Luminal narrowing after percutaneous transluminal coronary angioplasty. A study of clinical, procedural, and lesional factors related to long- term angiographic outcome. Coronary Artery Restenosis Prevention on Repeated Thromboxane Antagonism (CARPORT) Study Group

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Luminal Narrowing After Percutaneous Transluminal Coronary Angioplasty

A Study of Clinical, Procedural, and Lesional Factors Related to Long-term Angiographic Outcome

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Background. The renarrowing process after successful percutaneous transluminal coronary angioplasty (PTCA) is now believed to be caused by a response-to-injury vessel wall reaction. The magnitude of this process can be assessed by the change in minimal lumen diameter (MLD) at follow-up angiography. The aim of the present study was to find independent patient-related, lesion-related, and procedure-related risk factors for this luminal narrowing process. A model that accurately predicts the amount of luminal narrowing could be an aid in patient or lesion selection for the procedure, and it could improve assessment of medium-term (6 months) prognosis. Modification or control of the identified risk factors could reduce overall restenosis rates, and it could assist in the selection of patients at risk for a large loss in lumen diameter. This population could then constitute the target population for pharmacological intervention studies.

Methods and Results. Quantitative angiography was performed on 666 successfully dilated lesions at angioplasty and at 6-month follow-up. Multivariate linear regression analysis was performed to obtain variables with an independent contribution to the prediction of the absolute change in minimal lumen diameter. Diabetes mellitus, duration of angina <2.3 months, gain in MLD at angioplasty, pre-PTCA MLD, lesion length ≥6.8 mm, and thrombus after PTCA were independently predictive of change in MLD. Overall prediction of the model was poor, however; percentage-correct classification for a predicted change between −0.1 to −0.4 mm was approximately 10%. Lesions showing no change or regression (change >−0.1 mm) and lesions showing large progression (≤−0.4 mm) were more predictable (correct classification, 59.5% and 49.7%, respectively).

Conclusions. Renarrowing after successful PTCA as determined with contrast angiography is a process that cannot be accurately predicted by simple clinical, morphological, and lesion characteristics. (*Circulation.* 1993;88:975-985.)

KEY WORDS • angioplasty • restenosis • quantitative angiography

Luminal narrowing after percutaneous transluminal coronary angioplasty (PTCA) is a complex process that is only partially understood. Histological studies of coronary arteries after dilation, obtained by either autopsy or atherectomy, have provided evidence that strongly supports the concept of intimal hyperplasia or proliferation of smooth muscle cells of medial or intimal origin as the underlying cause of luminal narrowing after angioplasty.[1-3] Pharmacological agents aimed at reducing the absolute amount of intimal hyperplasia are currently being investigated in many clinical trials. In these trials, it is presumed that the clinical outcome is related to an anatomic substrate, ie, the prevention or reduction of reactive intimal hyperplasia after angioplasty.

If restenosis is viewed as an intraluminal growth process after a successful angioplasty, risk factors for restenosis should be risk factors for this growth process. The angiographically determined change in lumen diameter at follow-up is currently the only reliable indicator of the amount of reactive hyperplasia applicable to large study populations.

A model that accurately predicts the amount of luminal narrowing in the individual patient would be of value in several ways: First, it could be an aid in patient or lesion selection for the procedure because an accumulation of risk factors in the individual patient might indicate balloon angioplasty as an unattractive means of revascularization; second, it could improve assessment of medium-term (6 months) prognosis in the individual patient; third, modification or control of the identified risk factors could reduce overall restenosis rates; fourth,

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┌─────────────────────────────────────────────────┐
│  697 patients enrolled in CARPORT trial          │
│         │                                         │
│         ├──────► 48 failed PTCA (6.9%)            │
│         ▼                                         │
│  649 patients eligible for f-up angiography      │
│         │                                         │
│         ├──────►46 refused re-angiography         │
│         ├──────►18 contraindication for re-angiography │
│         ├──────► 2 died                           │
│         ├──────►8 f-up angiograms unsuitable for QCA │
│         ▼                                         │
│  575 patients with analyzable f-up angio(88.6%)  │
└─────────────────────────────────────────────────┘
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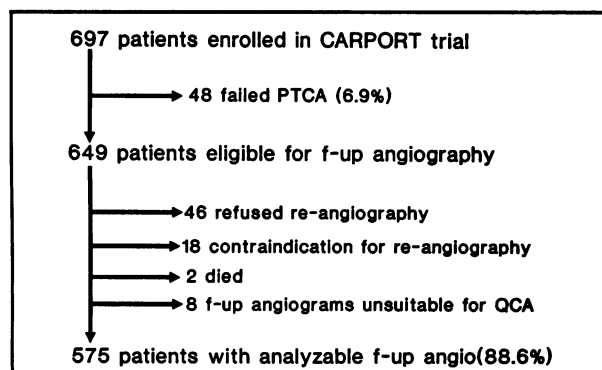
FIG 1.   *Patient flow chart. CARPORT, Coronary Artery Restenosis Prevention on Repeated Thromboxane Antagonism; PTCA, percutaneous transluminal coronary angioplasty; f-up, follow-up; QCA, quantitative coronary angioplasty.*

the model could assist in the selection of patients at risk for a large loss in lumen diameter. This population could then constitute the target population for pharmacological intervention studies because a larger mean loss in lumen diameter would permit the enrollment of a smaller number of patients in a study while maintaining an equal power. Therefore, patient-related factors, lesion-related factors, and procedural factors were correlated to the quantitative angiographic change in lumen diameter from postangioplasty angiogram to follow-up angiogram in the present study.

Methods

Study Population

The study population consisted of 697 patients that were originally randomized in six European centers (see "Appendix") for the CARPORT Trial.[4] In this randomized double-blind, placebo-controlled trial, a novel thromboxane A_2 receptor antagonist (GR32191B) was investigated for its ability to prevent the restenosis process after primary coronary angioplasty. Follow-up on these patients was done on a prospective basis, and all patients agreed to undergo repeat angiography at 6 months. Identical angiographic and clinical outcomes were observed,[4] so the placebo-treated and active treatment group were pooled for the present study. All patients with both stable and unstable angina and angiographically proven native coronary artery disease who were scheduled for primary angioplasty were considered for inclusion. Exclusion criteria for trial participation and their relative frequencies have been published earlier.[4]

Angioplasty success was defined as a <50% residual stenosis by visual inspection of the postangioplasty angiogram and no occurrence of in-hospital complications (death, acute myocardial infarction, repeat angioplasty, aortocoronary bypass grafting, or recurrence of symptoms) and was achieved in 649 patients (93.1%). Quantitative angiographic follow-up was available for 575 patients (88.6%), and this forms the study population (Fig 1).

Angioplasty Procedure and Follow-up Angiography

Coronary angioplasty was performed with a steerable, movable guide wire system via the femoral route. Standard available balloon catheters were used. Choice of balloon type and brand as well as inflation duration and inflation pressure were left to the discretion of the angioplasty operator. At the beginning of the angioplasty procedure, all patients received 10 000 IU of intravenous heparin for the first 2 hours and afterward, 5000 IU/h for as long as the procedure continued. All patients received 10 mg nifedipine every 2 hours for the first 12 hours after angioplasty. Thereafter, they received 20 mg slow-release nifedipine tablets three times during the second day after angioplasty.

Three coronary angiograms were obtained in each patient just before angioplasty, immediately after angioplasty, and at follow-up. To standardize the method of data acquisition and to ensure exact reproducibility of the angiographic studies, measurements were taken as described previously.[5-7] The angiograms were recorded in such a way that they were suited for quantitative analysis by the Coronary Angiography Analysis System (CAAS). All necessary details of the procedure were recorded, and drawings of the segments to be analyzed were made. For calibration purposes, the catheter tips were cut off for later measurement with a microcaliper. All angiograms were processed and analyzed in a central core laboratory. At least two views of all lesions were analyzed—orthogonal if possible. A difference in angulation of at least 30° was required for a view to be separately analyzed.

The follow-up coronary angiogram was performed at 6 months. If symptoms recurred within 6 months, coronary angiography was carried out earlier. If no definite restenosis was present and no revascularization procedure was performed and the follow-up time was less than 4 months, the patient was asked to undergo another coronary arteriogram at 6 months.

Quantitative Angiography

All cineangiograms were analyzed using the computer-assisted angiography analysis system (CAAS), which has been described and validated previously.[8,9] A computer-derived reconstruction of the original arterial dimension at the site of obstruction (assuming there is no disease present) is used to define the interpolated reference diameter. The area between the actual and reconstructed contours at the obstruction site is a measurement for the amount of atherosclerotic plaque and is expressed in millimeters squared. The length of the obstruction is determined from the diameter function on the basis of curvature analysis and is expressed in millimeters. In addition, this technique allows for the calculation of an eccentricity index of the lesion.[10] The index ranges from 0 (severe eccentric) to 1 (perfectly symmetrical). Since the analysis system cannot measure total occlusions, a value of 0 mm was substituted for the minimal lumen diameter, and the postangioplasty reference diameter was substituted for the reference diameter before PTCA. The mean change in minimal lumen diameter from postangioplasty angiography to follow-up angiography and from before angioplasty to after angioplasty was derived from matched angiographic views.

Potential Risk Factors Studied

The loss in minimal lumen diameter was assessed for factors reported to be predictive of luminal narrowing after successful PTCA. For categorical variables, the change in lumen diameter from postangioplasty angio-

gram to follow-up angiogram was determined in each category. Continuous variables were grouped into three equally sized subgroups (tertiles), and the change in minimal lumen diameter was assessed for each tertile.

Variables potentially predictive for luminal narrowing and eventually restenosis were divided into three general categories. (1) Patient-related factors are present systemically and thereby affect all dilated lesions in a single patient. These include age, sex, diabetes, unstable angina (defined as pain at rest requiring treatment with intravenous nitrates), extent of atherosclerotic disease (single or multivessel), previous myocardial infarction, previous CABG, previous angioplasty at another site, platelet count, cholesterol level, lipoprotein cholesterol levels (high-density and low-density lipoproteins), glucose levels, history of smoking, and continued smoking after the procedure. Because only eight patients had type I diabetes, diabetes type I and II were pooled. (2) Lesion-related factors are characteristics unique to each lesion. The following factors were assessed: minimal lumen diameter before and after PTCA, lesion length, eccentricity of the lesion, percentage diameter stenosis before and after PTCA, presence of visible collateral circulation to the dilated vessel, total occlusion before PTCA, plaque area before PTCA, vessel dilated (either left anterior descending artery, circumflex artery, or right coronary artery), presence of dissection after angioplasty (defined as filling defect within the lumen disappearing with the passage of contrast material [type A dissection, according to Dorros et al[11]]), and as contrast appearing outside the lumen, disappearing or persisting with the passage of contrast material (type B and C dissections, according to Dorros et al), relative gain in lumen diameter achieved by angioplasty (defined as the difference in obstruction diameter before and after angioplasty divided by the interpolated reference diameter [vessel size]), presence of thrombus before and after PTCA (defined as an intraluminal filling defect visible in all views, a visible embolization of intraluminal material downstream, or dye staining at the site of a total occlusion [interobserver concordance rate for the assessment of intracoronary thrombus in the core lab 89%]), and calcification of the lesion. (3) Procedure-related factors assessed were maximal measured balloon diameter, balloon-artery ratio (defined as the ratio of the quantitative angiographic diameter of the largest balloon at highest inflation pressure to the reference diameter), maximal inflation pressure, number of balloon inflations, and total duration of balloon inflation.

Data Analysis

The unit of analysis reported here is the stenotic lesion, not the patient. The primary outcome variable was the change in lumen diameter from directly after angioplasty to follow-up angiogram. For the univariate analysis, continuous variables were divided into tertiles, and the three subgroups were compared with respect to absolute lumen change using an ANOVA. For the subgroups defined by binary variables, lumen change was compared using a Student's *t* test.

To obtain independent predictors for the loss in lumen diameter, variables were entered in a stepwise multiple linear regression analysis in which the loss in lumen diameter was the dependent variable. Stepwise multiple linear regression analysis was performed (BMDP

statistical package, program 2R) to assess the relation between the variables mentioned in "Methods" (independent variables=X_i) and the loss in minimal lumen diameter from postangioplasty angiogram to follow-up angiogram (dependent variable=Y): $Y=A+\Sigma_iB_iX_i$, where A is the intercept and B_i is the ith regression coefficient. The standard BMDP 2R criteria of $F > 4$ for inclusion and $F < 3.9$ for elimination were applied.

Continuous variables were entered as such in the multivariate analysis except for variables with two of three tertiles showing approximately the same amount of loss in lumen diameter for each tertile. These were entered as discrete variables (lesion length ≥ 6.8 mm, cholesterol level ≥ 6.5 mmol/L, duration of angina < 2.3 months, and percent diameter stenosis before angioplasty $\geq 56.5\%$).

A second multiple linear regression analysis on a per-patient basis was done to confirm the per-lesion results, which might be biased because of lack of independence among multiple dilated lesions in the same patients. In this analysis, only the lesion that narrowed the most was taken into consideration.

To determine how well the regression model performs in predicting the magnitude of the restenosis process according to two frequently applied restenosis criteria and to illustrate the discrepancies between the two criteria, receiver operator characteristic (ROC) curves were constructed for each criterion. The criteria applied were: change in lumen diameter ≥ 0.72 mm at follow-up[5,8,12] and the classic criterion of an increase in diameter stenosis from $< 50\%$ before PTCA to $\geq 50\%$ at follow-up. The 0.72-mm value takes into account the limitations of coronary angiographic measurements and represents twice the long-term variability for repeat measurements of a coronary obstruction using the CAAS system.[8] The use of 1 SD would include 68.3% of the measurement variability, whereas the use of 2 SD ($2\times0.36=0.72$ mm) includes 95.5% of the measurement variability. The equivalent of the 0.72-mm value for diameter stenosis measurements is a change in diameter stenosis of 13%. In these ROC curves, sensitivity (true positive %) at different cut-off points of predicted change in minimal lumen diameter is graphed as a function of 100% minus specificity (false-positive %).

Results

Of 649 patients who had a successful angioplasty, 575 underwent satisfactory angiographic follow-up (follow-up rate, 88.6%) and formed the study population. Baseline characteristics of the study population are summarized in Table 1. A total of 666 lesions were successfully dilated. Restenosis rate was 32.6% (217 of 666 lesions) according to the >50% diameter stenosis criterion and 17.6% (117 of 666 lesions) if the criterion of ≥ 0.72-mm loss in lumen diameter was applied.

Univariate Analysis

Patient-related variables. Table 2 summarizes the changes in minimal lumen diameter for all analyzed patient-related variables. Of the 18 patient-related variables, only three (unstable angina, diabetes, and angina duration <2.3 months) showed a significantly larger loss in minimal lumen diameter at follow-up. The high loss in lumen diameter associated with the presence of these variables was probably caused by lesions that progressed toward total occlusion at follow-up. Indeed, if totally

TABLE 1. Baseline Characteristics of Study Patients

No. of patients	575
Lesions	666
Lesions per patient	1.16
Age (y)	56±9 (29-79)
Male sex (%)	464 (81%)
Follow-up time (d)	172±42 (10-349)
Extent of disease	
1 Vessel	381 (66.3%)
2 Vessels	156 (27.1%)
3 Vessels	38 (6.6%)
No. of lesions dilated	
1	485
2	74
3	11
MLD before PTCA (mm)	1.04±0.37 (0.00-2.83)
MLD after PTCA (mm)	1.76±0.38 (0.85-3.04)
MLD at follow-up (mm)	1.48±0.59 (0.00-3.15)
%DS before PTCA	60±13 (18-100)
%DS after PTCA	34±9 (6-76)
%DS at follow-up	45±19 (4-100)
Change in MLD at follow-up (mm)	−0.28±0.50

MLD, minimal lumen diameter; PTCA, percutaneous transluminal coronary angioplasty; %DS, percentage diameter stenosis.

occluded lesions at follow-up (n=42, 6.3%) were excluded from the analysis, then a trend toward a higher loss in lumen diameter in the presence of one of these factors still existed, although not statistically significant: diabetes: −0.27±0.39 versus −0.20±0.39 mm, P=.18; unstable angina: −0.20±0.39 mm versus −0.18±0.39 mm, P=.66; duration of angina <2.3 months, −0.24±0.37 mm versus −0.18±0.40 mm, P=.09.

Lesion-related variables. The preangioplasty lesion-related factors associated with a larger loss at follow-up were smaller minimal lumen diameter, lesion length ≥6.8 mm, higher percentage diameter stenosis, larger plaque area, total occlusion, and collateral circulation to the obstruction site (Table 3). The postangioplasty lesion-related factors associated with a greater loss at follow-up were a larger postangioplasty lumen diameter, lower percentage diameter stenosis after angioplasty (ie, a better angioplasty result), a higher relative gain achieved at angioplasty, and thrombus after angioplasty. Again, if total occlusions at follow-up were disregarded, the presence of total occlusions before angioplasty, collateral circulation, and thrombus after angioplasty were no longer associated with a significantly higher loss in minimal lumen diameter (total occlusion, −0.11±0.42 mm versus −0.20±0.39 mm, P=.25; collateral circulation, −0.23±0.41 mm versus −0.19±0.39 mm, P=.34; thrombus after angioplasty, −0.25±0.39 mm versus −0.20±0.39 mm, P=.67).

Procedure-related variables. None of the procedural factors assessed was associated with a significantly greater loss in lumen diameter at follow-up (Table 4).

Multiple Linear Regression Analysis

The stepwise multiple linear regression analysis showed two preangioplasty angiographic characteristics as predictive of luminal narrowing at follow-up, namely, length of the stenosis and the minimal lumen diameter

TABLE 2. Change in Minimal Lumen Diameter per Lesion for Patient-Related Variables

	Change in MLD at follow-up (mm)	P
Age (y)		
<52 (n=211)	−0.26±0.51	
52-61 (n=213)	−0.31±0.52	.54
≥61 (n=242)	−0.31±0.57	
Sex		
Male (n=533)	−0.28±0.50	.11
Female (n=133)	−0.37±0.65	
Diabetes I and II		
Yes (n=56)	−0.56±0.77	<.001
No (n=610)	−0.27±0.50	
Unstable angina (pain at rest)		
Yes (n=91)	−0.42±0.73	<.05
No (n=575)	−0.27±0.50	
Extent disease		
Single vessel (n=401)	−0.31±0.55	.45
Multivessel (n=265)	−0.28±0.52	
Ever smoked		
Yes (n=515)	−0.28±0.54	.28
No (n=151)	−0.34±0.53	
Still smoking at follow-up		
Yes (n=81)	−0.23±0.46	.22
No (n=585)	−0.34±0.53	
Previous MI		
Yes (n=253)	−0.33±0.60	.13
No (n=413)	−0.27±0.50	
Previous CABG		
Yes (n=20)	−0.22±0.42	.45
No (n=646)	−0.30±0.54	
Previous PTCA another site		
Yes (n=11)	−0.25±0.57	.77
No (n=655)	−0.29±0.54	
Duration of angina (mo)		
<2.3 (n=210)	−0.37±0.59	
2.3-8.5 (n=227)	−0.26±0.50	.06
≥8.5 (n=229)	−0.26±0.53	
Platelet count (10^6/mL)		
<168 (n=216)	−0.30±0.56	
168-175 (n=220)	−0.27±0.50	.48
≥175 (n=222)	−0.33±0.55	
Total cholesterol (mmol/L)		
<5.7 (n=225)	−0.32±0.56	
5.7-6.5 (n=217)	−0.34±0.58	.15
≥6.5 (n=216)	−0.26±0.47	
HDL cholesterol (mmol/L)		
<0.93 (n=190)	−0.32±0.58	
0.93-1.2 (n=197)	−0.26±0.49	.50
≥1.20 (n=188)	−0.31±0.54	
LDL cholesterol (mmol/L)		
<3.3 (n=166)	−0.36±0.59	
3.3-4.6 (n=169)	−0.31±0.52	.11
≥4.6 (n=157)	−0.24±0.47	
Glucose (mmol/L)		
<4.8 (n=234)	−0.26±0.47	
4.8-5.6 (n=213)	−0.30±0.54	.18
≥5.6 (n=210)	−0.35±0.61	
Hypertension		
Yes (n=223)	−0.31±0.54	.51
No (n=443)	−0.28±0.54	
AP class at baseline*		
I,II (n=290)	−0.27±0.49	.25
III,IV (n=376)	−0.32±0.59	

MLD, minimal lumen diameter; MI, myocardial infarction; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AP, angina pectoris.

*Canadian Cardiovascular Society classification.

TABLE 3. Change in Minimal Lumen Diameter per Lesion at Follow-up for Lesion-Related Variables

	Change in MLD at follow-up (mm)	P
MLD before PTCA (mm)		
<0.9 (n=219)	−0.37±0.58	
0.9-1.15 (n=216)	−0.31±0.51	<.02
≥1.15 (n=228)	−0.22±0.51	
MLD after PTCA (mm)		
<1.65 (n=220)	−0.16±0.48	
1.65-1.9 (n=221)	−0.33±0.50	<.001
≥1.90 (n=225)	−0.39±0.55	
Relative gain at PTCA		
<0.2 (n=230)	−0.13±0.45	
0.2-0.3 (n=209)	−0.33±0.49	<.001
≥0.3 (n=224)	−0.46±0.58	
Length obstruction (mm)		
<5.25 (n=229)	−0.23±0.46	
5.25-6.8 (n=195)	−0.24±0.51	<.01
≥6.8 (n=203)	−0.38±0.55	
Plaque area (mm²)		
<4.7 (n=208)	−0.21±0.45	
4.7-7.6 (n=212)	−0.29±0.53	<.03
≥7.6 (n=207)	−0.34±0.53	
Eccentricity		
<0.2 (n=210)	−0.31±0.52	
0.2-0.45 (n=205)	−0.26±0.50	.42
≥0.45 (n=212)	−0.27±0.50	
% Diameter stenosis before PTCA		
<56.5 (n=244)	−0.20±0.48	
56.5-64.5 (n=210)	−0.35±0.54	<.001
≥64.5 (n=209)	−0.35±0.58	
% Diameter stenosis after PTCA		
<29.5 (n=217)	−0.40±0.57	
29.5-38 (n=225)	−0.32±0.53	<.001
≥38 (n=224)	−0.17±0.49	
Vessel size (mm) (reference diameter)		
<2.4 (n=240)	−0.30±0.53	
2.4-2.85 (n=214)	−0.30±0.51	.91
≥2.85 (n=212)	−0.28±0.57	
Patency before PTCA		
Total occlusion (n=36)	−0.54±0.87	<.01
Patent (n=630)	−0.28±0.50	
Collateral circulation to obstruction site		
Yes (n=122)	−0.39±0.64	<.05
No (n=544)	−0.25±0.49	
Thrombus before PTCA		
Yes (n=32)	−0.32±0.51	.65
No (n=634)	−0.29±0.52	
Thrombus after PTCA		
Yes (n=16)	−0.71±0.90	<.01
No (n=650)	−0.28±0.52	
Vessel dilated		
LAD (n=321)	−0.27±0.46	
LCx (n=154)	−0.28±0.55	.36
RCA (n=191)	−0.34±0.63	
Calcified lesion		
Yes (n=233)	−0.29±0.50	.61
No (n=433)	−0.31±0.56	
Tandem lesion		
Yes (n=25)	−0.27±0.39	.82
No (n=641)	−0.29±0.54	
Dissection after PTCA		
Yes (n=125)	−0.32±0.59	.60
No (n=541)	−0.29±0.52	
Branch in stenosis		
Yes (n=194)	−0.31±0.49	.69
No (n=472)	−0.29±0.56	

MLD, minimal lumen diameter; PTCA, percutaneous transluminal coronary angioplasty; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery.

TABLE 4. Change in Minimal Lumen Diameter per Lesion at Follow-up for Procedure-Related Variables

	Change in MLD at follow-up (mm)	P
Maximal balloon diameter (mm)		
<2.35 (n=189)	−0.26±0.50	
2.35-2.7 (n=214)	−0.30±0.50	.11
≥2.7 (n=192)	−0.35±0.55	
Balloon-artery ratio		
<0.9 (n=201)	−0.27±0.55	
0.9-1.05 (n=201)	−0.29±0.53	.17
>1.05 (n=193)	−0.36±0.54	
No. of inflations		
1 (n=178)	−0.29±0.47	
2-4 (n=254)	−0.30±0.51	.55
>4 (n=234)	−0.35±0.57	
Maximal inflation pressure (atm)		
<8 (n=261)	−0.31±0.58	
8-10 (n=264)	−0.30±0.52	.43
≥10 (n=141)	−0.24±0.50	
Total inflation duration (s)		
<220 (n=202)	−0.30±0.54	
220-470 (n=230)	−0.28±0.52	.69
>470 (n=224)	−0.27±0.48	

MLD, minimal lumen diameter.

before angioplasty (Table 5). Only two clinical variables and two postangioplasty variables, namely, diabetes, duration of angina, the relative gain in lumen diameter achieved at angioplasty, and thrombus after angioplasty were found to be independently predictive for luminal narrowing after balloon angioplasty.

To rule out any influence of the investigational drug on our findings, the use of either the thromboxane A_2 receptor blocker GR32191 or placebo was forced into the model. Trial medication had only a very small, statistically insignificant contribution to the fit of the model (Table 5).

In an attempt to assess how well the model predicted the amount of luminal narrowing at follow-up, the percentage of correct classified lesions was calculated for five intervals of predicted change in lumen diameter (Table 7). Correct prediction by the model was poor, particularly in the range of predicted change from −0.1

TABLE 5. Multivariate Linear Regression Model for the Prediction of Change in Lumen Diameter

Model	Coefficient	SE of coefficient	F to remove
Intercept	0.40		
Relative gain at PTCA	−1.36	0.18	57.5
MLD before PTCA	−0.19	0.07	6.7
Lesion length ≥6.8 mm	−0.19	0.04	19.7
Diabetes	−0.34	0.07	20.7
Duration of angina <2.3 months	−0.11	0.04	6.2
Thrombus after angioplasty	−0.31	0.14	5.2
Allocation to GR32191B	0.03	0.04	0.5

Per-lesion analysis (n=666).

SE, standard error; PTCA, percutaneous transluminal coronary angioplasty; MLD, minimal lumen diameter.

TABLE 6.   Multivariate Linear Regression Model for the Prediction of Change in Lumen Diameter

Model	Coefficient	SE of coefficient	F to remove
Intercept	0.43		
Relative gain at PTCA	−1.42	0.20	51.0
MLD before PTCA	−0.22	0.08	7.2
Lesion length ≥6.8 mm	−0.19	0.04	16.9
Diabetes	−0.32	0.08	14.9
Duration of angina <2.3 months	−0.11	0.05	5.6
Thrombus after angioplasty	−0.31	0.14	5.2
Allocation to GR32191B	0.01	0.04	0.06

Per-patient analysis. For multilesion, only the most narrowed lesion was taken into account (n=575).

SE, standard error; PTCA, percutaneous transluminal coronary angioplasty; MLD, minimal lumen diameter.

TABLE 7.   Percentages of Correct Classification

Interval of predicted change in MLD	Percentage correct classification*
≤−0.4 mm	98/197 (49.7%)
−0.3 to −0.4 mm	9/116 (7.8%)
−0.2 to −0.3 mm	13/123 (10.5%)
−0.1 to −0.2 mm	12/106 (11.3%)
>−0.1 mm	72/121 (59.5%)

MLD, minimal lumen diameter.

*Total amount of lesions is 663 because gain could not be calculated for three lesions that were located distal to a total occlusion before percutaneous transluminal coronary angioplasty; therefore, the minimal lumen diameter is unknown.

to −0.4 mm. In fact, only 10% of lesions in the middle three categories were correctly classified by the model. On the other hand, lesions showing no change or regression and lesions showing large progression were more predictable. The information content of the model according to the ROC curves (Fig 2) was optimal for the "loss of ≥0.72 mm" restenosis criterion. For the ">50% diameter stenosis" criterion, the curve was very close to the line of "no prognostic value." If, in addition to >50% diameter stenosis at follow-up, a loss of at least 13% in percent diameter stenosis (twice the long-term variability for diameter stenosis measurements, using our analysis system) was required for a lesion to be classified as restenosis, a shift of the ROC curve to the left upper corner was apparent. These findings under-
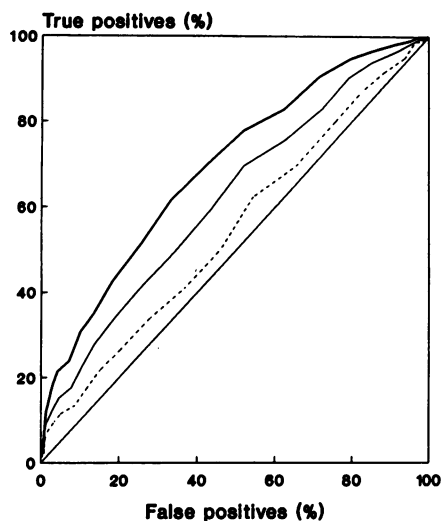

FIG 2.   *Receiver operator characteristic (ROC) curves for comparison of restenosis criteria at different cut-off points of predicted change in lumen diameter. The diagonal line is the line of identity or line of "no prognostic value." ROC curves on the line of identity have no prognostic value; those in the left upper corner are most informative. Solid curve: 0.72 mm criterion (area under curve, 69.6%); normal curve: 50% diameter stenosis criterion with a change in diameter stenosis at follow-up of at least 13% (area under the curve, 62.2%); dotted curve: 50% diameter stenosis criterion (area under curve, 54.8%).*

score the poor predictability of luminal narrowing and restenosis after balloon angioplasty and explain the differences between the restenosis criteria.

In an attempt to do an analysis on a per-patient rather than on a per-lesion basis, the analysis was repeated. In case of multilesion dilatations, only the lesion that narrowed the most was considered for this analysis. In Table 6, the results of this analysis are summarized. The same variables were retained with almost equal coefficients. Only a visible thrombus on the postangioplasty angiogram was not retained in the multiple linear regression analysis on a per-patient basis (F to enter was 3.6).

Discussion

During 15 years of percutaneous transluminal coronary balloon angioplasty, an abundance of clinical and experimental studies have been carried out in an attempt to elucidate factors that can predict the "Achilles' heel" of coronary angioplasty, namely progressive luminal narrowing after a successful procedure. Although many clinical, procedural, and lesion-related factors have been linked with a higher angiographic restenosis rate, results of these studies are sometimes conflicting. As pointed out by Beatt et al,[13] most of the discrepancies can be attributed to (1) patient selection, (2) the method of analysis, and (3) the definition of angiographic restenosis used.

Patient Selection

To obtain objective, unbiased results, all patients should be recatheterized after a predetermined follow-up period regardless of their symptomatic status. Failure to perform angiographic follow-up in a majority of patients will introduce bias in the assessment of the true change in minimal lumen diameter at follow-up. The restenosis rate according to a more or less arbitrary cut-off point will be biased toward higher values if symptomatic patients or patients with unfavorable anatomy after angioplasty are preferentially recatheterized. In this study, 88.6% of all patients with a successful angioplasty had a follow-up angiogram performed within a predetermined time frame of 6 months.

Method of Analysis

A well-validated quantitative angiographic analysis system should be used. Computer-assisted automated edge detection techniques enhance objectivity and reproducibility and reduce the high interobserver and intraobserver variability inherent to visual interpreta-

tion of the coronary angiogram.[14,15] The quantitative analysis system we applied for the analysis of the angiograms meets these requirements.[13] Recently we performed a study[16] comparing luminal dimensions 24 hours after angioplasty with those on the immediate postangioplasty angiogram using the same methodology as in the present study. Mean difference in minimal lumen diameter (accuracy) of 119 lesions was 0.00 mm, with a standard deviation (precision) of 0.20 mm. It was concluded that (1) in the first 24 hours after angioplasty, no major renarrowing takes place, and (2) variability of the CAAS measurements immediately after balloon dilatation is less than the long-term variability of the method.[8] It should be noted that this long-term variability was measured 8 years ago on stenoses not submitted to angioplasty and with a reference diameter of 3.6 mm (present study, 2.6 mm). Also, standardization of angiofilm recording was not performed in the CAAS variability study.[8] In that study, no attempt was made to standardize on technical characteristics of the x-ray gantry or on vasomotor tone (intracoronary injection of the same amount of nitrates before pre-PTCA, post-PTCA and follow-up angiography). We therefore feel that the long-term variability of the system under a strictly standardized angiography protocol is closer to 0.20 mm than the earlier reported 0.36 mm. However, even if a precision of 0.20 mm is regarded as correct in the setting of this study, part of the changes in lumen diameter fall within the measurement error of technique. This can be a possible reason for the poor fit of the multiple linear regression equation. Another point of concern with quantitative analysis of a lesion immediately after angioplasty is the amount of analyst interference with the automated edge detection technique. In our population, the amount of editing performed by the analysts was 3.7% before angioplasty, 4.2% after angioplasty, and 3.7% at follow-up angiography; that is, 4.2% of the automatically detected vessel contours were corrected by the analysts. The interobserver and intraobserver variability of the analysis of the postangioplasty angiogram is subject to ongoing investigation, and data are not yet available. We can therefore conclude that for quantitative analysis of the immediate postangioplasty angiogram, most likely the same variability values apply as for quantitative analysis of nondilated vessel segments.

Restenosis Criteria

The third factor influencing the restenosis rates is the restenosis criterion. The most frequently applied criterion in the literature is the >50% diameter stenosis at follow-up criterion. This criterion is historically based on the physiological concept of coronary flow reserve introduced by Gould and others[17] in 1974 and is taken because it represents the approximate value in animals with normal coronary arteries at which blunting of the hyperemic response occurs. Although this criterion may be of some relevance in determining a clinically significant stenosis in human atherosclerotic vessels, it is a static measurement of lesion severity and tells us nothing about the dynamic behavior of the restenosis process. If the "50% diameter stenosis at follow-up" criterion is applied, lesions with a suboptimal angioplasty result will preferentially be selected (ie, will have to undergo a small loss in lumen diameter to be classified as restenosed). Bourassa et al[18] have recognized this

shortcoming and thus considered lesions with ≥50% diameter stenosis at follow-up that did not show a change of at least 10% at follow-up as not "restenosed."

The predictive accuracy of the multivariate model for restenosis according to the 50% diameter stenosis criterion was very poor (Fig 2). If in addition a change in percent diameter stenosis of at least 13% (twice the long-term variability for percent diameter stenosis measurements) was required, then predictive accuracy of the model improved markedly, since lesions with a suboptimal angioplasty result no longer unduly influenced the restenosis rate. This requirement shifts the ROC curve to the left upper corner. A criterion that better reflects the dynamic behavior of the lesion after PTCA is the ≥0.72-mm loss in lumen diameter criterion as proposed by our group.[5,8,12] This criterion is not meant to be a restenosis criterion strictu sensu, since that also implies some sort of functional measure of lesion severity at follow-up, but rather an indicator of significant intraluminal growth as monitored angiographically.

Predictive Factors for Luminal Narrowing After Balloon Angioplasty

If restenosis is viewed as an intraluminal growth process after a successful angioplasty, risk factors for restenosis should be risk factors for this growth process. Therefore, we determined risk factors for the absolute amount of quantitative angiographic luminal narrowing rather than for the crossing of a more or less arbitrary cut-off point (eg, 50% diameter stenosis or loss ≥0.72 mm).

A distinction should be made between lesions that progress toward total occlusion and lesions that remain patent at follow-up, since it is likely that part of the luminal narrowing observed in former lesions is caused by thrombosis and not only by the fibroproliferative process. The larger luminal narrowing in lesions in patients with diabetes, unstable angina, in totally occluded lesions, lesions with visible collateral circulation, and lesions with a visible thrombus after angioplasty was largely determined by a higher incidence of total occlusions at follow-up.

Patient-Related Factors

Diabetes, unstable angina, and duration of angina shorter than 2.3 months were associated with more luminal narrowing at follow-up. If total occlusions at follow-up were disregarded, none of these variables showed significantly more narrowing. In multivariate analysis however, diabetes was independently predictive of luminal narrowing.

The assumption that risk factors for the magnitude of the restenosis process are similar to risk factors for atherosclerosis was not confirmed in the present study. Only diabetes was found to be independently related to the amount of luminal narrowing at follow-up. This finding has also been recognized by others.[19-26] In a recent study by Bourassa et al[18] using the same quantitative angiographic analysis system, diabetes was not found to be predictive of restenosis. Other classic risk factors for atherosclerosis such as male sex, systemic hypertension, high cholesterol level, and continued smoking after the PTCA were not found to be related to luminal narrowing in the present study. The controversy regarding these risk factors is considerable, with many

studies being positive for one or more patient-related factors and many studies being negative.[27,28]

Lesion-Related Factors

Preangioplasty variables. In univariate analysis, five preangioplasty variables were associated with more luminal narrowing at follow-up: minimal lumen diameter before angioplasty, percent diameter stenosis before angioplasty, length of stenosis, total occlusion before angioplasty, and collateral circulation to dilatation site. A relation between stenosis severity and restenosis rate has been shown previously.[18,20,21,29] It is conceivable that more severe lesions undergo more severe vessel wall damage during the procedure, a known trigger for the hyperplastic reaction.[30-32] In our multivariate analysis, the preangioplasty minimal lumen diameter was found to be an independent determinant of subsequent loss in lumen diameter. In longer lesions, more smooth muscle is possibly exposed to injury and platelet adhesion, which probably enhances the intimal hyperplastic reaction.

A relation between stenosis length and the restenosis process has also been described by others.[18,33,34] Total occlusion before angioplasty is a well-known factor connected with total occlusion at follow-up[35,36] and thus a large loss in lumen diameter at follow-up. Because total occlusion before angioplasty is part of the continuous-variables minimal lumen diameter and diameter stenosis before PTCA, total occlusion before angioplasty was not found to be an independent predictor of loss in lumen diameter.

Collateral circulation to the dilatation site will be more abundant in case of a severe stenosis or total occlusion. Since the severity of the lesion (minimal lumen diameter) before angioplasty was found to be an independent determinant for the absolute loss in lumen diameter at follow-up, the presence of collaterals was not retained in the model.

No differences in luminal narrowing was observed for the three coronary arteries. Others[23,28,37-39] have reported a higher incidence of restenosis for the left anterior descending artery, a finding recently challenged by Hermans et al.[41]

Postangioplasty variables. Relative gain achieved at PTCA was both in univariate and multivariate analysis the strongest predictor (largest F to remove in final model) of luminal narrowing at follow-up. This variable probably best reflects the amount of damage inflicted upon the vessel wall by the angioplasty balloon. It is conceivable that more damage to the vessel wall with more deep arterial injury will result in a more aggressive repair process.[1,30-32] Other postangioplasty variables that were related to more luminal narrowing at follow-up in univariate analysis were higher minimal lumen diameter after angioplasty, diameter stenosis after angioplasty <29.5%, and visible thrombus after angioplasty. Thus, a better postangioplasty result leads to more luminal narrowing or intimal hyperplasia at follow-up. Others have reported that a poorer postangioplasty result was predictive of restenosis.[18,21,23,29,37,42] In general, they applied the 50% diameter stenosis cut-off point and, as discussed above, lesions with a poor postangioplasty result will exceed this cut-off point with only minimal additional deterioration.

Because lesions with a low percent diameter stenosis and a large lumen diameter after angioplasty were also the lesions that underwent a high relative gain at angioplasty and since this variable was the strongest independent predictor of the absolute amount of luminal narrowing at follow-up, percent diameter stenosis after angioplasty and lumen diameter after angioplasty were not retained in the multivariate analysis.

Thrombus after angioplasty was retained in the multivariate model. Five of 16 lesions (31%) with a visible thrombus after angioplasty were totally occluded at follow-up and therefore showed a greater overall loss in lumen diameter.

We did not find an association between coronary dissection immediately after angioplasty and subsequent luminal renarrowing. Conflicting data have been reported concerning dissection and restenosis.[22,23,43-46] However, it is clear that severe dissections are associated with a higher acute complication[45] and restenosis rate, the latter probably due to a poorer angioplasty result in combination with the 50% diameter stenosis criterion.

Procedure-Related Variables

Balloon oversizing (balloon-artery ratio >1.05) was not related to more luminal narrowing at follow-up. Some investigators found a positive effect of balloon oversizing on restenosis[29,42] and others have not[18,42]; however, in a prospective randomized study, Roubin et al[44] found a higher incidence of acute complications in case of oversizing but no difference in restenosis rate.

Study Limitations

Although this study suggests several factors that may be determinants of luminal narrowing after coronary balloon angioplasty, it does not address the actual mechanism of restenosis. Vasomotion at follow-up angiography cannot be ruled out as a possible cause of the observed luminal renarrowing in individual lesions, although intracoronary nitrates in appropriate doses were administered before each angiography. Mean reference diameter was not different before PTCA, after PTCA, and at follow-up (2.64±0.56 mm, 2.70±0.53 mm, and 2.70±0.56 mm, respectively), suggestive of accurate control of vasomotion. Because of the relatively small sample sizes of some variables, β error cannot be ruled out in this study. Furthermore, in performing multiple statistical comparisons, there is a risk that some of them may reach significance by chance alone. The multivariate model was developed and tested in the same population. Generally, a model will be less accurate if assessment of fit is carried out in a different population. However, the poor fit of the model even when tested in the same population underscores the poor predictability of the restenosis process.

The analyses described in this study were based on data from a restenosis prevention trial (CARPORT). That trial was designed to investigate whether a certain drug was capable of reducing the amount of intimal hyperplasia relative to placebo treatment and not specifically to determine risk factors for this event. The post hoc nature of the present analyses might therefore have influenced the outcome of the analyses. In the CARPORT trial, only patients with a scheduled angioplasty for a primary lesion of the native coronary system could be entered. Therefore, several variables that have been found important in other analyses such as saphenous vein graft location and restenosed lesions could not be analyzed. At the time of

the design of the CARPORT trial, the risk factor ostial lesion was not known and therefore could not be included in the analysis.

According to the protocol, patients were to undergo repeat catheterization within the time window of 6 months±2 weeks. However, if symptoms reappeared before this predetermined time of follow-up, early angiography was performed. If no serious restenosis was found and/or no reintervention followed and the follow-up period was less than 4 months, the patient was asked to undergo another angiography 6 months after the balloon angioplasty. This 4-month cut-off point was derived from the studies by Nobuyoshi[47] and Serruys,[5] who showed the time relation of the restenosis process. In both studies, luminal narrowing continued up to 4 months after balloon dilatation and came to a halt afterward. In our population, 88 (13.1%) of the lesions were refilmed before 4 months of follow-up. It might be possible that these lesions would have further deteriorated if catheterization had been performed at 6 months, thereby influencing the analysis. Most of these patients underwent reintervention (PTCA, bypass grafting), and a minority refused repeat angiography. Early repeat angiography is an unavoidable aspect of this type of studies. It was considered unethical to delay angiography in patients with symptom recurrence. Minimal luminal diameter before angioplasty was 1.04 mm in both groups; after angioplasty this was 1.67 mm in the <4-month catheterization group and 1.78 mm in the 6-month catheterization group. At follow-up angiography, minimal lumen diameter was 1.06 mm in the <4-month catheterization group and 1.54 mm in the 6-month catheterization group. Mean loss in lumen diameter was 0.61 mm with early catheterization and 0.25 mm in the 6-month catheterization group. A mean lumen diameter of 1.06 mm at follow-up angiography in the early angiography group represents a recurrence to the preangioplasty state.

It is well known that developing atherosclerosis is accompanied by a compensatory enlargement of the vessel lumen.[48] This compensatory enlargement will camouflage for a long time the true amount of vessel wall thickening if determined by contrast angiography. Whether this process of compensatory enlargement plays a role in the restenosis process after balloon angioplasty is unknown. It could theoretically have some repercussions on measurements of change in lumen diameter when used as a measurement of the amount of intimal hyperplasia after angioplasty. Techniques that visualize the vessel wall in vivo, like intravascular ultrasound, could give an answer to this question.

Conclusions

Prediction of luminal narrowing with baseline clinical and quantitative angiography was shown to be poor. Only six variables, namely, minimal lumen diameter before angioplasty, relative gain at angioplasty, lesion length, diabetes, duration of angina, and thrombus after angioplasty, were found to be independent determinants of the hyperplastic intimal reaction after balloon angioplasty. Control of these factors alone, if at all possible, will not result in a reduction of the amount of luminal narrowing. Furthermore, since (elective) angioplasty is still a procedure performed to alleviate symptoms, it does not seem feasible to deny diabetics,

patients with recent onset angina, or patients with a severe lesion a balloon angioplasty procedure. Restenosis is obviously a process that cannot be predicted by simple clinical and morphological patient or lesion characteristics. Therefore, additional biochemical or histochemical factors[49] of importance in the restenosis process should be investigated and, where possible, tackled with appropriate pharmacological intervention.

The variable most strongly associated with the amount of luminal narrowing at follow-up was the relative gain at angioplasty. It must be noted that lesions with a large gain at PTCA not only can but also will undergo a larger loss in lumen diameter at follow-up. Because drugs currently under development to prevent the restenosis process after balloon angioplasty are designed to reduce the absolute amount of intimal hyperplasia, the highest possible benefit of a new drug treatment might be expected in lesions with the characteristics retained in the present multivariate model.

Appendix

References

1. Nobuyoshi M, Kimura T, Ohishi H, Horiuchi H, Nosaka H, Hamasaki N, Yokoi H, Koutaku K. Restenosis after percutaneous transluminal coronary angioplasty: pathologic observations in 20 patients. *J Am Coll Cardiol.* 1991;17:433-439.

*Principle investigator; †Chairman, Steering Committee.

2. Essed CE, Van den Brand M, Becker AE. Transluminal coronary angioplasty and early restenosis: fibrocellular occlusion after wall laceration. *Br Heart J.* 1983;49:393-396.

3. Safian RD, Gelbish JS, Erny RE, Schnitt SJ, Schmidt D, Baim DS. Coronary atherectomy: clinical, angiographic, and histologic findings and observations regarding potential mechanisms. *Circulation.* 1990:82:69-79.

4. Serruys PW, Rutsch W, Heyndrickx GR, Danchin N, Mast EG, Wijns W, Rensing BJ, Vos J, Stibbe J. Prevention of restenosis after percutaneous transluminal coronary angioplasty with thromboxane A_2 receptor blockade: a randomized, double-blind, placebo-controlled trial. *Circulation.* 1991;84:1568-1580.

5. Serruys PW, Luijten HE, Beatt KJ, Geuskens R, de Feyter PJ, van den Brand M, Reiber JHC, Ten Katen HJ, van Es GA, Hugenholtz PG. Incidence of restenosis after successful coronary angioplasty: a time-related phenomenon: a quantitative angiographic study in 342 consecutive patients at 1, 2, 3, and 4 months. *Circulation.* 1988;77:361-371.

6. Reiber JHC, Serruys PW, Kooyman CJ, Slager CJ, Schuurbiers JHC, den Boer A. Approaches toward standardization in acquisition and quantitation of arterial dimensions from cineangiograms. In: Reiber JHC, Serruys PW, eds. *State of the Art in Quantitative Coronary Angiography.* Dordrecht: Martinus Nijhoff Publishers; 1986:145-155.

7. Serruys PW, Deckers JW, Luijten HE, Reiber JHC, Tijssen JGP, Chadha D, Hugenholtz PG. Long acting coronary vasodilatory action of the molsidomine metabolite Sin I: a quantitative angiographic study. *Eur Heart J.* 1987;8:263-270.

8. Reiber JHC, Serruys PW, Kooyman CJ, Wijns W, Slager CJ, Gerbrands M, Schuurbiers JCH, den Boer A, Hugenholtz PG. Assessment of short, medium, and long-term variations in arterial dimensions from computer-assisted quantification of coronary cineangiograms. *Circulation.* 1985;71:280-288.

9. Reiber JHC, Serruys PW. Quantitative angiography. In: Marcus ML, Schelbert HR, Skorton DJ, Wolf GL, eds. *Cardiac Imaging, a Companion to Braunwalds Heart Disease.* New York: WB Saunders Co; 1991:211-280.

10. Rensing BJ, Hermans WRM, Beatt KJ, Laarman GJ, Suryapranata H, van den Brand M, De Feyter PJ, Serruys PW. Quantitative angiographic assessment of elastic recoil after percutaneous transluminal coronary angioplasty. *Am J Cardiol.* 1990;66:1039-1044.

11. Dorros G, Cowley MJ, Simpson J, Bentifoglio LG, Block PC, Bourassa M, Detre K, Gosselin AJ, Grüntzig AR, Kelsey SF, Kent KM, Mock MB, Mullins SM, Myler RK, Passamani ER, Stertzer SH, Williams DO. Angioplasty: report of complications from the NHLBI angioplasty registry. *Circulation.* 1983;67:723-730.

12. Serruys PW, Strauss BH, Beatt KJ, Bertrand ME, Puel J, Rickards AF, Meier B, Goy JJ, Vogt P, Kappenberger L, Sigwart U. Angiographic follow-up after placement of a self-expanding coronary artery stent. *N Engl J Med.* 1991;324:13-17.

13. Beatt KJ, Serruys PW, Hugenholtz PG. Restenosis after coronary angioplasty: new standards for clinical studies. *J Am Coll Cardiol.* 1990;15:491-498.

14. Meier B, Grüntzig AR, Goebel N, Pyle R, von Gosslar W, Schlumpf M. Assessment of stenoses in coronary angioplasty: inter- and intraobserver variability. *Int J Cardiol.* 1983;2:159-169.

15. Zir LM, Miller SW, Dinsmore RW, Gilbert JP, Harthorne JW. Interobserver variability in coronary angiography. *Circulation.* 1976;53:627-632.

16. Foley DP, Rensing BJ, Vos J, Deckers J, Serruys PW. Is there a need for angiography after 24 hours to assess the result of coronary balloon angioplasty in clinical studies? *Circulation.* 1992;85(suppl I):I-785. Abstract.

17. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical stenoses: instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. *Am J Cardiol.* 1974;33:87-94.

18. Bourassa MG, Lesperance J, Eastwood C, Schwartz L, Cote G, Kazim F, Hudon G. Clinical, physiologic, anatomic and procedural factors predictive of restenosis after percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol.* 1991;18:368-376.

19. Vandormael MG, Deligonul U, Kern MJ, Harper M, Presant S, Gibson P, Galan K, Chaitman BR. Multilesion coronary angioplasty: clinical and angiographic follow-up. *J Am Coll Cardiol.* 1987;10:246-252.

20. Holmes DR Jr, Vlietstra RE, Smith HC, Vetrovec GW, Kent KM, Cowley MJ, Faxon DP, Grüntzig AR, Kelsey SF, Detre KM, Van Raden MJ, Mock MB. Restenosis after percutaneous transluminal coronary angioplasty: a report from the PTCA registry of the National Heart, Lung, and Blood Institute. *Am J Cardiol.* 1984;53:77C-81C.

21. Lambert M, Bonan R, Cote G, Crepeau J, de Guise P, Lesperance J, David PR, Waters DD. Multiple coronary angioplasty: a model to discriminate systemic and procedural factors related to restenosis. *J Am Coll Cardiol.* 1988;12:310-414.

22. Fleck E, Regitz V, Lehnert A, Dacian S, Dirschinger J, Rudolf W. Restenosis after balloon dilatation of coronary stenosis: multivariate analysis of potential risk factors. *Eur Heart J.* 1988;9:15-18.

23. Ellis SG, Roubin GS, King SB III, Douglas JS Jr, Cox WR. Importance of stenosis morphology in the estimation of restenosis risk after elective percutaneous transluminal coronary angioplasty. *Am J Cardiol.* 1989;63:30-34.

24. Galan KM, Hollman JL. Recurrence of stenoses after coronary angioplasty. *Heart Lung.* 1986;15:585-587.

25. Arora RR, Konrad K, Badhwar K, Hollman JL. Restenosis after transluminal coronary angioplasty: a risk factor analysis. *Cathet Cardiovasc Diagn.* 1990;19:17-22.

26. Macdonald RG, Henderson MA, Hirschfeld JW Jr, Goldberg SH, Bass T, Vetrovec G, Cowley M, Taussig A, Whitworth H, Margolis JR, Hill JA, Jugo R, Pepine CJ. Patient related variables and restenosis after percutaneous transluminal coronary angioplasty: a report from the M-Heart group. *Am J Cardiol.* 1990;66:926-931.

27. Serruys PW, Rensing BJ, Luijten HE, Hermans WRM, Beatt KJ. Restenosis following coronary angioplasty. In: Meier B, ed. *Interventional Cardiology.* Bern: Hogrefe and Huber Publishers; 1990:79-115.

28. Califf RM, Ohman EM, Frid DJ, Fortin DF, Mark DB, Hlatky MA, Herndon JE, Bengtson JR. Restenosis: the clinical issue. In: Topol EJ, ed. *Textbook of Interventional Cardiology.* New York: WB Saunders Co; 1990:363-394.

29. Mata LA, Bosch X, David PR, Rapold HJ, Corcos T, Bourassa MG. Clinical and angiographic assessment 6 months after double vessel percutaneous coronary angioplasty. *J Am Coll Cardiol.* 1985; 6:1239-1244.

30. Liu MW, Roubin GS, King SB III. Restenosis after coronary angioplasty: potential biologic determinants and role of intimal hyperplasia. *Circulation.* 1989;79:1374-1387.

31. Sarembock IJ, La Veau PJ, Sigal SL, Timms I, Sussman J, Haudenschild C, Ezekowitz MD. Influence of inflation pressure and balloon size on the development of intimal hyperplasia after balloon angioplasty: a study in the atherosclerotic rabbit. *Circulation.* 1989;80:1029-1040.

32. Schwartz RS, Murphy JG, Edwards WD, Camrud AR, Vlietstra RE, Holmes DR. Restenosis after balloon angioplasty: a practical proliferative model in porcine coronary arteries. *Circulation.* 1990; 82:2190-2200.

33. Blackshear JL, O'Callaghan WG, Califf RM. Medical approaches to prevention of restenosis after coronary angioplasty. *J Am Coll Cardiol.* 1987;9:834-848.

34. Rensing BJ, Hermans WRM, Beatt KJ, van den Brand KM, Suryapranata H, de Feyter PJ, Serruys PW. Plastic and elastic changes after coronary balloon angioplasty, relation to restenosis. *Eur Heart J.* 1991;12:2112. Abstract.

35. Melchior JP, Meier B, Urban P, Finci L, Steffenino G, Noble J, Rutishauser W. Percutaneous transluminal coronary angioplasty for chronic total coronary arterial occlusion. *Am J Cardiol.* 1987; 59:535-538.

36. Serruys PW, Umans V, Heyndrickx GR, van den Brand M, de Feyter PJ, Wijns W, Jaski B, Hugenholtz PG. Elective PTCA of totally occluded coronary arteries not associated with acute myocardial infarction: short-term and long-term results. *Eur Heart J.* 1985;6:2-12.

37. Leimgruber PP, Roubin GS, Hollman J, Cotsonis GA, Meier B, Douglas JS Jr, King SB III, Grüntzig AR. Restenosis after successful coronary angioplasty in patients with single-vessel disease. *Circulation.* 1986;73:710-717.

38. Halon DA, Merdler A, Shefer A, Flugelman MY, Lewis BS. Identifying patients at high risk for restenosis after percutaneous transluminal coronary angioplasty for unstable angina pectoris. *Am J Cardiol.* 1989;64:289-293.

39. de Feyter PJ, Suryapranata H, Serruys PW, Beatt K, van Domburg R, van den Brand M, Tijssen J, Azar A, Hugenholtz PG. Coronary angioplasty for unstable angina: immediate and late results in 200 consecutive patients with identification of risk factors for unfavorable early and late outcome. *J Am Coll Cardiol.* 1988;324-333.

40. Finci L, Meier B, Steffino G, Urban P, Rutishauser W. Restenosis and repeat coronary angioplasty in Geneva. *Eur Heart J.* 1988;9:11-13.

41. Hermans WRM, Rensing BJ, Kelder JC, de Feyter PJ, Serruys PW. Restenosis in major coronary arteries: post angioplasty

restenosis rate between segments of the major coronary arteries. *Am J Cardiol.* 1992;69:194-200.

42. Renkin J, Melin J, Robert A, Richelle F, Bachy JL, Col J, Detry JM, Wijns W. Detection of restenosis after successful coronary angioplasty: improved clinical decision making with use of a logistic model combining procedural and follow up variables. *J Am Coll Cardiol.* 1990;16:1333-1340.

43. Leimgruber PP, Roubin GS, Anderson HV, Bredlau CE, Whitworth HB, Douglas JS Jr, King SB III, Grüntzig AR. Influence of intimal dissection on restenosis after successful coronary angioplasty. *Circulation.* 1985;72:3:530-535.

44. Matthews BJ, Ewels CJ, Kent KM. Coronary dissection: a predictor of restenosis? *Am Heart J.* 1988;115:547-554.

45. Roubin GS, Douglas JS, King SB III, Lim S, Hutchinson N, Thomas RG, Grüntzig AR. Influence of balloon size on initial success, acute complications, and restenosis after percutaneous transluminal coronary angioplasty. *Circulation.* 1988;78:557-565.

46. Nichols AB, Smith R, Berke AD, Shlomitz RA, Powers ER. Importance of balloon size in coronary angioplasty. *J Am Coll Cardiol.* 1989;13:1094-1100.

47. Nobuyoshi M, Kimura T, Nosaka H, Mioka S, Ueno K, Yokoi H, Hamasaki N, Horiochi H, Ohishi H. Restenosis after successful percutaneous transluminal coronary angioplasty: serial angiographic follow-up of 299 patients. *J Am Coll Cardiol.* 1988;12:616-623.

48. Glagov S, Weisenberg E, Zarens CK. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med.* 1987;316:1371-1376.

49. Eber B, Schumacher M, Auer-Grumbach P, Toplak H, Klein W. Elevated IgM-anticardiolipin antibodies in patients with restenosis following PTCA. *Eur Heart J.* 1991;12:2107. Abstract.