 15% and 31%, respectively, according to the 50% diameter stenosis criterion. This underscores the observation that the greater initial gain after stent implantation compensates for the late loss, and thus the improved initial result and not the lessened neointimal hyperplasia is responsible for a reduced incidence of restenosis. The clinical importance of this matter has been outlined previously; that is, the degree of obstruction at follow-up is strongly related to the recurrence of angina and myocardial ischemia.[47, 48]

The pathophysiologic mechanism(s) responsible for restenosis are largely unknown. Schwartz et al.[32, 33] studied the relationship between the degree of vessel wall injury after coil implantation in porcine coronary arteries and the extent of subsequent neointimal thickening. They found that the severity of vessel injury correlated strongly with neointimal thickness. Consistent with this hypothesis, the relationship between relative gain (as an index of vessel wall injury) and relative loss (as an index of neointimal thickening) has recently been analyzed after balloon angioplasty, Wiktor stent (Medtronic Inc., Minneapolis, Minn.) implantation, and directional atherectomy. In all instances a linear relationship was found with a correlation coefficient of 0.26, 0.39 and 0.65, respectively.[53, 54] In contrast to these observations, such a correlation was not found after Wallstent implantation in this study. This observation was unexpected, and because it is at variance with all other reports we believe the fact that there was no predetermined time to control angiographic study, which is reflected by the large standard deviation of time to follow-up (6.3 ± 3.7 months compared with 5.1 ± 1.4 months), explain this discrepancy.

Use of the angiographic data emerging from this study may be justified to improve statistical power calculations in a randomized study. Indeed the proper design of a randomized study comparing different interventional techniques not only requires selection of the appropriate angiographic variable reflecting the restenosis process in a well-validated system of quantitative coronary angiography with known accuracy, precision, and variability but also requires a sufficient number of patients undergoing repeat angiography at a predetermined time for restudy to adequately compare the effects of the two types of treatment. This number depends on (1) the variablity in outcome among patients, (2) the magnitude of the difference in outcome, and (3) the alpha and beta errors.[55] Given the herein reported variability in outcome of 0.75 mm (stent population) and 0.54 mm (balloon population) and the difference in outcome of 0.29 mm, 208 patients (104 per treatment group) are

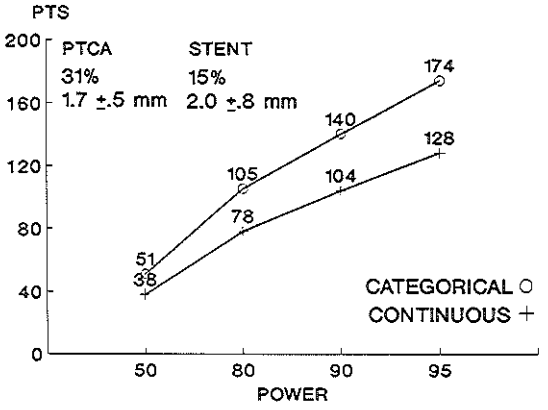

Fig. 6. Power calculations for randomized study using continuous and categorical approach based on retrospective comparison of short- and long-term angiographic results of stent implantation and balloon angioplasty.

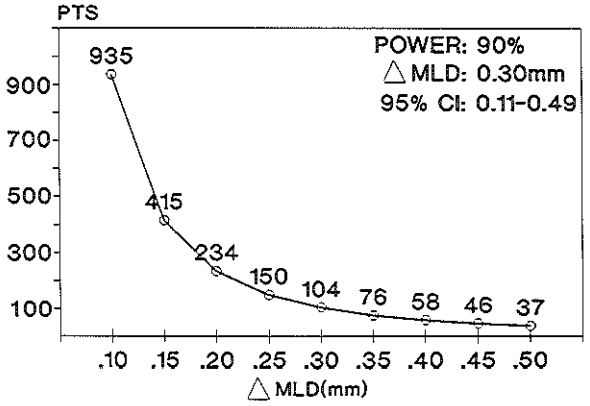

Fig. 7. Number of patients needed for randomized study using continuous approach defining restenosis, with power of 90% and based on difference in minimal luminal diameter *(MLD)* at follow-up between stent implantation and balloon angioplasty ranging from 0.11 to 0.49 mm.

needed for a randomized study, accepting an alpha error of 0.05 and a beta error of 0.10 (power of 90%, Fig. 6). Changing the power of the study in one way or another will affect the number of patients needed. Accepting a greater chance of missing an effective treatment (large beta error and thus reduced power), substantially fewer patients are needed. The observed difference of 0.30 mm is only a point estimate of the true value that lies within the range of 0.11 to 0.49 mm (95% confidence interval). A true difference at these extremes would imply 935 or 37 patients per treatment group, respectively (Fig. 7).

In conclusion, Wallstent implantation results in greater immediate and long-term increases in mini-

mal luminal diameter than balloon angioplasty. The higher initial gain after stent implantation compensates for the late loss, and thus an improved initial result and not a decrease in neointimal hyperplasia is responsible for the reduced incidence of restenosis. Although this study based on matching is a retrospective comparison of two selected populations, it offers insight into the effects of different interventional techniques, forecasting the results of a randomized study and yielding statistical information that might be helpful for the proper design of such a study (sample size, type II error).

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CHAPTER 10

CLINICAL AND ANGIOGRAPHIC RESULTS OF THE PILOT PHASE OF THE BENESTENT STUDY

The Benestent Study Group.

INTRODUCTION

Despite increased operator experience and improvements in catheter design, the risk of abrupt vessel closure and late restenosis continue to limit the safety and efficacy of balloon angioplasty (PTCA) [1,2]. To address these two major shortcomings, a number of new treatment modalities have been advocated, either as an adjunct to PTCA or as a stand alone therapy. One of these is the intracoronary stent [3]. The intracoronary stent is at present the only catheter technology which scaffolds the vessel from its endoluminal site. It has proved not only to be successful in treating coronary dissections and thus in preventing acute or threatened closure but also may reduce the incidence of restenosis by optimizing the immediate angiographic results [4,5]. The latter appeared to be especially true in case of single stent implantation for a de novo lesion in a native coronary artery [6]. Unfortunately, all coronary stents currently available are metallic and thus highly thrombogenic. In the early days of stenting, subacute stent thrombosis was noted in an unacceptable high number of patients [7]. However, with gained experience and insights, and the implementation of a stringent anticoagulation regimen the thrombosis rate gradually decreased to a level which is currently below the incidence of PTCA related abrupt vessel closure [8]. To prevent stent thrombosis, a meticuluous and intensive anticoagulation is mandatory. This exposes the patient to an increased risk of major bleeding and puncture site related complications [9]. Despite these limitations and despite the fact that it is still uncertain whether stent implantation reduces the restenosis rate, they are increasingly being used in an exponential and, sometimes, uncontrolled fashion. Therefore, a number of European interventional cardiologists took the initiative to set up a working group on intracoronary stenting and to design and conduct a multicenter randomized study with the objective of analyzing and comparing the safety and efficacy between stent implantation and PTCA in patients with stable angina pectoris and a single de novo lesion in a native coronary artery. This study originally started in Belgium and the Netherlands and is therefore called the Benestent Study. The purpose of this chapter is to report the data of the pilot study.

METHODS

Patients

All consecutive patients who were scheduled to undergo PTCA of a single de- novo lesion in a native coronary artery because of symptoms of stable angina pectoris were entered into the trial, provided that none of the following clinical- and angioplasty-related exclusion criteria applied:

- *Clinical exclusion criteria*: 1) age under 30 or above 75 years, 2) potentially child bearing women, 3) contraindication to anticoagulation and/or antiplatelet therapy with acetyl salicylic acid, 4) intended surgical interventions, 5) no candidate for bypass surgery, 6) life expectancy less than 1 year or factors making follow-up difficult or

unlikely, 7) unstable angina or evolving myocardial infarction, and 8) previous participation in this study or participation in another study with any investigational drug or device within the past 30 days.
- *Angioplasty-related exclusion criteria*: 1) intended angioplasty of a lesion in a vessel smaller than 3.0 mm and/or longer than 15 mm and/or supplying a large myocardial infarction area, 2) presence of other lesion(s) in the same vessel segment, 3) ostial lesions, 4) lesions giving origin to a large side branch or with a large side branch proximal or distal from the target lesion but having an ostial stenosis which would be covered after stenting the target lesion, 5) lesion in a bend of > 45 degrees, 6) presence of intracoronary thrombus and 7) intended angioplasty of a lesion in a vessel supplied by a venous or arterial graft.

The study was carried out according to the declaration of Helsinki and informed consent had to be obtained in every patient.

Randomization

After informed consent was obtained, the randomization center at the Core Laboratory Cardialysis, Rotterdam, The Netherlands was contacted via a telephone service. Following a screening interview to document the operator eligibility and patient demographic data, a random assignment was given to either PTCA or stent implantation. To guarantee an equal distribution of both treatments per center, the randomization sequence was developed on a site basis in blocks of 6 treatment assignments.

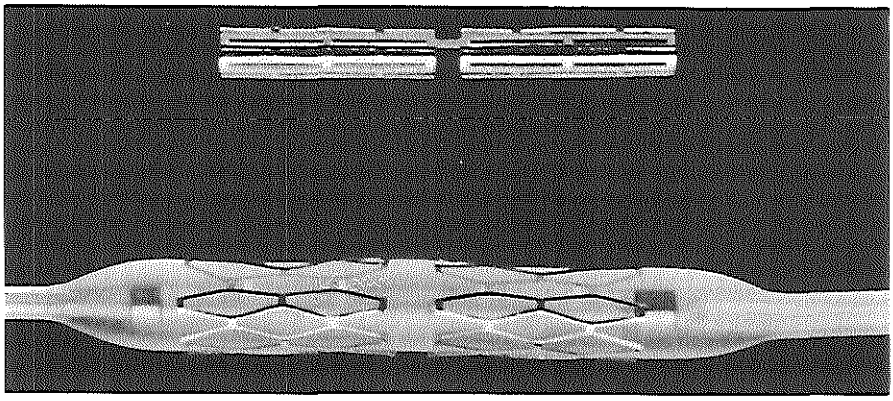

Fig. 1. The Palmaz-Schatz stent is an articulated device consisting of two shorter segments (7mm each) of slotted tubes connected by a small bridging strut (1mm). Initially, each tube consisted of eight rows of staggered rectangles (slots) and was later modified into twelve rows. Upon expansion, each rectangular slot adopts a diamond-like configuration while preserving the length of the stent. The stent is mounted on a commercial available balloon catheter and can expand 4 to 6 times the collapsed diameter.

Stent used

In this study, the articulated Palmaz-Schatz stent was used (Figure 1). The operator was free to use either the Sheath Delivery System (stent mounted on a balloon catheter by the manufacturer and covered by a protective sheath) or the "bare or naked" Palmaz-Schatz stent which had to be mounted on a conventional angioplasty balloon catheter by the operator himself.

Anticoagulation protocol

The anticoagulation and antiplatelet drug therapy in patients who received a stent and in those who were treated with PTCA are shown in Figure 2. In case of PTCA, the anticoagulant drug therapy consisted of a bolus of 10.000 U of heparin for the first hour of the procedure followed by an additional bolus if necessary. No special monitoring of the activated Partial Thromboplastin Time (aPTT) or Activated Clotting Time (ACT) was requested during the procedure. It was left at the discretion of the operator to continue heparin after the procedure for 24 hrs or longer if he or she felt this was necessary. In case of stent implantation, detailed monitoring of the anticoagulation was performed by measuring the aPTT or ACT for the heparin therapy and the Thrombo-Test (TT) or International Normalized Ratio (INR) for the oral anticoagulant drug therapy (Warfarin). Heparin therapy consisted of a bolus of 10.000 U after insertion of the arterial sheath, and repeated once just before stent implantation. After stent implantation, no further heparin was administered to allow sheath removal on the day of stenting when the aPTT or ACT reached twice the normal value. One to 6 hours after sheath removal, heparin therapy was reinstituted by administering a bolus of 5000 U in association with a continuous intravenous infusion, titrated according the aPTT or ACT. In the mean time, a total of 1000 cc of dextran was infused

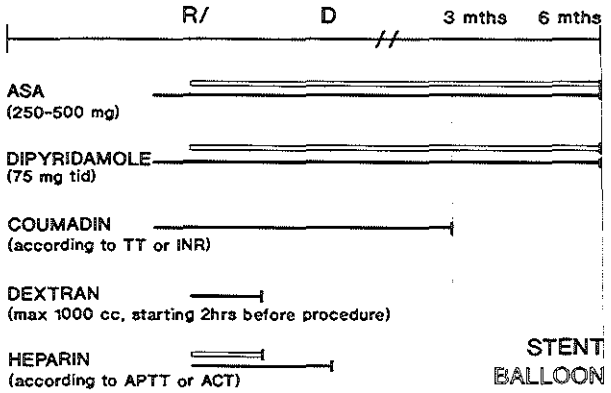

Fig. 2. Anticoagulant and antiplatelet drug therpay in patients undergoing PTCA and stent implantation.

intravenously. The dose of heparin was progressively decreased when TT (warfarin) was in the therapeutic range for at least 36 hours (3 consecutive measurements). The patient was discharged when TT had been stabilized at the therapeutic level.

Additional drug therapy and medication at dischrage

In addition to these anticoagulants and antiplatelet drugs, calcium antagonists were administered in both treatment groups. When calcium antagonists were already being taken before randomization they could be continued. If not, diltiazem CR 120 mg b.i.d. was administered until discharge. The medication at discharge consisted of warfarin for 3 months, acetylsalicylic acid 250 - 500 mg/day and dipyridamole 75 mg t.i.d. for 6 months in patients who received a stent while only the latter 2 drugs were adminsitered in the patients who were treated with PTCA. Other cardiac drugs were continued if the patient were taking these drugs for other reasons than angina pectoris (e.g. hypertension). Antiplatelet drugs including non-steroidal anti-inflammatory drugs other than acetylsalicylic acid were not allowed.

PTCA and stent implantation procedure and follow-up angiography

- PTCA was performed with a steerable, movable guide wire system via the femoral or brachial approach. Choice of balloon and brand as well as inflation pressure and duration were left at the operator's discretion. Stent implantation was performed after predilatation of the target lesion with an undersized balloon catheter to facilitate stent delivery. A balloon/stent assembly, equal or 0.50 mm larger than the vessel to be stented was then positioned at the lesion site followed by a single dilatation up to 6 atmospheres during 30 sec. to deploy the stent. The balloon was then deflated and removed. In case of incomplete expansion or in case of suboptimal luminal result, additional balloon inflation within the stent was performed.
- For the purpose of the study, three coronary angiograms were obtained in each patient - one just before the intervention, one immediately after, and one at follow-up. To achieve maximal vasodilatation, each angiogram was preceded by either nitroglycerin or isosorbide dinitrate given intracoronarily. Angiograms were recorded in such a way that they were suitable for quantitative analysis by the computer-assisted Coronary Angiography Analysis System (CAAS), described in detail elsewhere [10]. All necessary details of the procedure were recorded in the case record form and drawings of the segments to be analyzed were made by the investigator. Before the post-intervention angiogram, radiopaque guide wires were removed to avoid interference with automated edge detection. For calibration purposes, the catheter tip not filled with contrast had to be clearly visible in each filmed view preferably near the center of the screen and were cutt off and sent with the cinefilm to the angiographic core laboratory (Cardialysis, Rotterdam, The Netherlands). To standardize the method of data acquisition and to ensure exact reproducibility of post-intervention and follow-up angiograms, measures were undertaken as has been described earlier [2,11].

Follow-up Evaluation

After successful PTCA (less than 50% diameter stenosis post-PTCA without occurrence of any of the clinical events during hospital stay described below) or stent implantation (it was recommended to obtain a diameter stenosis less than 20% post stenting), patients returned to the outpatient clinic at 1, 3 and 6 months for an interview, physical examination and electrocardiography. At 6-month follow-up, an excercise test was performed according to the Bruce protocol. The follow-up coronary angiogram was performed at the 6-month visit. If symptoms recurred within 6 months, coronary angiography was carried out earlier. If the time to follow-up was less than 3 months and if no definite restenosis was present and no repeat intervention was performed, the patient was asked to undergo another coronary angiography at the predetermined 6 months.

End points

Distinction was made between primary clinical and primary angiographic end points. In addition, a number of secondary clinical and angiographic end points were evaluated.

- The primary clinical end points of the study were the occurrence of any of the following: cardiac death, intracranial hemorrhage or stroke, myocardial infarction, the need for repeat intervention (PTCA, stent, atherectomy or other) or bypass surgery of the previously treated lesion between the initial procedure (PTCA or stent implantation) and repeat angiography at 6 ± 1 months (or 6 months calendar time if 6 months repeat angiography is not performed). This combined end point included periprocedural infarction, emergency bypass surgery or bailout stent implantation. In addition, the functional class according to the Canadian Cardiovascular Society at 6 month follow-up was assessed. An indication to perform repeat intervention or bypass surgery based on the findings at 6 month repeat angiography constituted an end point provided that the treating physician could substantiate the decision on the basis of findings at angiography in combination with chest pain and/or electrocardiogic or scintigraphic evidence of myocardial ischemia either at rest or exercise. All events which were potential end points were centrally reviewed by the critical event committee.

End point definitions were as follows: *cardiac death*: all deaths were considered cardiac unless an unequivocal non-cardiac cause can be established. *Intracranial hemorrhage*: all cerebrovascular accidents occurring in patients receiving anticoagulant drug therapy were considered as intracranial hemorrhage unless computer tomography of the brain unequivocally demonstrated an ischaemic stroke. *Myocardial infarction*: the presence of at least two of the following : (1) occlusion of a previously patent coronary artery; (2) prolonged chest pain; (3) a serial enzyme pattern typical for myocardial infarction with at least one cardiac enzyme raised to more than twice the local upper limit for normal; (4) the development of a new Q-wave. *Repeat intervention*: repeat intervention of the previously dilated or stented

lesion (e.g., PTCA, atherectomy or other) after the initial procedure which was considered completed at the time when the guiding catheter was removed out of the arterial sheath. Angiographic assessment without subsequent intervention was not considered as an end point. *Bypass surgery*: emergency or elective bypass surgery involving the previously dilated or stented segment. Emergency bypass surgery was defined as immediate transfer from the angioplasty suite to the operative room during the initial treatment phase. Bailout stent implantation in patients who underwent PTCA was considered equivalent to emergency bypass surgery. However, stent implantation was considered as a bailout stent implantation only in case of TIMI flow grade 0 or I after PTCA or in case of worsening of the TIMI flow by one grade. In all instances an attempt to improve the suboptimal result with a perfusion balloon catheter had to carried out before bailout stenting could be considered. Coronary bypass surgery or revascularization by means of percutaneous intervention involving other coronary arteries did not constitute an end point.
- Secondary clinical end points were: 1) the occurrence of symptoms and signs of (recurrent) myocardial ischemia (i.e., chest pain with ST-segment or T-wave changes on the electrocardiogram) without myocardial necrosis over the period from the initial procedure until hospital discharge, 2) cross-over of the assigned treatment to another and 3) the incidence, severity and location of bleeding events other than intracranial hemorrhage.

- The primary angiographic end point of this study was the minimal luminal diameter at follow-up as determined by quantitative angiography. If a revascularization procedure involving the dilated or stented segment had been performed before 6 months repeat angiography, the last angiogram obtained before the intervention, if available, was used as an end point, irrespective of the timing of repeat intervention (hours, days, weeks). In the absence of a 6 months repeat angiogram, the last angiogram obtained within the previous 3 months, if available, was used, provided that no end point had taken place. For each dilated or stented segment, the minimal luminal diameter was taken as the mean values from multiple matched projections.

Secondary angiographic end points included 1) the changes in the minimal luminal diameter and percentage diameter stenosis (100% x [reference diameter - minimal luminal diameter/ reference diameter) following intervention and at follow-up angiography, 2) evidence of restenosis at 6 months repeat angiography indicated by a change from < 50% stenosis post PTCA or stent implantation to > 50% at follow-up and by a decrease in minimal luminal diameter ≥ 0.72 mm, 3) cross-over of the assigned treatment to another and the incidence, severity and location of bleeding complications other than intracranial hemorrhage.

Analytical plan

The main clinical analysis consisted of a single comparison between the 2 study groups of the primary clinical end point, irrespective of the time of occurrence, involving all randomized patients with the exception of those in whom no PTCA or

stent implantation had taken place (intention to treat analysis). In addition to a total account of all clinical events (non-mutually exclusive analysis), the clinical events were ranked according to the highest category on a scale ranging from: 1, death, 2, intracranial hemorrhage or stroke, 3, myocardial infarction, 4, bailout stent implantation/emergency bypass surgery, 5, elective bypass surgery, 6,repeat PTCA.

The main angiographic analysis consisted of a single comparison between the 2 study groups with analyzable angiograms. For both the clinical and angiographic end points, randomized patients in whom an intervention has taken place were analyzed in their assigned treatment group irrespective of the angioplasty technique used according to the intention-to-treat principle. Additionally, an efficacy analysis was performed according to the technique actually used at the time of the intervention, irrespective of the randomization, implying the inclusion of the patients who crossed over from the assigned treatment to the other. A per protocol analysis will be performed for the total study population of the Benestent Study (n = 520 patients). The latter is defined by the analysis of those patients who have received the assigned treatment as dictated by the randomization and which thus excludes the patients who crossed over from one treatment to the other.

RESULTS

Between June and December 1990, a total of 60 consecutive patients were randomized at 8 participating centers. Of these, 27 patients were randomized to stent implantation and 33 patients to PTCA. Their baseline clinical and angiographic characteristics are depicted in Table 1 and 2. No baseline differences were observed between the two groups. Figure 3 shows the flow diagram of the patients randomized and their actual treatment.

Clinical results

Implantation success rate: Five out of the 27 patients randomized to stent did not receive a stent. In two patients, neither a stent implantation nor a PTCA was performed because of unability to cross an unexpected totally occluded coronary artery in one and because neither a stent nor a balloon catheter could be advanced to the target lesion despite the presence of a guide wire in situ in the other. The first patient received medical treatment, the second was referred for elective bypass surgery. Three other patients did not receive a stent but were successfully treated with PTCA. In two patients the operator decided not to implant a stent because the size of the target vessel proved to be much to small (1.83 mm) during on-line quantitative coronary analysis in one patient and because of inappropriate fitting of the guiding catheter in the ostium of the left main stem in the other. In the remaining patient, stent implantation was attempted but a tortuous segment proximal to the target lesion prevented stent delivery. In this patient, the stent which was mounted on a conventional balloon catheter by the operator, dislodged from the balloon when

Table 1. Baseline clinical characteristics.

	Stent	PTCA
n	27	33
age (mean ± SD)	58 ± 11	58 ± 11
male	18 (67%)	23 (70%)
CCS Class I	1 (4%)	0
II	7 (26%)	9 (27%)
III	13 (48%)	18 (55%)
IV	4 (15%)	5 (15%)
Non-exertional	2 (7%)	1 (3%)
Prior MI	5 (19%)	7 (21%)
Prior CABG	0	0
Prior PTCA	0	0
Hypertension	7 (26%)	10 (30%)
Hypercholesterolemia	6 (22%)	9 (27%)
Smoking	5 (19%)	10 (30%)
Diabetes	2 (7%)	2 (6%)

MI: myocardial infarction, CABG: coronary artery bypass grafting
No statistically significant differences were observed between the two treatment groups.

Table 2. Baseline angiographic characteristics.

	Stent (N = 27)	PTCA (N = 33)
RD(mm)	2.82 ± 0.50	2.82 ± 0.45
MLD(mm)	0.99 ± 0.30	0.99 ± 0.22
DS(%)	64 ± 12	64 ± 8
RA (mm^2)	6.44 ± 2.24	6.43 ± 2.15
MLCA(mm^2)	0.88 ± 0.53	0.82 ± 0.62
AS(%)	88 ± 10	88 ± 12
Length (mm)	6.3 ± 2.3	6.6 ± 1.9
Plaque(mm^2)	7.7 ± 4.2	8.1 ± 3.4
Symmetry	0.5 ± 0.3	0.5 ± 0.2
Target vessel LAD	18 (67%)	27 (82%)
LCX	5 (18%)	2 (6%)
RCA	4 (15%)	4 (12%)

No statistically significant differences were observed between the two treatment groups.

pulling back the balloon/stent assembly and embolized into the femoral artery. The postoperative course was uneventful. In one patient randomized to PTCA, a bailout stent was implanted because of coronary dissection.

Clinical events: A total account, and ranking of clinical events, following stent implantation and PTCA is depicted in Table 3 and 4. Since the postoperative course and long-term clinical follow-up was uneventful in the three patients who crossed over from stent implantation to PTCA, there was no difference between the intention to treat and efficacy analysis.

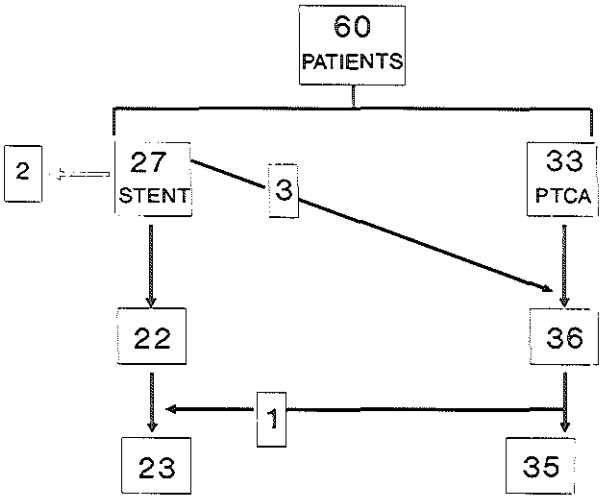

Fig. 3. Diagram illustrating the patient flow after randomization. See text for further explanations.

All clinical events during hospital stay were related to either subacute stent thrombosis or abrupt vessel closure after PTCA. Stent thrombosis was documented in two patients at day 2 and 3 after implantation while abrupt vessel closure after PTCA occurred at 30 min. and 1 day after the procedure. Both patients with subacute stent thrombosis underwent repeat PTCA and emergency bypass surgery. The postoperative course was uneventful in one. The other patient sustained an anterior myocardial infarction (CPK 3035 U/l). The two patients with (sub)acute vessel closure after PTCA were treated with repeat PTCA with uneventful course, except for a small non-Q wave myocardial infarction (CPK 280 U/l) in one.

One patient randomized to stent implantation received two stents. Implantation of the first stent in the first segment of the right coronary artery resulted in dissection type C in association with a significant residual stenosis. A second stent was successfully implanted with restoration of the antegrade flow. The immediate and long-term clinical and angiographic outcome was uneventful. As already mentioned above, one patient randomized to PTCA received a stent because of dissection after PTCA.

One patient died three weeks following successful stent implantation due to hypovolemic shock and infection in association with repeated surgical repair of an arterio-venous fistula. Two patients (one in each group) sustained an acute myocardial infarction. This event was related to repeat coronary intervention in the patient in the PTCA group. This patient underwent directional atherectomy 4 months after PTCA, which was complicated by a small infarct (CPK 202 U/l) and a transient ischemic cerebrovascular accident. The other patient sustained a Q-wave myocardial infarction 4 months after stent implantation. The cause of this event remains unclear. There was no evidence of angina whatsoever at the time of the infarct and control

Table 3. Total account of clinical events following stent implantation and PTCA.

	Stent (N = 27)	PTCA (N = 33)	RR (95% CI)
Death			
pre-discharge	0	0	
post-discharge	1	0	
All	1	0	NA
ICH/stroke			
pre-discharge	0	0	
post-discharge	0	1	
All	0	1	NA
AMI			
pre-discharge	1	1	
post-discharge	1	1	
All	2	2	1.22 (0.18 ; 8.11)
EmCABG/bail-out stent			
pre-discharge	3	1	
post-discharge	0	0	
All	3	1	3.67 (0.40 ; 33.3)
Elective CABG			
pre-discharge	-	-	
post-discharge	2	2	
All	2	2	1.22 (0.18 ; 8.11)
re-PTCA			
pre-discharge	2	2	
post-discharge	1	10	
All	3	12	0.31 (0.10 ; 0.97)
Total account of events	11	18	0.75 (0.43 ; 1.30)

ICH : Intracranial hemorrhage, (Em)CABG : (Emergency) bypass surgery, RR : relative risk, 95 % CI : 95 % Confidence interval, NA : not applicable.

angiography 2 months later revealed apart from some radiolucency at the origin of the first septal perforator which was covered by the stent, no other abnormalities. In contrast to the PTCA patients, the two patients in the stent group sustained a transmural myocardial infarction (CPK 3035 and 1620 U/l).

The major difference between the two study groups, was the need for elective revascularization during follow-up. Bypass surgery or repeat PTCA was performed in three patients randomized to stent implantation compared to twelve patients randomized to PTCA (Table 3). The 6-month event and symptom free survival (freedom from death, intracranial hemorrhage or stroke, myocardial infarction, bypass surgery or repeat intervention and angina pectoris) was 67% after stent implantation and 55% after PTCA.

No patient in the PTCA group sustained a major bleeding or puncture site related complication compared to seven patients in the stent group (surgical repair and transfusion because of pseudoaneurysm: 2, surgical repair: 1, surgical repair and transfusion because of an arterio-venous fistula: 1, transfusion because of groin

Table 4. Clinical events following stent implantation and PTCA according to a ranking scale ranging from death to re-PTCA.

	Stent (N = 27)	PTCA (N = 33)	RR (95 % CI)
Death			
pre-discharge	0	0	
post-discharge	1	0	
All	1	0	NA
ICH/stroke			
pre-discharge	0	0	
post-discharge	0	1	
All	0	1	NA
AMI			
pre-discharge	1	1	
post-discharge	1	0	
All	2	1	2.44 (0.23 ; 25.5)
EmCABG/bail-out stent			
pre-discharge	2	1	
post-discharge	0	0	
All	2	1	2.44 (0.23 ; 25.5)
Elective CABG			
pre-discharge	0	0	
post-discharge	2	2	
All	2	2	1.22 (0.18 ; 8.11)
re-PTCA			
pre-discharge	0	0	
post-discharge	1	9	
All	1	9	0.14 (0.02 ; 1.01)
Total	8	14	0.70 (0.35 ; 1.41)

Abbreviations: see Table 3.

hematoma: 3 patients). The hospital stay was (mean ± sd) 2.2 ± 1.3 days for the patients who underwent PTCA compared to 11.5 ± 5.7 in the patients who received a stent.

Angiographic results

Table 5 and Figures 4-7 summarize the quantitative angiographic findings. A total of 54 out of the 58 patients (93%) eligible for follow-up completed their angiographic follow-up study at (mean ± sd) 5.3 ± 1.9 months. According to both the intention to treat and the efficacy analysis, the increase in minimal luminal diameter immediately after stent implantation was significantly greater than after PTCA. Despite a higher loss, the minimal luminal diameter at follow-up proved to be greater after stent implantation than after PTCA. This did not reach statistical significance, due to the small number of patients treated. However, the 95% confidence interval of the difference in minimal luminal diameter at follow-up between the two treatment groups was −0.13 to 0.57 mm according to the intention to treat analysis and

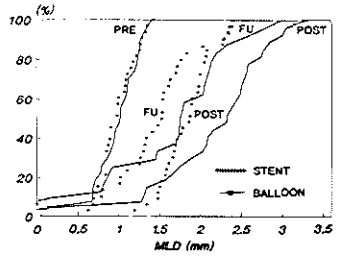

Fig. 4. Cumulative distribution curves of the minimal luminal diameter and its changes post PTCA or post stent implantation and at follow-up according to the intention to treat analysis. X-axis: minimal luminal diameter, Y-axis: relative number of patients.

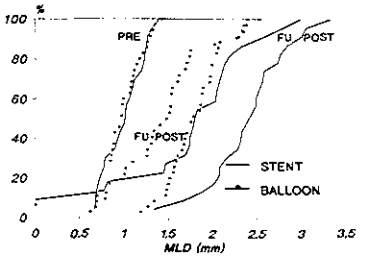

Fig. 5. Cumulative distribution curves of the minimal luminal diameter and its changes post PTCA or post stent implantation and at follow-up according to the efficacy analysis. X-axis: minimal luminal diameter, Y-axis: relative number of patients.

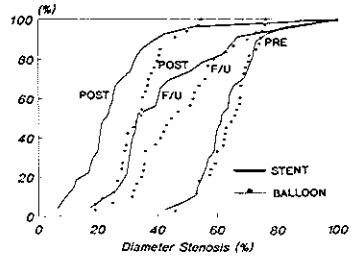

Fig. 6. Cumulative distribution curves of the percent diameter stenosis and its changes post PTCA or post stent implantation and at follow-up according to the intention to treat analysis. X-axis: diameter stenosis, Y-axis: relative number of patients.

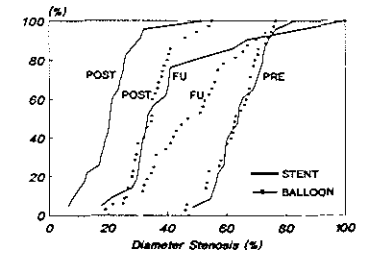

Fig. 7. Cumulative distribution curves of the percent diameter stenosis and its changes post PTCA or post stent implantation and at follow-up according to the efficacy analysis. X-axis: diameter stenosis, Y-axis: relative number of patients.

−0.03 - 0.69 mm according to the efficacy analysis. The incidence of restenosis is shown in Table 6.

DISCUSSION

This is the first report describing the results of a randomized study in which stent implantation was compared with balloon angioplasty. It needs to be stressed that it concerned the pilot phase in which only a limited number of patients have been randomized and treated.

- Taking into account this small sample size, the first striking feature is the low stent

Table 5. Changes in minimal luminal diameter (MLD) and diameter stenosis (DS) following stent implantation and PTCA

	Intention to treat analysis		
	Stent (N = 27)	PTCA (N = 33)	P
MLD (mm)			
pre	0.99 ± 0.30	0.99 ± 0.22	NS
post	2.19 ± 0.70	1.85 ± 0.31	0.01
FU	1.67 ± 0.77	1.45 ± 0.59	NS
DS (%)			
pre	64 ± 12	64 ± 8	NS
post	27 ± 18	34 ± 9	0.04
FU	41 ± 23	50 ± 19	NS
	Efficacy analysis		
	Stent (N = 23)	PTCA (N = 35)	P
MLD (mm)			
pre	1.00 ± 0.24	1.00 ± 0.21	NS
post	2.41 ± 0.46	1.81 ± 0.31	<.0001
FU	1.75 ± 0.77	1.42 ± 0.58	NS
DS (%)			
pre	65 ± 8	63 ± 8	NS
post	22 ± 10	35 ± 8	<.0001
FU	43 ± 22	50 ± 19	NS

All changes within each treatment group (paired t-test) were highly significant. The reference diameter (2.82 ± 0.50 and 2.82 ± 0.45 mm) remained unchanged.

Table 6. Incidence of restenosis following stent implantation and PTCA

	Intention to treat analysis	
	Stent (N = 27)	PTCA (N = 33)
0.72 mm	29%	27%
50% DS	30%	47%
	Efficacy analysis	
	Stent (N = 23)	PTCA (N = 35)
0.72 mm	27%	28%
50% DS	24%	50%

implantation success rate. It contrasts with the general experience in which a success rate exceeding 90% has been reported [9]. Patient selection cannot fully explain this high implantation success rate reported in the literature since this also holds for a randomized study with its specific in- and exclusion criteria. Most likely, the difference is explained by the fact that in nonrandomized studies, failed attempts may not always have been registered and/or reported. The protocol of the Benestent Study requests that only patients with a vessel larger than 3.0 mm be included. Despite this, the median value of the reference diameter proved to be 2.91 mm (range 1.83 - 4.10

mm) and 2.83 mm (range 2.14 - 4.12 mm) for the stent and PTCA group, respectively. Detailed analysis of this angiographic variable of the 60 patients herein reported discloses that a total of 42 patients or 70% of the total study population had a vessel smaller than 3.0 mm. The erroneous inclusion of the patient with a vessel as small as 1.83 mm was due to the fact that neither the field size of the image intensifier nor the size of the diagnostic catheter used in the refering institution were known which resulted in a wrong visual estimation of the vessel size. When the true vessel size became apparent during on-line quantitative coronary angiography just prior to the actual treatment, it was wisely decided not to implant a stent. Apart from the risk of subacute stent thrombosis in such a patient, successful stent delivery was not very likely considering the profile of the Sheath Delivery System of the Palmaz-Schatz stent (5 F). True failure of stent delivery occurred in 4 patients. In addition to the patient with a vessel of 1.83 mm, the target vessel proved to vary between 2.03 and 2.90 mm in three other patients. In one of these patients, stent delivery failed due to a tortuous segment proximal to the target lesion. This underscores that in addition to vessel size and catheter profile and appropriate fitting of the guiding catheter, longitudinal flexibility of the device are prerequisites for successful implantation. Improvements in stent design are currently under way to improve the stent profile and longitudinal characteristics [12]. It is of note that with progress of the Benestent study, the implantation success rate increased to 94% in the first 129 consecutive patients [13].

- One patient died three weeks after stent implantation. Although the stent was patent at pathologic examination, death has to be considered procedure- and thus stent-related. In retrospect, one may argue whether this patient should have been referred for surgical repair of an arterio-venous fistula. This is usually well tolerated and is generally not considered as an indication for surgery.
- The incidence of vessel closure was identical between the two treatment groups. Stent thrombosis occurred in 2 out of the 23 patients (9%). Although the number of patients in the pilot phase is too small to draw any firm conclusions, it is in accordance with the general experience reporting an incidence, expressed as the weighted average of all studies, of 8.2% [14]. Such an incidence of stent thrombosis is too high to be accepted but is influenced by the high incidence of stent thrombosis in the early days of stent implantation during which an incidence of 20% within the first two weeks has been reported [7]. Recent studies report a much lower stent thrombosis rate. The overall incidence of stent thrombosis following Palmaz-Schatz stent implantation is 3.3% and just recently an incidence of 0.4% was reported [8,14]. Noteworthy is that the stent thrombosis rate in the first 129 consecutive patients of the Benestent study was 2.3% [13]. In contrast to abrupt vessel closure after PTCA which generally occurs within 24 hrs after the procedure, stent thrombosis appears to occur after a lapse of a few days [15]. In the current study, stent thrombosis occurred at day 1 and 3 after implantation. Although clinical, haemostatic and angiographic variables may be found to predict stent thrombosis, it remains largerly an unpredictable event. Notwithstanding the utmost importance of proper institution of the anticoagulant drug therapy, the cause of stent thrombosis is

most likely multifactorial. Bail out stent implantation, small stent size or final stent diameter and left ventricular function have been identified as independent predictors of subacute stent thrombosis [15,16]. It remains controversial whether the use of multiple stents is associated with an increased risk of stent occlusion. Shaknovich et al. did not observe a difference in the subacute stent thrombosis rate between single and multiple stent implantation (3.9% and 3.7%, respectively) while in the single center experience reported by Doucet et al., the use of multiple stents was identified as an independent predictor [15,17]. Perhaps, one of the major determinants is flow. One of the patients with stent thrombosis herein reported had a lesion distal to the stented segment. This may have contributed to this event or even be the actual cause.
- Not unexpected, the incidence of major bleeding complications was significantly higher and the hospital stay was longer in patients treated with a stent. The overall incidence expressed as weighted average of groin hematomas and of pseudoaneurysm reported in the literature is 7.5% (range 2.7% - 26%) and 4.2% (range 0.0% - 10.8%), respectively [14]. These numbers represent the overall experience including the experience of the first period of intracoronary stenting during which the anticoagulation protocol evolved and during which thrombolytics were quite often used [7]. Despite improvements in postoperative management and unification and improved monitoring of the anticoagulation, these numbers have not decreased [14,18]. This may be related to a more aggressive application of the anticoagulation regimen to avoid stent thrombosis. Indeed, while there is a clear trend towards a reduced stent thrombosis rate, the incidence of vascular access site related complications did not drop [14]. The use of new hemostatic devices may have a beneficial influence. Controlled compression with a belt-held pneumatic compression device proved to be higly successful and reduced the incidence of pseudoaneurysm in our hands and those of others [19].
- Despite the risk of stent thrombosis and the need for an intensive anticoagulation, the symptom and event free survival (freedom from death, cerebrovascular accident, myocardial infarction, bypass surgery or repeat intervention) was higher following stent implantation than following PTCA (67% versus 55%). These long-term clinical results of the patients treated with PTCA in the pilot phase of the Benestent Study is strikingly similar to the long-term clinical results reported in the PARK Study. In this study, which is a multicenter randomized, double-blind, placebo controlled trial evaluating the effects of ketanserin in the prevention of restenosis, the symptom and event free survival was 54% in the ketanserin group and 51% in the placebo group [20]. The difference in the long-term clinical results of the current study, is largely explained by the difference in the need for repeat intervention or elective bypass surgery between the two study groups. A total of three patients in whom a stent was implanted needed bypass surgery (two patients) or repeat PTCA (one patient) compared to twelve patients (bypass surgery: 2 patients, repeat PTCA or directional atherectomy: 10 patients) in whom a PTCA was performed. The reduced need for repeat intervention or surgical revascularization is most likely explained by the significantly superior improvement in stenosis geometry after stent implantation (Table 5). According to both the intention to treat and efficacy analysis the increase

in minimal luminal diameter was 1.20 ± 0.75 mm and 1.40 ± 0.43 mm after stent implantation compared to 0.85 ± 0.30 mm and 0.81 ± 0.28 mm after PTCA. Despite a greater loss at follow-up, the minimal luminal diameter still proved to be greater in patients who received a stent compared to patients in whom a PTCA was performed. This did not reach statistical significance due to the small number of patients treated. Noteworthy is the value of the minimal luminal diameter at follow-up in the PTCA group. It was equal or less than 1.45 mm. This value was found to correlate with recurrence of angina at follow-up in a population with single vessel disease who underwent a single site balloon dilatation [21]. Furthermore, the angiographic data shown in table V and VI underscore the concept that the higher initial gain following stent implantation compensates for the late loss and thus that improved initial results and not lessened neointimal hyperplasia is responsible for a reduced incidence of angiographic restenosis [5,6].

CONCLUSIONS

In this limited number of patients randomized to either stent implantation or balloon angioplasty, the long-term clinical and angiographic outcome proved to be superior in patients who received a stent. However, this was achieved at the cost of a significant risk of vascular access site complications and a longer hospital stay. These results have encouraged the investigators to start with the definite study in which a total of 520 patients will be randomized.

APPENDIX

Steering Committee
P.W. Serruys, MD (Chairman), H. Emanuelsson, MD, G.R. Heyndrickx, MD, P.P.T. de Jaegere, MD, F. Kiemeneij, MD, C. Macaya, MD, J. Marco, MD, P. Materne, MD.

Ethics and Safety Committee
F. Verheugt, MD, J. Tijssen, PhD, G. de Backer, MD.

Critical Event Committee
P.W. Serruys, MD, P.P.T. de Jaegere, MD, P.J. de Feyter, MD, F. Kiemeneij, MD, P. vande Heuvel, MD.

Angiographic assessment committee
P.W. Serruys, MD, P.P.T. de Jaegere, MD, W. Rutsch, MD, B. de Bruyne, MD, V. Legrand, MD.

Benestent Study Group

Participating Clinics and invesgigators.
The following institutions and investigators participated in the Benstent study. The number of patients enrolled at each center are given in parenthesis, with specification of the patients enrolled in the pilot study:

1) University Hospital San Carlos, Madrid, Spain [76]: C. Macaya, MD, principal investigator, F. Alfonso, MD, J. Goicolea, MD, A. Iniguez.
2) University Hospital Rotterdam - Dijkzigt, Thoraxcenter, Rotterdam, The Netherlands (57 of whom 23 in the pilot study): P.P.T. de Jaegere, MD, principal investigator, P.W. Serruys, MD, P.J. de Feyter, MD, M.A. Morel, RN.
3) Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands (50 of whom 18 in the pilot phase): F. Kiemeneij, MD, principal investigator, G.J. Laarman, MD, R. vander Wieken, MD.
4) Freie Universität Berlin, Universitätsklinikum Rudolf Virchow/Charlottenburg, Berlin, Germany [39]: W. Rutsch, MD, principal investigator.
5) Onze Lieve Vrouw Ziekenhuis, Aalst, Belgium (38 of whom 5 in the pilot phase): G. Heyndrickx, MD, principal investigator, B. de Bruyne, MD.
6) Med. Clin. I. Sahlgrenska Hospital, Goteborg, Sweden [36]: H. Emanuelsson, MD, principal investigator, P. Albertsson, MD.
7) Clinique Pasteur, Toulouse, France (32 of whom 1 in the pilot phase): J. Marco, MD, principal investigator, J Fajadet, MD, S. Doucet, MD.
8) Sart-Tilman, Centre Hospitalier Universitaire, Liège, Belgium (32 of whom 6 in the pilot phase): V. Legrand, MD, principal investigator.
9) Hôpital Citadelle, Liège, Belgium (19 of whom 2 in the pilot phase): P Materne, MD, principal investigator, J Boland, MD.
10) Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina [19]: J. Belardi, MD, prinicipal investigator, J. Berrocal, MD.
11) Royal Brompton, National Heart, London, United Kingdom [12]: U. Sigwart, MD, prinicipal investigator, N. Buller, MD.
12) Centro Cuore, Milano, Italy (11): A. Colombo, MD, prinicipal investigator, L. Maiello, MD.
13) CHUV, Lausanne, Switzerland (11): J.J. Goy, principal investigator, E. Eeckhout, MD.
14) Middelheim Ziekenhuis, Antwerpen, Belgium (10 of whom 3 in the pilot phase): P. van den Heuvel, MD, principal investigator, F. van den Brande, MD.
15) Gregorio Maranon, Madrid, Spain (10): J. Delcan, MD, principal investigator, E. Garcia, MD.
16) Ziekenhuis de Weezenlanden, Zwolle, The Netherlands (8): H. Suryapranata, MD, principal investigator, J. Hoorntje, MD.
17) St. Antonius Ziekenhuis, Nieuwegein, The Netherlands (8): Th. Plokker, MD, principal investigator, G. Mast, MD.

18) Hospital Maggiore, Trieste, Italy (8): S. Klugmann, MD, principal investigator, E. di Garzia, MD, A. Salvi, MD.
19) Hôpital Cantonal Universitaire, Genève, Switzerland (7): P. Urban, prinicipal investigator, E. Camenzind.
20) Academisch Ziekenhuis Groningen, The Netherlands (6): P. den Heijer, MD, principal investigator, R. van Dijk, MD.
21) Academisch Medisch Centrum, Amsterdam, The Netherlands (6): J. Piek, MD, principal investigator, K. Koch, MD.
22) Christian Albrechts University, Kiel, Germany (6): R. Simon, MD, principal investigator, Fr. Herrmann, MD.
23) Centre Cardiologique de Nord, Paris, France (5): M.C. Morice, MD, principal investigator, T. Royer, MD.
24) James Hospital, Dublin, Ireland (5): P. Crean, MD, prinicipal investigator.
25) Catharina Ziekenhuis, Eindhoven, The Netherlands (3 of whom 2 in the pilot phase): H. Bonnier, MD, principal investigator, J. Koolen, MD, F. Bracke, MD.
26) Clinique Universitaire St. Luc, Université Catholique Louvain, Bruxelles, Belgium (2): W. Wijns, MD, principal investigator, J. Renkin, MD.
27) CHUR, Nancy, France (2): N. Danchin, MD, prinicipal investigator, Y. Juillière, MD.
28) Policlinique Volney, Rennes, France (2): C. Bourdonnec, MD, principal investigator.

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CHAPTER 11

INTRACORONARY STENTING

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Current Medicine, 1993, in press.

INTRODUCTION

Percutaneous Transluminal Coronary Angioplasty by means of balloon catheters (PTCA) is now widely accepted as an effective treatment for selected patients with obstructive coronary artery disease. Gained operator experience and improved catheter technology have increased the immediate success rate to more than 90% and reduced the incidence of procedure related complications[1,2]. However, abrupt vessel closure during or immediately following PTCA and late restenosis continue to limit the safety and effectiveness of this procedure [3,4].

Abrupt closure has been reported to occur in 2 to 10% of patients treated and is the major determinant of in-hospital morbidity and mortality [3]. When refractory to prolonged balloon inflation, dilatation with an oversized balloon and/or adjunct thrombolytic therapy, emergency bypass surgery may be necessary to limit myocardial damage. Even then, abrupt closure is associated with a 3 to 6% mortality and up to a 50% frequency of periprocedural myocardial infarction [5-9].

The incidence of restenosis varies between 20 and 57%, depending on the definition used, patient population studied and time to and completeness of follow-up angiography. It necessitates repeat intervention or eventually bypass surgery in up to 20% of the patients [1,4,10].

To address these two major shortcomings, a number of new devices have been developed. One of these, is the intracoronary stent. The first clinical experience with stent implantation dates back to the late sixties when Charles Dotter implanted tube grafts in peripheral arteries [11]. His intention was to reduce the high rate of restenosis in patients who had undergone peripheral balloon angioplasty of occluded femoro-popliteal arteries. While in his initial experiments using plastic tube grafts all stents thrombosed within 24 hours of implantation, the results improved when using stainless steel coils. Since then, the development of intravascular stents has progressed steadily. At present, a number of different stents for coronary use are available, each with its own specific design, physico-chemical characteristics and mode of implantation (Table 1). Distinction can be made between self-expanding and balloon-expandable stents. The first is a spring-like design that can be constrained

Table 1. Design and characteristics of stents in clinical evaluation.

Stent	Configuration	Filament Composition	Filament Thickness (mm)	Stent Diameter (mm)	Stent Length (mm)	Surface Area (%)	Radio-paque
Self-expanding							
Wallstent	Wire-mesh	Stainless steel	0.07-0.10	3.5-6.0	21-45	18.5-20	No
Balloon-expandable							
Palmaz-Schatz	Slotted tube	Stainless steel	0.08	3.0-4.0	15	10	No
Gianturco-Roubin	Coil	Stainless steel	0.15	2.0-4.0	20	10	No
Wiktor	Coil	Tantalum	0.125	3.0-4.5	15-17	5-10	Yes
Strecker	Woven-wire	Stainless steel Tantalum	0.07	2.0-3.5	15-25	-	No Yes

to a small diameter and then expands to a predetermined dimension when the constraint is removed. The balloon-expandable stent relies on plastic deformation of metal beyond its elastic limits.

While the long-term impact of stent implantation in terms of safety and efficacy still remains to be determined, its demonstrated ability to improve the immediate angioplasty results and therefore its potential for reducing the incidence of late restenosis and its application as a bail-out device have stimulated an explosive use of these devices. The purpose of this paper is to summarize the clinical experience with stent implantation in human coronary arteries.

STENT TO TREAT ABRUPT VESSEL CLOSURE

Acute symptomatic occlusion refractory to repeat dilatation with or without adjunctive pharmacologic treatment is one of the most troublesome situations one may encounter during coronary angioplasty and is associated with a significant morbidity and mortality [3,5-9]. Therefore, any technique or device capable of restoring and maintaining antegrade flow, stabilizing the clinical condition and obviating the need for emergency bypass surgery would be most welcome.

The rationale for using intracoronary stents in this situation is based on their unique physical properties. At present, it is the only catheter based technology which provides a scaffold for the instrumented vessel. It prevents vessel collapse and tacks back intimal and medial tears, sealing the thrombogenic subintimal space. This was first demonstrated in pathologic studies in which a balloon-expandable stent was implanted in diseased human cadaver coronary arteries (Figure 1) [12]. Clinical experience with bail-out stent implantation was first reported by Sigwart et al. [13]. In a very limited number of patients, the self-expanding Wallstent was implanted which resulted in an immediate restoration of adequate coronary flow with normalization of the ECG and relief of symptoms with no evidence of acute myocardial infarction. Since then, each of the clinically available stents have been used for this purpose with encouraging results (Figure 2A+B, Table 2). All authors report a high implantation success rate which is remarkable taking into account the technical difficulties one may encounter in a bail-out situation. Disappearance of angiographic landmarks and spasm of the vessel segment may render stent delivery and correct positioning very laborious. Therefore, extra operator experience and skill is required. The selection of the device may influence the delivery success rate. In case of dissection in a vessel with an acute takeoff or tortuosity, stents with a higher longitudinal flexibility such as the self-expanding Wallstent and the balloon-expandable coil stents (Wiktor, Gianturco-Roubin and Strecker stent) may preferably be used instead of the stents with a more rigid mesh structure. Although the radiopacity of the Wiktor stent may be helpful in correct positioning, comparable delivery rates have been reported with non-radiopaque stainless-steel devices (Table 2).

Obviously, the ultimate goal of bail-out stent implantation is the reduction and possibly the elimination of the acute ischemic complications due to acute vessel

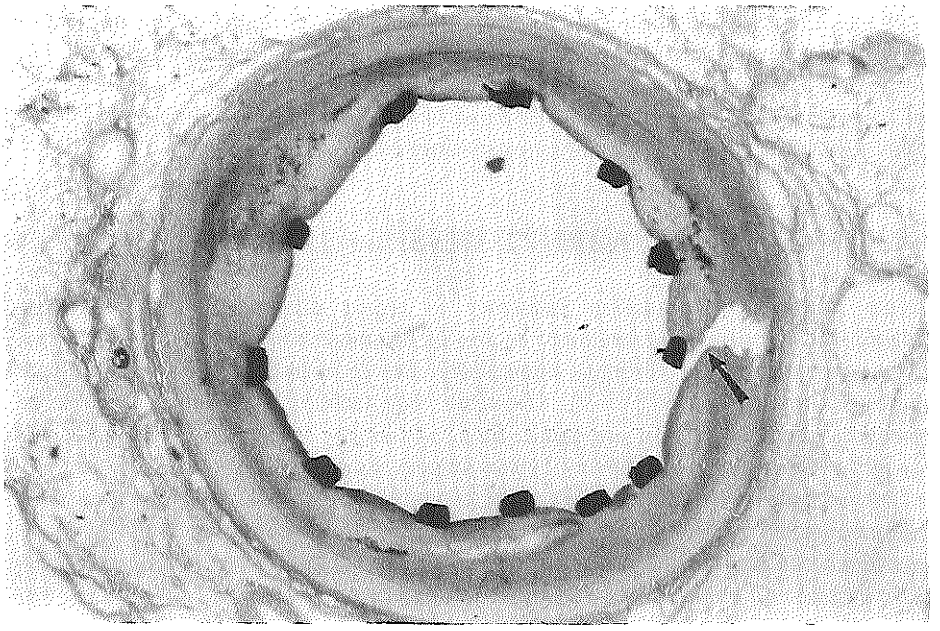

Fig. 1. Transversal section of a human cadaver coronary artery. The intimal and medial tear is tacked back by the stent.
Reproduced with permission from Schwartz et al. Circulation 1989; 79:445–457.

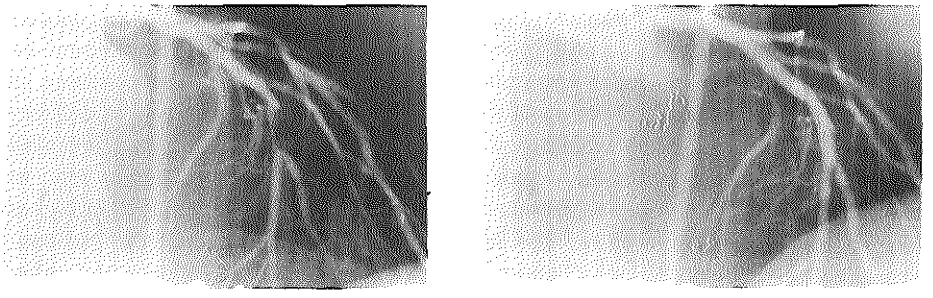

Fig. 2A + B. Dissection of the left anterior descending artery after PTCA (panel A), which was effectively treated with stent implantation (panel B).

Table 2. In-hospital events following stent implantation for threatened or acute occlusion after PTCA.

Author	Ref.	Year	Study Period	n pts.	n. stents	Successful stent delivery	Complications		Subsequent occlusion		
							Death	AMI	Em CABG	Incidence	Time interval
Wallstent											
Sigwart et al.	(13)	'87	n.r.	4	4	100%	0	0	0	0	0
Sigwart et al.	(14)	'88	'86-'88	11	13	100%	1 (9%)	0	0	1 (9%)	n.r.
de Feyter et al.	(15)	'90	'89-'90	15	19	100%	1 (6.6%)	2 (13.3%)	9 (60%)*	3 (20%)	day 0 - 7
Goy et al.	(16)	'92	n.r.	17	n.r.	100%	0	1 (5.8%)	0	1 (5.8%)	day 0
Palmaz-Schatz stent											
Haude et al.	(17)	'91	n.r.	15	22	100%	0	0	1 (6.7%)	1 (6.7%)	day 0
Herrmann et al.**	(18)	'92	'88-'91	56	n.r.	98%	2 (3.6%)	11 (20%)	7 (13%)	9 (16%)	day 1-10
Reifart et al.	(19)	'92	'90-'91	64	71	95%	4 (6%)	2 (3%)	7 (11%)	20 (31%)	day 0-19
Gianturco-Roubin stent											
Roubin et al.	(20)	'92	'89-'91	115	137	96%	2 (1.7%)	8 (6.7%)***	5 (4.2%)	9 (7.6%)	day 1 - 5
Strecker stent											
Reifart et al.	(19)	'92	'90-'91	48	56	97%	5 (10%)	1 (2%)	3 (6%)	10 (21%)	day 0-19
Wiktor stent											
Vrolicx et al.	(21)	'92	'91	119	n.r.	95%	4 (3%)	n.r.	7 (6%)	14 (12%)	n.r.
Total				464			19 (4.1%)	25 (10.6%)	39 (8.4%)	68 (14.7%)	
95% CI							2.3-5.9%	7.4-13.8%	5.8-10.9%	11.5-17.9%	

pts = patients; AMI = acute myocardial infarction; Em. CABG = emergency bypass surgery. * :Including the 8 patients in whom the stent was used as bridge to surgery. **:Events within 30 days after stent implantation are reported. ***:if patients in whom stent was implanted because of evolving AMI are excluded: 4%; CI = confidence interval.

closure. It is the general appreciation of many interventional cardiologists that stents indeed do reduce the need for emergency bypass surgery and incidence of acute myocardial infarction [20]. Unfortunately, data from randomized studies proving the superiority of stents to other techniques or devices are lacking. Nevertheless, the incidence of major cardiac events following bail-out stent implantation compare very favourably with those after abrupt closure following PTCA (Table 3).

Some have advocated that intracoronary stents should be available in all centers for bail-out procedures [33]. This could lead to an exponential (over)use of these devices not taking into account potential technical and clinical pitfalls in bail-out stent implantation. Firstly, the coronary angiogram may be misleading in the distinction between dissection and intracoronary thrombus as the cause of acute occlusion. In latter case, the stent may exacerbate the pathological process rather than have a beneficial effect. Secondly, apart from correct positioning of the stent, the choice of the stent size may be difficult because acute coronary occlusion is often associated with spasm of the reference vessel segment. With respect to the clinical pitfalls, one should note that patients with acute occlusion are often clinically unstable, with long-lasting periods of ischemia, hemodynamic deterioration and extensive dissection which may have induced activation of platelets and the clotting system, all of which may lead to an increased risk of thrombosis which is higher following bail-out stent implantation.

The incidence of subacute stent thrombosis has been reported to vary between 9-18% following bail-out stent implantation, compared with 2 to 3% after elective stent implantation [34,35]. To avoid stent thrombosis, an intensive and meticulous anticoagulation is necessary. This, in turn, exposes the patient to an increased risk of serious bleeding complications (Table 4).

Since antegrade flow should be restored as soon as possible and since bail-out stent implantation is not without risk, one should avoid unnecessary stenting by first using classical manoeuvres such as prolonged inflation with or without an oversized balloon, but, avoid extensive vessel wall damage by frequent and repetitive balloon inflations. In this respect, the use of a temporary stent may offer an alternative to permanent intravascular stenting provided it may be retrieved in a time period short enough to avoid anticoagulation but sufficient long enough to effectively control the dissection [43]. If this proves to be superior to the general manoeuvres of using prolonged balloon inflations, oversized balloons or autoperfusion balloon catheters, it may avoid the morbidity associated with permanent stenting or emergency bypass surgery.

There are no clear guidelines with respect to the decision to refer the patient for semi-elective bypass surgery after successful bail-out stent implantation. This decision should be based on a number of factors such as the clinical status of the patient after stenting (relief of angina, normalization of ECG and/or haemodynamic parameters), angiographic factors (TIMI flow, presence or absence of intracoronary thrombus, complete or incomplete covering of the dissection, residual stenosis, territory at risk, presence or absence of collaterals), procedural factors (number and size of stents used) and indication for bail-out stent implantation (suboptimal result versus threatened or frank vessel closure).

Table 3. In-hospital events following (sub)acute occlusion during or immediately after PTCA.

Author	Ref	Year	Study Period	n pts.	Incidence (sub) acute occlusion	Complications		
						Death	AMI	Em. CABG
Dorros et al.	(22)	'83	'77-'81	1500	69 (4.6%)	3 (4.3%)	25 (36%)	50 (72%)
Hollman et al.	(23)	'83	'80-'82	935*	20 (2.1%)	0	5 (25%)	5 (25%)
Shiu et al.	(24)	'85		209	20 (9.5%)	2 (10%)	5 (25%)	14 (70%)
Simpendorfer et al.	(25)	'87	'83-'85	1500	32 (2.0%)	-	14 (44%)	4 (13%)**
Sinclair et al.	(26)	'88	'81-'86	1160	54 (4.7%)	1 (1.9%)	19 (35%)	18 (33%)
Ellis et al.	(27)	'88	'82-'86	4772	210 (4.4%)	4 (2.9%)***	56 (40%)***	78 (55%)***
Meyerovitz et al.	(28)	'88	'84-'86	514	44 (8.5%)	1 (2.3%)	1 (2.3%)	13 (30%)
Gaul et al.	(29)	'89	'80-'86	714	22 (3.1%)	0	6 (27%)	6 (27%)
Detre et al.	(30)	'90	'85-'86	1801	122 (6.8%)	6 (4.9%)	49 (40%)	49 (40%)
de Feyter et al.	(31)	'91	'86-'88	1423	104 (7.3%)	6 (6.0%)	37 (36%)	30 (31%)
Lincoff et al.	(32)	'92	'88-'90	1319*	109 (8.3%)	9 (8.3%)	≤10 (9.2%)	33 (30%)
Total				15847	806 (5.1%)	32 (4.1%)	227 (28%)	300 (37%)
95% CI					4.8-5.4%	3.8-4.4%	27-29%	36-38%

pts = patients; * = procedures; ** = an additional 9 pts (28%) underwent semi-elective bypass surgery; *** = subgroup analysis of 140 pts; CI = confidence interval.

Table 4. Incidence of hemorrhagic complications and pseudoaneurysm following stent implantation.

Author	Ref	Year	Study Period	n. pts	Hemorrhagic complications				
					ICH	Groin	Gastrointestinal	Other	Pseudoaneurysm
Sigwart et al.	(14)	'88	'86-'88	11	0	1 (9.1%)	0	0	n.r.
Urban et al.	(36)	'89	'86-'88	13	0	1 (7.8%)	0	0	1 (7.8%)
Levine et al.	(37)	'90	'88-'89	37	0	1 (2.7%)	0	1 (2.7%)	4 (10.8%)
Schatz et al.	(38)	'91	'87-'89	226	1 (0.4%)	8 (3.5%)	2 (0.9%)	3 (1.3%)	3 (1.3%)
Haude et al.	(17)	'91	n.r.	15	0	1 (6.7%)	0	0	0
Haude et al.	(39)	'91	n.r.	50	0	3 (6.0%)	2 (4.0%)	0	0
de Scheerder et al.	(40)	'92	'88-'90	69	2 (2.9%)	18 (26%)	2 (2.9%)	1 (1.4%)	7 (10%)
Roubin et al.	(20)	'92	'89-'91	115	0	7 (6.1%)	4 (3.5%)	3 (2.6%)	4 (3.5%)
de Jaegere et al.	(41)	'92	'90	50	0	6 (12%)	3 (6.0%)	0	n.r.
Herrmann et al.	(18)	'92	'88-'91	56	0	2 (3.6%)	5 (8.9%)	3 (5.4%)	5 (8.9%)
Carrozza et al.	(42)	'92	'88-'91	220	-	-	-	-	12 (5.5%)
Total				862	3 (0.5%)	48 (7.5%)	18 (2.8%)	11 (1.7%)	36 (4.2%)
95% CI					0.04-1.0%	5.5-9.5%	1.5-4.1%	0.7-2.7%	2.9-5.5%

pts = patients; ICH = intracranial hemorrhage; n.r. = not reported; CI = confidence interval.

Although the recurrence of stenosis at follow-up is not an issue at the moment in bail-out stent implantation, some authors have reported a restenosis rate as low as 23% [44]. It is interesting to note that in a recent study the indication for stent implantation (elective or bail-out stent implantation) was not identified as a risk factor of restenosis [45].

STENTS TO PREVENT RESTENOSIS

To solve the problem of restenosis, one has to understand its biology and the pathophysiologic mechanisms involved. It is evident from histologic studies that any kind of injury applied to the vessel wall, whatever its nature, will invariably be associated with neointimal hyperplasia as a non-specific tissue reaction leading to restenosis when excessive [46,47]. Immediately after stent implantation, neointimal hyperplasia is confined to the area in direct contact with the stent wires and consists of organized thrombus covered by a monolayer of endothelial cells. In a short period of time, thrombus is replaced by myofibroblastic cells and at 4 weeks the neointimal hyperplasia covers the entire stented segment (Figure 3A + B) [46]. Both animal studies and postmortem pathologic observations in humans have shown that the degree of this vessel wall reaction is related to the severity of vessel wall injury (Figure 4) [47,48]. Recent studies using quantitative coronary angiography lend support to this concept by showing that excessive oversizing of the stent relative to the vessel reference diameter is predictive for late angiographic narrowing [45,49]. Furthermore, it has recently been demonstrated that there is a positive linear correlation between the relative gain - as index of vessel wall injury - and relative loss - as index of neointimal thickening - following stent implantation (Figure 5) [50,51].

From the above, it is clear that intracoronary stent implantation can not be expected to eliminate restenosis. However, it may reduce the incidence of angiographic restenosis by optimizing and improving the immediate angiographic results. It is now well recognized that in addition to the long-term changes in stenosis geometry after PTCA, more immediate changes occur which contribute to restenosis. It has been shown for example that nearly 50% of the immediate gain of PTCA is lost due to elastic recoil of the vessel wall [52]. This compares with recoil of only 8% following Wiktor stent implantation in diseased human coronary arteries and of 9% in non-atherosclerotic coronary arteries of the pig [46,53].

In addition, the stent may reduce the angiographic restenosis rate by creating a more patent vessel lumen which may accommodate subsequent neo-intimal hyperplasia. A number of studies using quantitative angiography have shown that stent implantation indeed results in a significant further improvement in stenosis geometry than PTCA (Table 5). Although these data are stemming from indirect comparisons between nonrandomized studies, there is a more than a 1.0 mm increase in minimal luminal diameter after stent implantation compared to less than 1.0 mm

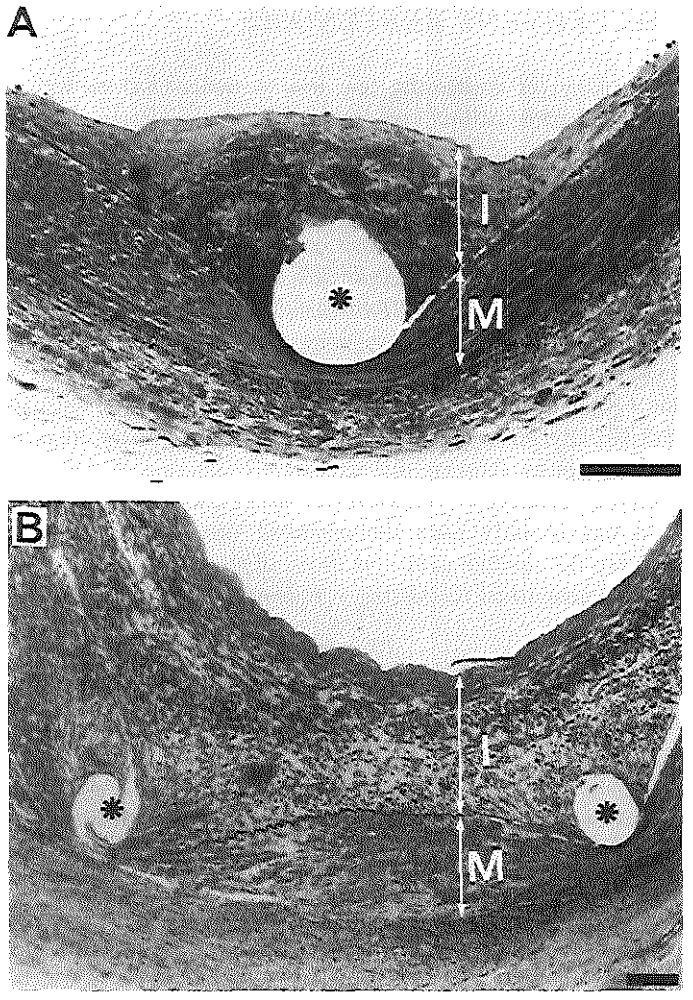

Fig. 3A + B. Transversal section of the left anterior descending artery 1 week after Wiktor stent implantation (panel A) and of the left circumflex artery 4 weeks after stent implantation. During the first week, neointimal hyperplasia is confined to the area in direct contact with the stent wires while at 4 weeks the stented segment is completely covered by neointimal hyperplasia.
Reproduced with permission from van der Giessen et al. Circulation 1991; 83:1788-1798.

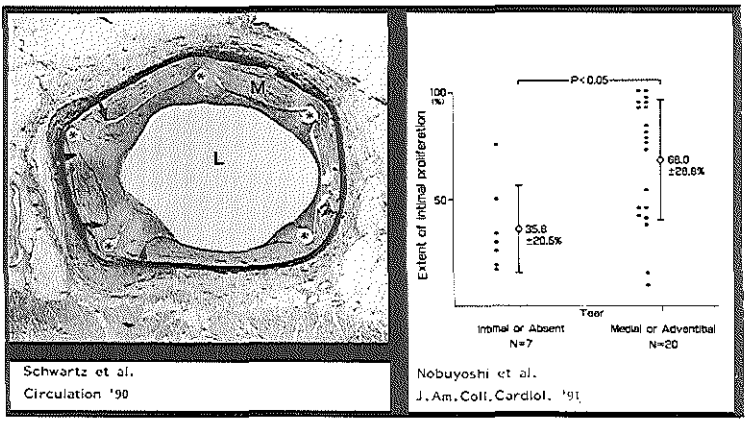

Fig. 4. Exessive stent oversizing with deep penetration of the stent wire into the media results in a more pronounced neointimal hyperplasia (left panel). Deep arterial injury during balloon angioplasty (right panel) is associated with more extensive intimal proliferation.
Reproduced with permission from Schwartz et al. Circulation 1990; 82:2190–2200 and from Nobuyoshi et al. J Am Coll Cardiol 1991; 17:433–439.

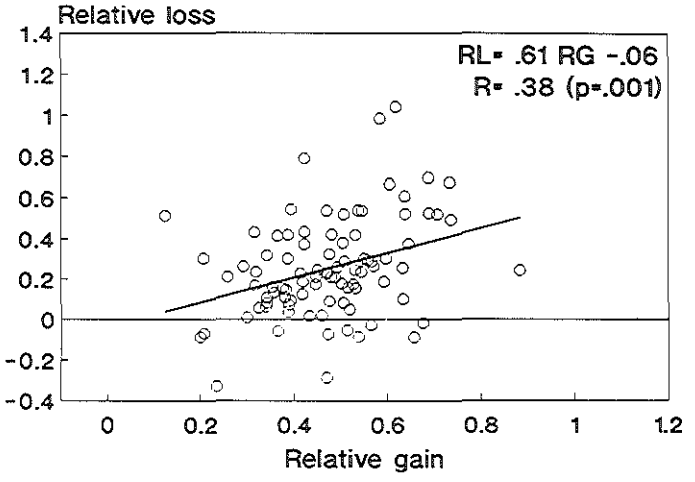

Fig. 5. The relation between relative gain (increase in minimal luminal diameter normalized for vessel size) and relative loss (decrease in minimal luminal diameter normalized for vessel size) was studied using quantitative coronary angiography. There is a weak but positive linear correlation between the two variables suggesting that a larger vessel trauma will result in a greater loss.

Table 5. Immediate and long-term changes in minimal luminal diameter (MLD) following balloon angioplasty and stent implantation

Author	Ref.	n pts.	MLD-pre	MLD post-PTCA	MLD post-stent	MLD at follow-up		Incidence of Restenosis (%, per pat)	
						all pts	pts without subacute occl.	50%	0.72 mm crit.
Balloon angioplasty									
Serruys et al.	(1)	261*	0.99 ± 0.35	1.77 ± 0.34	-	1.46 ± 0.59	-	-	19
Mercator Study	(54)	309*	0.98 ± 0.35	1.77 ± 0.34	-	1.48 ± 0.54	-	28	16
Rensing et al.	(55)	1353	1.03 ± 0.36	1.78 ± 0.36	-	1.50 ± 0.57	-	31**	17**
Benestent	(59)	60	0.99 ± 0.22*****	1.85 ± 0.31	-	1.45 ± 0.59	-	47	27
			1.00 ± 0.21******	1.81 ± 0.31	-	1.42 ± 0.58		50	28
Stent implantation									
Wallstent									
Serruys et al.	(56)	105	1.21 ± 0.56	1.88 ± 0.43	2.48 ± 0.51	1.68 ± 1.20	2.26 ± 0.78	14	33
Strauss et al.	(57)	166***	1.17 ± 0.52	-	2.53 ± 0.53	1.59 ± 1.08	1.99 ± 0.81	18	34
		101****	1.39 ± 0.64	-	2.81 ± 0.69	2.03 ± 1.27	2.21 ± 1.16	39	54
Palmaz-Schatz stent									
Haude et al.	(39)	50	1.00 ± 0.57	2.02 ± 0.47	3.26 ± 0.31	2.39 ± 1.15	-	24	37
Fischman et al.	(58)	205	-	-	-	1.92 ± 0.57	-	34	50**
Benestent	(59)	60	0.99 ± 0.30*****	-	2.19 ± 0.70	1.67 ± 0.77		30	27
			1.00 ± 0.24******	-	2.41 ± 0.46	1.75 ± 0.77		24	29
Wiktor stent									
De Jaegere et al.	(41)	50	1.09 ± 0.26	1.80 ± 0.32	2.45 ± 0.35	1.59 ± 0.79	1.78 ± 0.60	29	45

pts = patients; * = Control group (there was no difference in the changes in MLD between control group and active treatment group); ** = incidence of restenosis per lesion; *** = stent implantation in native vessels; **** = stent implantation in venous bypass grafts;*****=intention to treat analysis; ******=efficacy analysis.

after balloon angioplasty. Moreover, stent implantation results in a residual diameter stenosis of less than 20% with normalization of the calculated resistances to flow and pressure drop across the stenosis [60,61].

Despite a larger loss in minimal luminal diameter at follow-up, the minimal luminal diameter is still greater after stent implantation than in patients who underwent balloon angioplasty. Therefore, it is not surprising that in comparison with PTCA, the incidence of restenosis is higher when using the 0.72 mm criterion, but, is lower when using the 50% diameter stenosis criterion (Table 5). It underscores the concept that improved initial results compensate for late neointimal hyperplasia which in turn explains the lower restenosis rate according to the 50% diameter criterion.

To readily answer the question of whether stent implantation reduces the incidence of restenosis, randomized comparisons are needed. The Benestent study is a multicenter randomized study comparing stent implantation with PTCA in patients with stable angina pectoris and a de novo lesion in a native coronary artery [62]. The data from the pilot phase, which started in June 1991, confirm the angiographic findings of the above mentioned nonrandomized studies [63]. At follow-up angiography, the obstruction diameter of the patients in whom a stent was implanted proved to be higher than in patients who underwent PTCA. Furthermore, the incidence of restenosis was lower (Table 5).

To fully appreciate the role and value of intracoronary stenting, it is not sufficient to only determine the restenosis rate. All aspects of stent implantation have to be considered, especially the in-hospital complications and the long-term clinical outcome. The intrinsic thrombogenicity of all metalic stents currently available is a matter of concern. It exposes the patient to the risk of stent thrombosis which may result in a fatal or non-fatal acute myocardial infarction and/or emergency bypass surgery. An intensive anticoagulation is therefore imperative to avoid stent thrombosis but exposes the patient to the risk of major bleeding and puncture site related complications (Table 4 and 6). The anticoagulation protocol which is now widely used consists of acetyl salicylic acid, dipyridamole, dextran, heparin and oral anticoagulants during the acute phase followed by a combination of antiplatelet therapy and oral anticoagulants during the next three to six months. This is based on animal studies indicating less thrombus formation on stents pretreated with acetyl salicylic acid, dipyridamole, heparin and dextran and on clinical experience, showing a (sub)acute closure rate of 18% in absence of oral anticoagulation [38,66]. This polypharmacologic approach has recently been questioned by Simon et al. who failed to demonstrate any beneficial effect of dextran and dipyridamole in the prevention of acute closure [67]

Oral anticoagulation in combination with antiplatelet therapy has to be maintained until complete endothelialization of the stent. Although the time period in which this process occurs in humans is unknown, experimental animal studies have shown that stents become embedded in the vessel wall and are covered by endothelium in 1 to 4 weeks [46,68,69].

Table 6. In-hospital events and incidence of (sub)acute occlusion following stent implantation

Author	Ref	Year	Study Period	n. pts	n. stents	In-hospital events			(Sub)acute occlusion	
						Death	AMI	Em. CABG	Incidence	Time interval
Wallstent										
Urban et al.	(36)	'89	'86-'88	13	20	0	0	0	0	-
Serruys et al.	(56)	'91	'86-'89	105	117	5 (4.7%)	n.r.	n.r.	21 (20%)	day 0 - 14
Goy et al.	(64)	'91	'86-'87	56	68	2 (3.6%)	5 (8.9%)	1 (1.8%)	4 (7.1%)	day 1 - 7
Strauss et al.	(57)	'92	'86-'90	265	373	11 (4.2%)	n.r.	n.r.	40 (15%)	n.r.
de Scheerder et al.	(40)	'92	'88-'90	69	136	3 (4.3%)	5 (7.2%)	4 (5.8%)	7 (10%)	day 1 - 12
Palmaz-Schatz stent										
Levine et al.	(37)	'90	'88-'89	37	45	n.r.	n.r.	n.r.	1 (2.7%)	day 8
Schatz et al.	(38)	'91	'87-'89	226	321	0	6 (2.8%)	2 (0.9%)	8 (3.7%)	day 2 - 11
Haude et al.	(39)	'91	n.r.	50	61	1 (2.0%)	3 (6.0%)	2 (4.0%)	8 (16%)	day 0, 5-9
Carrozza et al.	(42)	'92	'88-'91	220	250	0	0	1 (0.4%)	1 (0.4%)	day 8
Colombo et al.	(65)	'92	'89-'91	100	126	2* (2.0%)	2 (2.0%)	4 (4.0%)**	3 (3.1%)	day 4-6
Wiktor stent										
de Jaegere et al.	(41)	'92	'90	50	50	0	5 (10%)	1 (2%)	5 (10%)	day 0 - 5
Total				1191		24 (2.0%)	26 (3.3%)	15 (1.9%)	98 (8.2%)	
95% CI						1.2-2.8%	2.3-4.3%	1.1-2.7%	6.6-9.8%	

pts = patients; AMI = acute myocardial infarction; Em.CABG = emergency bypass surgery, n.r. = not reported

* reported as not stent related; ** including 2 patients in whom a stent was implanted as a bridge to surgery; CI = confidence interval.

Improvements of the stent design are currently being investigated to reduce its thrombogenic properties. A potential solution is the change of the surface characteristics of the stents by either seeding the stent with endothelial cells or by coating the stent with either a thin layer of a synthetic polymer - with or without the addition of a drug such as low molecular weight heparin - or with polymerized fibrinogen (biopolymer coating) [70,71,72]. Another option is the development of biostable polymer stents which are entirely composed of a synthetic polymer [73]. It has been shown that polymer surfaces are smoother and thereby limit the adhesion of air bubbles and cellular elements, associated with thrombosis and tissue proliferation, respectively. Furthermore, by varying polymerization processing techniques, the mechanical properties can be manipulated in such a way that polymer stents can be constructed which settle themselves in a much smoother fashion against the arterial wall, which may reduce the acute and chronic vessel wall damage.

As long as a "non-thrombogenic" stent is not available, the risk of thrombosis may be reduced by a more fine tuning of the anticoagulation therapy. This can be done by measuring prothrombin fragment 1 + 2 [74]. An increase in these fragments reflects an activation of the coagulation system which may be predictive of stent thrombosis. It offers the clinician sufficient time to adjust the anticoagulation therapy. This in combination with local vascular hemostatic devices may also reduce bleeding and vascular complications which unnecessarily prolongs the hospital stay [74,75].

Despite these limitations of all stents in clinical use, it is noteworthy that the results of the pilot phase of the Benestent study disclosed a 6-month event and symptom free survival (freedom from death, myocardial infarction, bypass surgery, repeat PTCA) of 67% after stent implantation compared to 55% after PTCA [63]. It may be inferred that the lessons of the past have been learned resulting in better patient selection, improved implantation technique and postoperative management.

STENTS FOR VENOUS BYPASS GRAFTS

The management of patients with recurrence of angina pectoris after coronary artery bypass operation poses a problem. Repeat coronary artery bypass grafting is technically more difficult and is associated with a higher morbidity and mortality. Furthermore, symptomatic improvement and long-term clinical results are less satisfactory compared with a first bypass operation [76]. Angioplasty of vein grafts may offer an alternative to re-operation. The immediate results of PTCA have been shown to be favorable in patients with discrete lesions in venous bypass grafts, but are considerably less in diffusely diseased grafts [77-79]. Furthermore, the incidence of restenosis varies between 40 to 70% depending on lesion site and extent of graft diseases [80-83].

Therefore, it is not surprising that a number of new interventional techniques are currently being used to improve the immediate and long-term results of PTCA in bypass grafts.

As for native coronary arteries, the Wallstent was the first stent implanted in saphenous vein grafts with an almost 100% successful implantation success rate and a subacute stent thrombosis rate which proved to be lower (8-10%) than in native coronary arteries (19%) [36,40,56,57]. This was achieved, however, at the cost of an unacceptably high incidence of major bleeding complications, including fatal intracranial hemorrhage, and vascular access site bleedings [40].

More favourable initial results have recently been reported with the Palmaz-Schatz stent [84]. Subacute stent thrombosis rate amounted to only 1.1% compared with 6.0% in native coronary arteries. However, there was a significant higher frequency of major cardiac events such as death and myocardial infarction (6%) in patients with stent implantation in saphenous vein grafts compared with patients in whom a stent was implanted in native coronary arteries (2%) [84].

Restenosis following stent implantation in vein grafts has been reported to be 35 and 54% according to the 50% diameter stenosis and 0.72 mm criteria, respectively, which is significantly higher than following stent implantation in native coronary arteries (18 and 34%, respectively) [57]. Despite this difference in restenosis rate, the one-year event free survival (freedom from death, myocardial infarction, bypass surgery or angioplasty) was similar for bypass grafts (50%) and for native vessels (55%). It is noteworthy that 25 to 30% of the adverse events were unrelated to the stented lesion, but due to progression of disease [40,57].

A low overall restenosis rate of 22% to 28% has recently been reported following Palmaz-Schatz stent implantation which, moreover, did not differ from the restenosis rate in native coronary arteries (30%) [42,84]. Considering the incidence of restenosis of 13% in case of single stent implantation for a de novo lesion in a bypass graft, the overall low restenosis rate may be explained by a preponderance of de novo lesions and by the larger vessel size of vein grafts.

Despite these promising results, the wide variety of patients treated in a non-randomized fashion precludes any firm conclusions with respect to the role and merits of stent implantation in venous bypass grafts. Current indications for stent implantation may be 1) patients with an increased risk for embolization of friable graft material such as in case of diffusely diseased grafts with long lesions since the stent can contain this material, 2) patients with ostial or very proximal graft stenosis since they are at higher risk of restenosis after balloon angioplasty, and 3) in case of the need of emergency bypass surgery since the ischemic period is substantially longer because more time is needed to dissect free the heart [85].

One should realize, however, that especially in the first category of patients, stent implantation may only provide a temporary solution but not long lasting clinical improvement due to further progression of disease [40,57,85].

HOW CAN WE IMPROVE THE RESULTS?

The intrinsic thrombogenicity of all stents currently available and consequently the need for an intensive anticoagulation are the major limitations of the use of

intracoronary stents. However, one may reduce the risk of subacute stent thrombosis and bleeding complications by taking into account some obvious clinical and angiographic parameters. One should stay away from the noncompliant patient or the patient with concomitant non-cardiac disease which interferes with the anti-coagulation. Since frequent blood sampling is mandatory for proper institution of the anticoagulation, one should check the availability and quality of arm veins. In the very obese patient, it may difficult to find or puncture one. These patients are, furthermore, at higher risk of vascular access site bleedings.

Stents should not be implanted in vessels smaller than 3.0 mm since this is associated with an increased risk of stent thrombosis [86]. There are conflicting data on the risk of stent thrombosis following the use of multiple stents. In one study, it was found to be an independent predictor of stent thrombosis while in another there was no difference in thrombosis rate between single and multiple stent implantation [86,87]. It is unclear whether the presence of intracoronary thrombus is an absolute contra-indication for stent implantation. In the series reported by Fischman et al., a thrombus was observed in 8% of the patients. Despite this, only 3.8% of the total study population sustained a stent thrombosis which was predominantly explained by an 18% incidence of stent thrombosis in the first 39 patients who did not receive warfarin [38,58].

As already outlined above, a more detailed monitoring of the anticoagulation therapy may be helpful in the prevention of stent thrombosis. It may, furthermore, be speculated that with the advent of new and more potent anticoagulant drugs such as hirudin, the risk of stent thrombosis will be reduced [88].

Access site bleedings may be reduced by more appropriate patient selection, quality of puncture and timing of sheath removal. Obese patients and patients with chronic cough or who suffer from obstipation are more prone to access site related bleedings because of frequent Valsalva manoeuvres. The puncture should be low to optimize postoperative hemostasis. Sheath removal on the day of stenting is, furthermore, associated with less bleeding complications [42]. Although the use of collagen plugs may be attractive for time efficiency, they do not reduce bleeding complications [89]. Other techniques are currently available such as a controlled compression with a belt-held pneumatic compression device. It proved to be higly successful and reduced the incidence of pseudoaneurysm in our hands and those of others [75].

The ultimate solution, of course, is the non-thrombogenic stent. The intensive research to achieve this goal is currently restricted to the experimental laboratory. However, it will invariably result in a next generation of less or eventually non-thrombogenic devices.

In addition to these immediate results of stent implantation, the battle against restenosis is promising. The lowest restenosis rate so far reported amounts to 13% in case of single stent implantation for a de novo lesion in a native coronary artery [58]. In addition to patient selection, this may be achieved by a more complete stent dilatation resulting in an almost negligible residual diameter stenosis post stent implantation [90].

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SUMMARY

To address the two major shortcomings of balloon angioplasty (abrupt vessel closure and late restenosis), a number of new catheter technologies have been developed and entered clinical testing. The data presented and discussed in this thesis focus on the clinical and angiographic aspects of intracoronary stent implantation in human coronary arteries.

It has been hypothesized that intracoronary stenting may reduce the incidence of restenosis by improving the immediate angiographic results. Therefore, in the first part, special attention was paid to the changes in stenosis geometry immediately after stent implantation using quantitative coronary angiography. The data of non-randomized comparisons in chapter 2, 3 and 5 indicate that stent implantation indeed results in a superior improvement in stenosis geometry compared with balloon angioplasty. No difference was observed between balloon-expendable and self-expanding devices (chapter 3). Furthermore, the data of chapter 5 confirm that stent implantation effectively prevents recoil. In populations with identical baseline stenosis characteristics, directional atherectomy and stent implantation result in a similar immediate improvement (chapter 4).

However, to fully appreciate the role and merits of intracoronary stent implantation, it is not sufficient to consider only these technical aspects which potentially may explain a reduction in the incidence of restenosis. All aspects must considered and in particular the immediate and long-term clinical outcome. It is of utmost importance for as well the patient as the society, which faces exploding health care costs, to select the most appropriate treatment. This means the treatment which produces more health than harm and which yields more health benefits and/or less risks than alternative treatments or the natural course of the disease. This matter is in detail eloborated in part two.

There is no doubt that stents can be implanted with a high technical success rate. However, this is done at the cost of a high incidence of in-hospital events related to, on one hand, the intrinsic thrombogenicity of the device with the risk of (sub)acute thrombotic occlusion and, on the other hand, the need for an intensive anti-coagulation associated with an increased bleeding risk and vascular complications. The necessity of anticoagulation prolongs the hospital stay and is one of the factors which renders the procedure more expensive. These aspects are discussed in chapter 6, 10 and 11.

One of the methods to assess the proper role and merits of intracoronary stenting is the conduction of a randomized trial. The results of the pilot phase of the Benestent Study is discussed in chapter 10. Despite the above mentioned limitations of intracoronary stents, the most striking feature is the superior 6-month symptom and event-free survival in patients who received a stent. Of course, the small number of patients included precludes any firm conclusions at present. Furthermore, one

should bear in mind that even if randomization guarantees homogeneity between the two treatment groups and thus allows comparison of two treatment modalities, it will not tell the whole story since a substantial number of patients do not enter the trial due to the in- and exclusion criteria outlined in the protocol. The lower restenosis rate after stent implantation is explained by the observation that the higher initial gain after stent implantation compensates for the late loss and thus improved initial results and not lessened neointimal hyperplasia is responsible for a reduced incidence of restenosis (chapter 9). The role and merits of stent implantation in venous bypass grafts remains unclear. Based on current data on reoperation and experience with balloon angioplasty and stent implantation in venous bypass grafts, stent implantation may be envisaged in 1) patients with an increased risk for embolization of friable graft material, 2) patients with ostial or very proximal graft stenosis, and 3) in those needing emergency bypass surgery (chapter 8).

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