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Patient, Lesion, and Procedural Variables as Risk Factors for Luminal Re-Narrowing After Successful Coronary Angioplasty: A Quantitative Analysis in 653 Patients with 778 Lesions

Walter R. M. Hermans, Benno J. Rensing, *David P. Foley, †Jan G. P. Tijssen, ‡Wolfgang Rutsch, §Hakan Emanuelsson, ||Nicolas Danchin, ¶William Wijns, **François Chappuis, and Patrick W. Serruys on behalf of the Multicenter European Research trial with Cilazapril after Angioplasty to prevent Transluminal coronary Obstruction and Restenosis (MERCATOR) study group

*Thoraxcenter, Dijkzigt, Rotterdam, The Netherlands, *Research Fellow of the Irish Heart Foundation; †Academic Medical Center, Department of Clinical Epidemiology and Biostatistics, Amsterdam, The Netherlands; ‡Universitäts Klinikum Virchow, Berlin, Germany; §University of Göteborg, Sweden; ||CHU Brabois, Vandoeuvre, France; ¶St. Luc University Hospital, Brussels, Belgium; and **Hôpital Cantonal, Geneva, Switzerland*

Summary: Follow-up angiography at 6 months was obtained in 94% of the 693 patients (778 successfully dilated coronary lesions) enrolled in the Multicenter European Research trial with Cilazapril after Angioplasty to prevent Transluminal Coronary Obstruction and Restenosis (MERCATOR) trial—a double-blind, placebo-controlled trial—to study the effects of cilazapril 5 mg b.i.d. on restenosis [defined as the mean loss in minimal luminal diameter during follow-up, assessed by an interpolated edge detection technique (coronary angiography analysis system)] and long-term clinical outcome. No statistically significant difference could be detected between treatment and placebo groups with regard to clinical outcome or restenosis. The purpose of this ancillary study was to determine which, if any, patient, lesion, or procedural factors were predictive of restenosis. The identification of such factors could be helpful in the selection of lesions suitable for angioplasty and, if modifiable or controllable, potentially reduce restenosis. A stepwise multiple linear regression analysis was performed to identify independent predictors of restenosis. The following variables were retained in the model in order of significance: (a) relative gain (difference between the minimal luminal diameter pre- and post-percutaneous transluminal coronary angioplasty (PTCA), normalized for vessel size), (b) minimal luminal diameter post-PTCA, and (c) dilatation of another vessel than right coronary artery. The fit of the model was poor; where the predicted change in minimal luminal diameter was <0.1 mm, 0.1–0.3 mm, >0.3 mm, the corresponding percent correct classification was 30, 52, and 55%. The present study illustrates that the restenosis phenomenon cannot accurately be predicted by patient, lesion, and procedural variables. **Key Words:** PTCA—Restenosis—QCA.

The major limitation of the long-term success of percutaneous transluminal coronary angioplasty (PTCA) is still restenosis (1–19). Fourteen years after its introduction by Andreas Gruntzig in 1977 as an alternative treatment modality for patients with asymptomatic or symptomatic coronary artery disease (20), more than 400,000 patients were treated by PTCA worldwide in 1991, and most likely this number will increase further in future (21). Histologic, experimental, and clinical research has provided us with information that enables us to understand better the recurrence of successfully dilated coronary lesions. This untoward phenomenon is now recognized by many researchers as an intimal proliferation of smooth-muscle cells together with an abundant matrix production (22–40).

Quantitative coronary analysis is the most reliable available method of assessing coronary arterial luminal changes over time and has demonstrated that the change in minimal luminal diameter between post-PTCA and follow-up angiography is the most non-

Address correspondence and reprint requests to Dr. P. W. Serruys at Catheterization Laboratory, Thoraxcenter, Erasmus University, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands.

ambiguous measurement to describe the continuous process of restenosis at present time (41–47).

Recent developments in pharmacologic therapy and new percutaneous intracoronary revascularization techniques have failed to inhibit or prevent restenosis (47–55). On the other hand, a variety of patient-, procedural-, and lesion-related factors have been associated with an increased risk of restenosis (Table 1) (1–15,18,19); however, the ability to predict in individual cases which patient or lesion will be affected by restenosis is poor.

A model that could predict which of the dilated lesions will re-narrow would be of value in many ways: (a) It could help to identify patients and lesions at high risk for luminal re-narrowing during the first 6 months. Such patients could then be offered another interventional technique or alternatively could be invited to participate in clinical trials of new pharmacological agents because they are at high risk. Their selection could potentially reduce the number of patients required in a study to evaluate new treatment. (b) It could provide more insight into the restenosis phenomenon

TABLE 1. *Summary of studies using multivariate analysis techniques to find variables with increased risk for restenosis*

Study (ref. no.)	No. of patients	Angio. follow-up (%)	Definition restenosis	Restenosis (%)	Risk factors		
					Patient	Lesion	Procedural
Holmes et al. (1)	665	84%	NHLBI I or IV	34% pts	Male Severity angina No history of MI	Bypass graft	—
Mata et al. (2)[a]	63	96%	↑ DS > 30% or DS > 70%	23% lesion	—	LAD or LCX > RCA % DS post-PTCA (40% vs. 20%) calcified lesion	Bar (0.9 vs. 1.1)
Leimgruber et al. (3)	1,758	57%	>50% DS	30% pts	Unstable angina	LAD ↑ % DS post-PTCA Gradient > 15 mm Hg	Absence of intimal dissection
Myler et al. (4)[b]	286	57%	>50% DS	57% pts 43% lesion	Diabetes Hypercholesterolemia New onset angina Current smoking	>95% DS pre-PTCA	↑ Max pressure
Guiteras Val et al. (5)	181	98%	↑ ≥30% DS	28% pts 25% lesion	Variant angina Multivessel	↑ % DS post-PTCA low % DS pre–post	—
Vandormael et al. (6)[b]	209	62%	>50% DS	50% pts	Male Diabetes	Prox. LAD Longer lesions	—
de Feyter et al. (7)[c]	179	88%	>50% DS	32% pts	Worsening AP or Post-MI AP	—	—
Fleck et al. (8)	110	86%	MLCA > 1 mm² (QCA)	44% lesions	—	—	—
Halon et al. (10)[c]	84	56%	>70% DS	25%	—	Multiple irregularities Decrease coronary perfusion	—
Quigley et al. (9)[d]	114	88%	>50% DS	32% pts	Unstable angina Hypertension Diabetes	—	—
Renkin et al. (11)[e]	278	47%	>50% DS	—	—	MLD post-PTCA	—
Rupprecht et al. (12)	676	70%	>50% DS or loss >50% of gain	29% pts	Unstable angina	↑ % DS pre-PTCA ↑ % DS post-PTCA	Long single inflation
Bourassa et al. (13)	376	66%	≥50% DS + 10% ↑ post-follow-up	36% pts 35% lesion	Severity angina	Length >10 mm % DS post-PTCA	—
MacDonald et al. (14) + Hirshfeld et al. (15)	694	74%	≥50% DS	40% lesion	—	Length >10 mm Vein graft LAD % DS pre-PTCA % DS post-PTCA	Optimal BAR (1.1–1.3)
Present study	693	94%	Loss in MLD	—	—	↑ Relative gain ↑ MLD post-PTCA LAD or LCX	—

Angio. follow-up, % of successfully dilated patients with angiographic follow-up; AP, angina pectoris; bar, balloon-artery ratio; DS, diameter stenosis; Fup, follow-up; LAD, left anterior descending artery; LC, left circumflex; MI, myocardial infarction; MLCA, change in minimal cross sectional area; MLD, minimal luminal diameter; NHLBI, National Heart Lung Blood Institute classification; pts, patients; RCA, right coronary artery; ↑, increase; ↓, decrease; PTCA, percutaneous transluminal coronary angioplasty.

[a] Multivessel dilatation; [b]multilesion dilatation; [c]unstable angina; [d]for restenosis; [e]angiography + exercise thallium scintigraphy.

by the identification of particular variables. (c) It might be helpful in the evaluation of new interventional devices.

The MERCATOR trial—Multicenter European Research trial with Cilazapril after Angioplasty to prevent Transluminal coronary Obstruction and Restenosis—was set up to study the efficacy of a new angiotensin-converting enzyme inhibitor, cilazapril, in the prevention of luminal re-narrowing after successful coronary angioplasty. All patients were asked to have a follow-up angiogram 6 months later or earlier if symptoms warranted. As an ancillary study, patient, lesion, and procedural factors were prospectively collected to determine which, if any, were predictive for luminal re-narrowing at follow-up.

PATIENTS AND METHODS

The study population consisted of 735 patients who were originally enrolled in 26 centers for the MERCATOR trial (Appendix I). The trial was carried out according to the declaration of Helsinki (1963), revised in Venice (1983). In this randomized, double-blind, placebo-controlled trial, cilazapril was investigated for its ability to prevent restenosis after primary coronary angioplasty. The results of the comparison between cilazapril and placebo have been reported elsewhere (48). All symptomatic and asymptomatic patients, aged 25–75 years excluding women with childbearing potential, who had angiographically proven significant narrowing in one or more major coronary arteries and who signed informed consent before the PTCA procedure, were considered to be eligible. Exclusion criteria were PTCA performed to revascularize acute myocardial infarction, history of sustained hypertension, maintenance therapy of diuretics, Q-wave myocardial infarction before 4 weeks of study entry, previous and or failed PTCA at the same site, or PTCA of a bypass graft.

Informed consent was obtained in 735 recruited patients before the PTCA procedure and were randomly assigned to cilazapril or placebo, but only 693 patients with a successful PTCA (defined as a visually assessed diameter stenosis of less than 50% post-PTCA) who met all inclusion and exclusion criteria as stated in the protocol and formed the study population (Fig. 1). Clinical or angiographic benefit could not be demonstrated, so that the placebo and active treatment group could be pooled for the present study (48). Of the 693 randomized patients, 653 (or 94%) had a follow-up angiogram suitable for quantitative analysis and this forms the study population (Fig. 1).

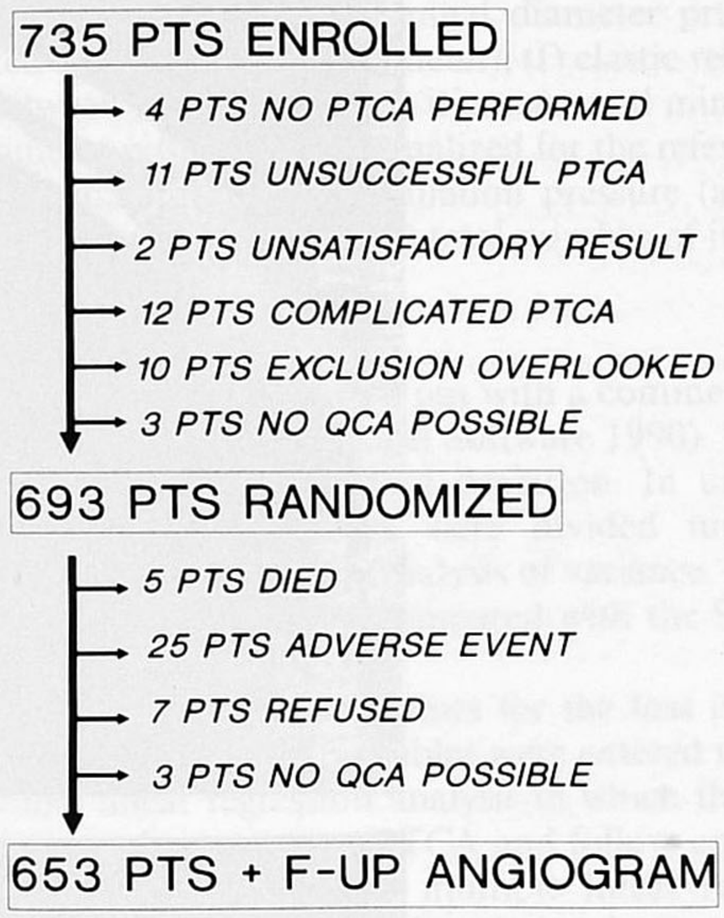

FIG. 1. Patient flowchart in MERCATOR trial. ANGIO, angiogram; EXCL, exclusion; Fup, follow-up, OLOOKED, overlooked, PTS, patients, PTCA, percutaneous transluminal coronary angioplasty; QCA, quantitative coronary analysis.

PTCA procedure and angiographic analysis

At the beginning of the procedure all patients received a bolus of 10,000 IU intravenous heparin. After 2 h, an additional infusion of 5,000 IU/h was given until the end of the procedure. Use of a calcium-channel blocker for 48 h post-PTCA was permitted. Aspirin 160–250 mg/day was given for 6 months to all patients (56,57). Choice of guiding catheter, guidewire, balloon type, inflation duration and pressure were left to the discretion of the operator.

Three angiograms were obtained in each patient, just before PTCA, immediately after PTCA, and at follow-up. To standardize the method of data acquisition and to ensure exact reproducibility of PTCA and follow-up angiograms, specific precautions were taken as described elsewhere (16,41,44,47). To avoid potential coronary spasm, either nitroglycerin 0.1–0.3 mg or isosorbide dinitrate 1–3 mg was given intracoronary for each coronary artery involved at pre-PTCA, post-PTCA, and at follow-up angiography. All contour positions of the catheter and the arterial segment were corrected for pincushion distortion introduced by the image intensifiers. All cineangiograms were quantitatively analyzed using the coronary angiography analysis system (CAAS), which has been validated and described in detail (41,44). All angiograms were processed and analyzed in a central core laboratory. An example of an analysis is shown in Fig. 2.

The follow-up coronary angiogram was performed at 6 months follow-up. If symptoms recurred within six 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 3 months, the patient was asked to undergo another coronary arteriogram at 6 months.

The absolute values of the stenosis diameter as well as the reference diameter are measured by the computer using the known contrast-empty catheter diameter as a scaling device. For that purpose the catheter tips were retained for accurate measurement with a micrometer. Because the algorithm is not able to measure total occlusions and lesions with TIMI-1 perfusion, a value of 0 mm was substituted for the minimal lumen diameter and 100% for the percent diameter stenosis. In these cases the post-PTCA reference diameter was substituted for the reference diameter pre-PTCA or at follow-up. For each dilated segment, the pre-PTCA, the post-PTCA, and follow-up minimal lumen diameter and diameter stenosis were derived from the mean value from multiple matched projections (41,44,47).

Patient, lesion, and procedural risk factors

The loss in minimal luminal diameter that occurred after angioplasty until follow-up angiography, per lesion dilated, was assessed for patient, lesion, and procedural risk factors,

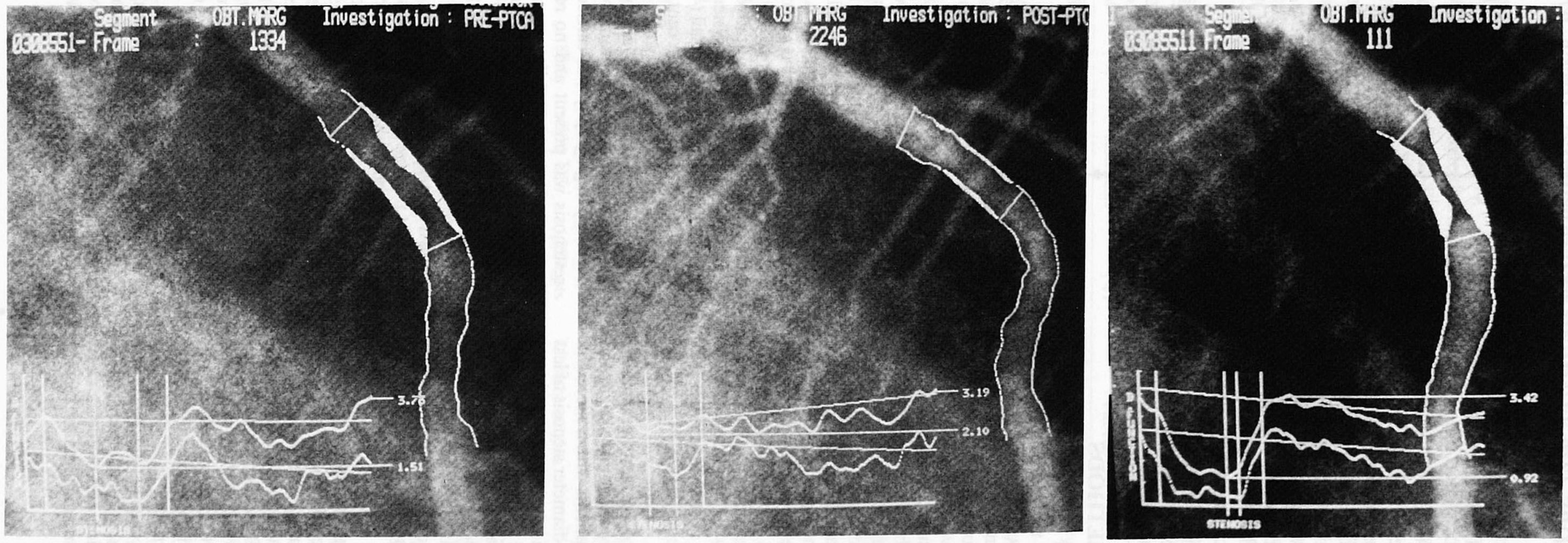

FIG. 2. A single frame of a narrowing in the left circumflex marginal branch before dilatation (**left**), after dilatation (**middle**) and at follow-up (**right**). The diameter along the analyzed segment is depicted on the diameter function curve (upper curve). The minimal luminal diameter is 1.51 mm (A), 2.10 mm (B), and 0.92 mm (C), respectively. The length of the stenosis is determined with curvature analysis. The white area represents the atherosclerotic plaque.

prospectively recorded in each participating center. Some of the lesional factors (type of lesion, branch involved in stenosis, lesion located in bend, calcification of lesion, thrombus post-PTCA, dissection post-PTCA) were assessed by the core laboratory blinded for the code and clinical data. For each categorical variable, the change in minimal luminal diameter between post-PTCA and follow-up was determined in each category. Continuous variables were grouped into three equally sized subgroups (tertiles) and the loss in minimal luminal diameter between post-PTCA and follow-up was assessed in each tertile.

Patient-related factors are systemically present and therefore affect all dilated lesions: (a) age, (b) gender, (c) non–insulin-dependent diabetes, (d) previous myocardial infarction, (e) history of smoking, (f) smoking at entry of the study, (g) extent of coronary atherosclerotic disease (single or multivessel), (h) number of sites dilated (1 or >1), (i) angina CCS class (0, 1, 2 versus 3, 4), (j) pain at rest (yes or no), (k) unstable angina (defined as pain at rest requiring treatment with intravenous nitrates), (l) duration of angina (days), (m) medication taken, and (n) cholesterol level at baseline (58).

Lesion-related factors are unique for each lesion: (a) and (b) minimal luminal diameter before and after PTCA, (c) relative gain (difference between the minimal luminal diameter before and after angioplasty, normalized for the vessel size), (d) and (e) % diameter stenosis before and after PTCA, (f) vessel size, (g) lesion length (determined from the diameter function on basis of curvature analysis), (h) atherosclerotic plaque area before PTCA (defined as the area between the actual and reconstructed contours at the obstruction site), (i) eccentricity of the lesion before PTCA (symmetry index: defined as the coefficient of the left hand distance between the reconstructed interpolated reference diameter and actual vessel contours and the right hand distance between reconstructed and actual contours at the site of obstruction. In this equation the largest distance between actual and reconstructed contours becomes the denominator. A symmetrical lesion has a value of 1 and a severely eccentric lesion has a value 0), (j) curvature (bending) of the analyzed segment before PTCA (is computed as the average value of all the individual curvature values along the centerline of the coronary segment, with the curvature defined by the rate of change of the angle through which the tangent to a curve turns in moving along the curve and which for a circle is equal to the reciprocal of the radius. The curvature value was determined in the projection in which the analyzed segment appeared longest between two defined landmarks, the least foreshortened view), (k) patency of the vessel before PTCA, (m) vessel dilated (right coronary artery versus left anterior descending versus left circumflex), (n) location of lesion dilated in the vessel (proximal versus middle versus distal), (o) qualitative assessment of lesion morphology, i.e., type of lesion, involvement of side branch in lesion, balloon for dilatation located at a bend, calcification of lesion, dissection after PTCA, and thrombus after PTCA (59–62).

Procedural-related factors are unique for each lesion: (a) minimal balloon diameter of the largest balloon with the highest pressure used, (b) balloon material used (compliant (PolyVinylChloride, PolyEthelyne, PolyOlefin Copolymer) versus noncompliant (PolyEthelyne Terphelate and Hydracross), (c) and (d) balloon–artery ratio [size of the inflated balloon at highest pressure used (either measured or according size of manufacturer) divided by reference diameter of the analyzed vessel], (e) stretch (difference between minimal balloon diameter and minimal luminal diameter pre-PTCA, normalized for the reference diameter), (f) elastic recoil (difference between minimal balloon diameter and minimal luminal diameter post-PTCA, normalized for the reference diameter), (g) maximal balloon inflation pressure (atm), (h) total inflation duration(s), and (i) total number of inflations (63–65).

Statistical methods

Statistical analysis was carried out with a commercial statistical package (BMDP Statistical Software 1990). Data are presented as mean ± 1 standard deviation. In univariate analysis, continuous variables were divided into three subgroups and compared with analysis of variance. Categorical or discrete variables were compared with the Student *t* test.

To obtain independent predictors for the loss in lumen diameter per lesion dilated, variables were entered in a stepwise multiple linear regression analysis in which the loss in lumen diameter between post-PTCA and follow-up was the independent variable. Stepwise multiple linear regression analysis was performed to assess the relationship between the variables mentioned in the "Patients and Methods" section (independent variables = X_i) and the loss in minimal luminal diameter from after angioplasty to follow-up angiogram (dependent variable = Y): $Y = \beta_0 + \beta_i x_i$ where β_0 is the intercept and β_i is the i^{th} regression coefficient. The standard BMDP 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 variables with 2 of 3 tertiles showing approximately the same amount of loss in lumen diameter. These were entered as discrete variables (duration of angina, balloon–artery ratio, maximal balloon inflation pressure, total inflation time) (66). The code (placebo or cilazapril) of the treatment was forced into the model to rule out any influence of the investigational drug.

To determine how well the regression model performs in predicting restenosis according to two frequently applied restenosis criteria (a) ≥0.72 mm change in minimal luminal diameter between post-PTCA and follow-up (16,44,49), (b) >50% diameter stenosis at follow-up and to describe the discrepancies of the two criteria, receiver operator characteristics (ROC) curves were constructed for each criterion. In these ROC curves sensitivity (true positive %) at different cutoff points of predicted change in minimal diameter is graphed as a function of 100% − specificity (false-positive %).

RESULTS

Of the 693 randomized patients, 653 (94%) with 778 lesions (1.2 lesion/patient) had a follow-up angiogram suitable for quantitative analysis. The mean age was 58 ± 8 years, and 82% of the patients were males. The average follow-up time was 164 ± 44 days. More than 62% of the patients had one-vessel disease, 31% two-vessel disease, and only 6% had three-vessel disease. There was an increase in overall minimal luminal diameter from 1.02 ± 0.38 mm before PTCA to 1.78 ± 0.36 mm post-PTCA and with subsequent decrease to 1.51 ± 0.57 mm at follow-up. Using categorical criterion, restenosis rate was 30% according to the >50% diameter stenosis criterion and 18% if the criterion of ≥0.72 mm loss in lumen diameter at follow-up was used.

Variables predictive for change in minimal luminal diameter during follow-up

Patient related variables. Statistically significant association was detected for two patient-related variables and loss in minimal luminal diameter between post-PTCA and follow-up. A greater loss in minimal luminal diameter was observed in association with the number of sites dilated and duration of the angina, with a greater loss in minimal luminal diameter if only one site is dilated and if symptoms are of recent origin (Table 2).

Lesion-related variables. Statistically significant association was detected for eight pre- or post-PTCA variables and loss in minimal luminal diameter between post-PTCA and follow-up. A greater loss in minimal luminal diameter was observed in association with *preprocedural variables:* (a) lower values of minimal luminal diameter, (b) higher values of diameter stenosis, (c) occluded vessel, (d) lesions in left anterior descending artery, and (e) calcified lesion; and with *postprocedural variables:* (a) higher values for minimal luminal diameter after PTCA, (b) lower values for diameter stenosis after PTCA, and (c) higher ratio of relative gain (Table 3).

Procedural-related variables. Statistically significant association was detected for two lesion-related variables and loss in minimal luminal diameter between post-PTCA and follow-up. A greater loss in minimal luminal diameter was observed in association with the total inflation time and stretch, with a greater loss in minimal luminal diameter with longer total inflation time and with more stretch (Table 4C).

Multiple linear regression analysis

The stepwise multiple linear regression analysis showed that (a) relative gain, (b) minimal luminal diameter post-PTCA, and (c) dilatation of another vessel than right coronary artery were independently predictive for luminal narrowing at follow-up. Trial medication, which was forced into the model, had only a very small statistically insignificant contribution to the fit of the model (Table 5).

To assess the value of the model at predicting the degree of luminal narrowing at follow-up, the percentage of correctly classified lesions was calculated for five intervals of predicted change in lumen diameter. Correct prediction by the model was poor, especially in the lower range. On average only 30% of lesions were correctly classified. On the other hand, lesions that showed moderate or more severe change were more predictable, although the percentage is still low (Table 6). The information content of the model according to the ROC curves was best for ≥0.72 mm cutoff criterion (Fig. 3). These findings underscore the very poor predictability of luminal renarrowing after balloon coronary angioplasty and explains the discrepancies between the two restenosis criteria with >0.72 mm decrease in minimal luminal diameter as an "active criterion" and the 50% diameter stenosis as a "static criterion."

TABLE 2. *Change in minimal luminal diameter per lesion dilated for patient-related clinical variables*

Variable	*n*	Change in MLD (mm) (post-PTCA − follow-up)	*p* value
Age (yr)			
<55	256	0.30 ± 0.58	
55–62	263	0.25 ± 0.50	0.52
>62	259	0.26 ± 0.48	
Sex			
Male	649	0.28 ± 0.53	0.21
Female	129	0.22 ± 0.48	
Diabetes type II			
Yes	45	0.32 ± 0.48	0.52
No	733	0.27 ± 0.52	
History of myocardial infarction			
Yes	328	0.28 ± 0.54	0.70
No	450	0.26 ± 0.50	
Ever smoked			
Yes	603	0.25 ± 0.49	0.08
No	175	0.33 ± 0.59	
Currently smoking			
Yes	127	0.21 ± 0.53	0.16
No	651	0.28 ± 0.51	
Extent of coronary artery disease[a]			
Single vessel	424	0.30 ± 0.51	0.11
Multi vessel	316	0.23 ± 0.54	
Number of sites dilated			
1	536	0.30 ± 0.52	0.02
>1	242	0.20 ± 0.50	
CCS-class at baseline[b]			
I, II	441	0.26 ± 0.52	0.68
III, IV	365	0.28 ± 0.51	
Pain at rest			
Yes	260	0.29 ± 0.51	0.46
No	518	0.26 ± 0.52	
"Unstable angina"			
Yes	72	0.29 ± 0.49	0.72
No	706	0.27 ± 0.52	
Duration of angina (days)[c]			
<86	252	0.33 ± 0.55	
86–305	258	0.29 ± 0.52	0.01
>305	256	0.19 ± 0.48	
Medication			
None	39	0.34 ± 0.62	
Mono	195	0.25 ± 0.53	
Double	369	0.29 ± 0.52	0.34
Triple	175	0.22 ± 0.47	
Total cholesterol (mmol/L)[d]			
<5.7	239	0.26 ± 0.53	
5.7–6.6	254	0.26 ± 0.51	0.97
>6.6	245	0.25 ± 0.51	

PTCA, percutaneous transluminal coronary angioplasty.
[a] Not assessed in 38 lesions.
[b] CCS, Canadian Cardiovascular Society classification (ref. 58).
[c] Not assessed for 12 lesions.
[d] Not assessed in 40 lesions.

DISCUSSION

Many different patient-, procedural-, and lesion-related variables have been proposed as being predictive of restenosis (Table 1), with little agreement between

TABLE 3. *Change in minimal luminal diameter (MLD) per lesion at follow-up (Fup) for lesional-related variables*

Variable	*n*	Change in MLD (mm) (post-PTCA − follow-up)	*p* value
MLD pre-PTCA (mm)			
<0.92	260	0.36 ± 0.55	
0.92–1.14	258	0.27 ± 0.51	0.0001
>1.14	260	0.17 ± 0.47	
MLD post-PTCA (mm)			
<1.60	256	0.16 ± 0.49	
1.60–1.90	263	0.25 ± 0.47	0.0001
>1.90	259	0.40 ± 0.57	
Relative gain at PTCA			
<0.22	258	0.09 ± 0.43	
0.22–0.33	259	0.20 ± 0.48	0.0001
>0.33	261	0.51 ± 0.55	
% Diameter stenosis pre-PTCA			
<55	252	0.19 ± 0.45	
55–64	276	0.24 ± 0.48	0.0001
>64	250	0.38 ± 0.61	
% Diameter stenosis post-PTCA			
<29	258	0.40 ± 0.50	
29–37	258	0.29 ± 0.48	0.0001
>37	262	0.12 ± 0.54	
Vessel size (mm)			
<2.35	247	0.26 ± 0.45	
2.35–2.80	262	0.30 ± 0.54	0.59
>2.80	269	0.25 ± 0.56	
Length obstruction pre-PTCA (mm)[a]			
<5	241	0.27 ± 0.47	
5–6.7	243	0.22 ± 0.48	0.41
>6.7	243	0.26 ± 0.55	
Atherosclerotic area plaque pre-PTCA (mm^2)[a]			
<4.7	240	0.24 ± 0.46	
4.7–7.3	244	0.23 ± 0.45	0.57
>7.3	243	0.28 ± 0.58	
Symmetry index[a]			
<0.24	232	0.22 ± 0.46	
0.24–0.45	250	0.26 ± 0.50	0.55
>0.45	245	0.27 ± 0.53	
Curvature analyzed segment[a]			
<14	234	0.22 ± 0.45	
14–22	235	0.21 ± 0.43	0.66
>22	235	0.19 ± 0.45	
Patency pre-PTCA			
Total occlusion	51	0.54 ± 0.68	0.0001
Patent	727	0.25 ± 0.50	
Vessel dilated			
RCA	222	0.21 ± 0.59	
LAD	360	0.32 ± 0.49	0.05
LCx	196	0.24 ± 0.47	
Location of vessel dilated			
Proximal	292	0.27 ± 0.51	
Middle	339	0.28 ± 0.53	0.95
Distal	147	0.26 ± 0.52	
Qualitative lesion morphology assessment[a]			
Type lesion			
Concentric	352	0.23 ± 0.47	
Eccentric	295	0.27 ± 0.54	
Tandem	38	0.17 ± 0.43	0.42
Multiple irregularities	41	0.31 ± 0.51	
Side branch in stenosis			
Yes	413	0.27 ± 0.51	0.94
No	364	0.27 ± 0.53	
Lesion located at bend point			
Yes	65	0.24 ± 0.54	0.67
No	713	0.27 ± 0.52	
Calcified lesion			
Yes	80	0.16 ± 0.47	0.04
No	698	0.28 ± 0.52	
Dissection post-PTCA			
Yes	247	0.28 ± 0.60	0.57
No	531	0.26 ± 0.48	
Thrombus post-PTCA			
Yes	29	0.34 ± 0.73	0.48
No	749	0.27 ± 0.51	

PTCA, percutaneous transluminal coronary angioplasty.
[a] Not available in 51 total occlusions before PTCA.

the various studies. This may be due to deficiencies in their methodology relating to important areas: (a) patient selection, (b) method of analysis, and (c) definition of restenosis (45). Most of the early studies were retrospective analyses of a small number of (symptomatic) patients not recatheterized at a predetermined time, and used different arbitrary categorical definitions of restenosis.

In the present trial, 94% of all randomized patients had follow-up angiography, eliminating potential bias in the assessment of the true change in luminal diameter of the dilated lesion during follow-up if only symptomatic patients had follow-up angiography. All baseline and follow-up films were processed and analyzed at the same angiographic core laboratory using an automated interpolated edge detection technique (CAAS), which has been extensively validated and described in the literature, thereby reducing the inter- and intra-observer variability inherent to visual interpretation of coronary angiograms (41–44).

Recently, two published ancillary studies of restenosis prevention trials prospectively collected patient, procedural, and lesional factors to determine which of these factors were predictive for restenosis. They identified different factors as predictive of restenosis despite using the same restenosis criterion (diameter stenosis >50% at follow-up) (13–15). The criterion of a diameter stenosis >50% at follow-up is the most frequently used, although, of historical relevance (67), it does not differentiate between a suboptimal result immediately after PTCA and a minor deterioration at follow-up. For example, an increase in diameter stenosis of 35% from

TABLE 4. *Change in minimal luminal diameter (MLD) per lesion at follow-up (Fup) for procedural-related variables*

Variable	*n*	Change in MLD (mm) (post-PTCA − follow-up)	*p* value
Minimal balloon diameter (mm)			
<2.15	209	0.23 ± 0.46	
2.15–2.51	213	0.30 ± 0.50	0.22
>2.51	209	0.30 ± 0.52	
Balloon material			
Noncompliance	400	0.29 ± 0.51	0.20
Compliance	377	0.24 ± 0.53	
Balloon-artery ratio[a]			
<0.98	169	0.22 ± 0.49	
0.98–1.11	245	0.30 ± 0.56	0.24
>1.11	217	0.30 ± 0.49	
Balloon-artery ratio[b]			
<1.05	259	0.23 ± 0.53	
1.05–1.20	264	0.33 ± 0.53	0.07
>1.20	255	0.25 ± 0.49	
Stretch			
<0.43	209	0.10 ± 0.41	
0.43–0.55	209	0.31 ± 0.49	0.0001
>0.55	213	0.41 ± 0.58	
Elastic recoil			
<0.15	209	0.32 ± 0.51	
0.15–0.27	209	0.26 ± 0.51	0.26
>0.27	213	0.25 ± 0.52	
Maximal balloon inflation pressure (atm)			
<7	219	0.20 ± 0.51	
7–9	285	0.29 ± 0.54	0.09
>9	274	0.30 ± 0.50	
Total inflation times (s)			
<145	245	0.20 ± 0.49	
150–240	285	0.29 ± 0.52	0.05
>240	248	0.31 ± 0.55	
Number of inflations			
1	94	0.24 ± 0.43	
2–4	544	0.27 ± 0.53	0.88
>4	140	0.27 ± 0.53	

PTCA, percutaneous transluminal coronary angioplasty.
[a] Measured balloon diameter in 621 lesions.
[b] Balloon size according to manufacturer.

10% post-PTCA to 45% at follow-up is not classified as restenosis, whereas an increase of only 6% from 45% post-PTCA to 51% at follow-up is. If distinction is to be identified between restenosis and a suboptimal result, one could add that a change of 13% in diameter stenosis between post-PTCA and follow-up should be present, as this reflects the long-term variability of the measurements. As restenosis is a continuous intraluminal growth process—that can be measured by quantitative techniques in large scale populations—absolute change in minimal luminal diameter (or loss at follow-up) was chosen as the dependent factor for the assessment of risk factors for regrowth of the lesion (68). Although potentially useful because of the ability to compare vessels of different sizes, the change in minimal luminal diameter between post-PTCA and follow-up normalized for the reference diameter (relative loss) was not used in this analysis, as the relative loss is not independent from the vessel size (Fig. 4A). As loss in minimal luminal diameter during follow-up seems to be independent of the vessel size (Fig. 4B) this was chosen (69,70).

TABLE 5. *Multivariate linear regression model for the prediction of change in lumen diameter at follow-up*

	Coefficient	SE	*F* remove
Intercept	−0.33		
Code	−0.04	0.04	1.73
Relative gain	0.95	0.12	65.73
MLD post-PTCA	0.21	0.05	14.95
Vessel dilated (RCA vs. LAD + LC)	−0.11	0.04	7.80

All variables with a value of $p < 0.15$ in univariate analysis were entered into the model. The code was forced into the model.

SE, standard error; PTCA, percutaneous transluminal coronary angioplasty; RCA, right coronary artery; LAD, left anterior descending artery; LC, left circumflex; MLD, minimal luminal diameter.

Predictors for luminal renarrowing during follow-up

Patient-related factors. Patients undergoing PTCA for recent-onset angina exhibited greater mean loss in minimal luminal diameter during follow-up. Perhaps this is related to the tendency of lesions associated with new onset angina to be biologically more active ("softer") and more compliant and therefore more amenable to the dilating forces of the balloon. Consequently, a better initial result is obtained with a greater "relative gain." Long presence of stable angina pectoris is associated with more calcification in the lesion, and therefore less gain in minimal diameter can be achieved. Besides that, less viable cells are present, and therefore less intimal hyperplasia develops.

Patients with more than one site dilated during the same procedure have less mean loss in minimal luminal diameter during follow-up. A possible explanation could be that in addition to the culprit lesion, a less severe lesion is dilated, as it is not always clear which lesion is causing the anginal symptoms. As this results in an average minimal luminal diameter before dilatation that is higher and an average gain that is lower, the subsequent average loss will be lower.

TABLE 6. *Percentages of correct classification*

Interval of predicted change in minimal luminal diameter (post-PTCA − follow-up)	Correct classification
<0.1 mm	91/300 (30%)
0.1–0.2 mm	20/82 (24%)
0.2–0.3 mm	19/72 (26%)
0.3–0.4 mm	7/64 (11%)
≥0.4 mm	97/260 (37%)

PTCA, percutaneous transluminal coronary angioplasty.

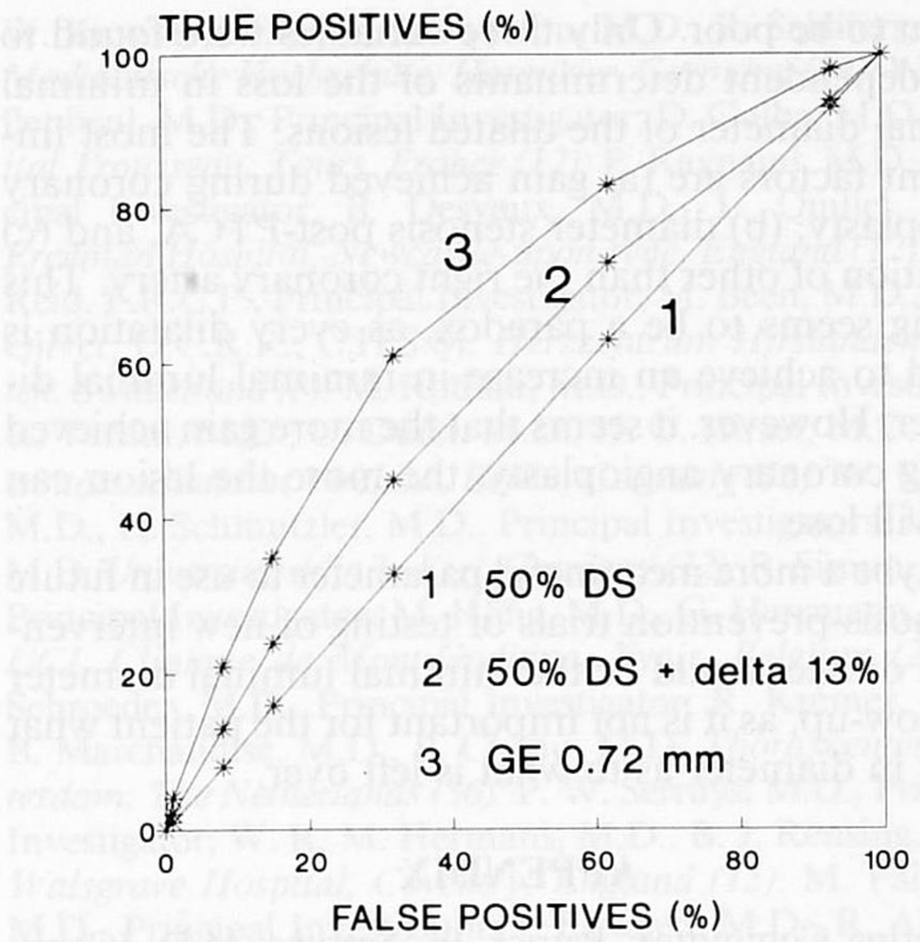

FIG. 3. Receiver–operator curves (ROC curves) for comparison of restenosis criteria at different cutoff points of predicted change in lumen diameter. The diagonal line is the line of identity or line of "no prognostic value." ROC curves on the line of identity have no prognostic value, those in the left upper corner are most informative. Solid curve: 0.72 mm criterion, normal curve: 50% diameter stenosis (DS) criterion with a change in diameter stenosis at follow-up of at least 13%, dotted curve: 50% diameter stenosis criterion.

Lesion-related factors. The one factor most strongly associated with luminal renarrowing after angioplasty was "relative gain" achieved by the angioplasty procedure. This is the ultimate paradox of treatment with coronary balloon angioplasty; the greater the initial "relative gain," the greater the subsequent loss. The final result or "relative gain" of an angioplasty procedure is the combination of permanent plastic and reversible elastic changes, i.e., a combination of deep arterial injury and reversible stretch imposed on the diseased vessel wall. The more severe the stenosis is, the more deep arterial damage will occur, resulting in a more aggressive repair process. This phenomenon has been observed in animal models of arterial injury and is a perfectly logical consequence of the healing process (24–26).

In univariate analysis the separate variables were also highly significant: minimal luminal diameter before and after PTCA, diameter stenosis before and after PTCA, and the presence of totally occluded vessels, but only minimal luminal diameter post-PTCA, other than relative gain, was retained in the multivariate linear regression model.

High values of post-PTCA diameter stenosis has been reported to be associated with higher restenosis rates (Table 1), although confusion could be caused by suboptimal dilatation (i.e., 49% diameter stenosis) in which case only a small loss (i.e., 2% increase in diameter stenosis) is required to exceed this categorical cut-off point of 50%. However, in our study *low* values of diameter stenosis post-PTCA is associated with more loss.

Totally occluded vessels have been reported to be associated with higher restenosis rates using "traditional" restenosis criteria (71,72), but was not retained as a separate factor in our analysis. This is because total occlusions are part of the continuous variable minimal luminal diameter, which is, by means of the relative gain, the most important predictor.

There have been many conflicting studies whether the dilated vessel is a risk factor for restenosis (Table

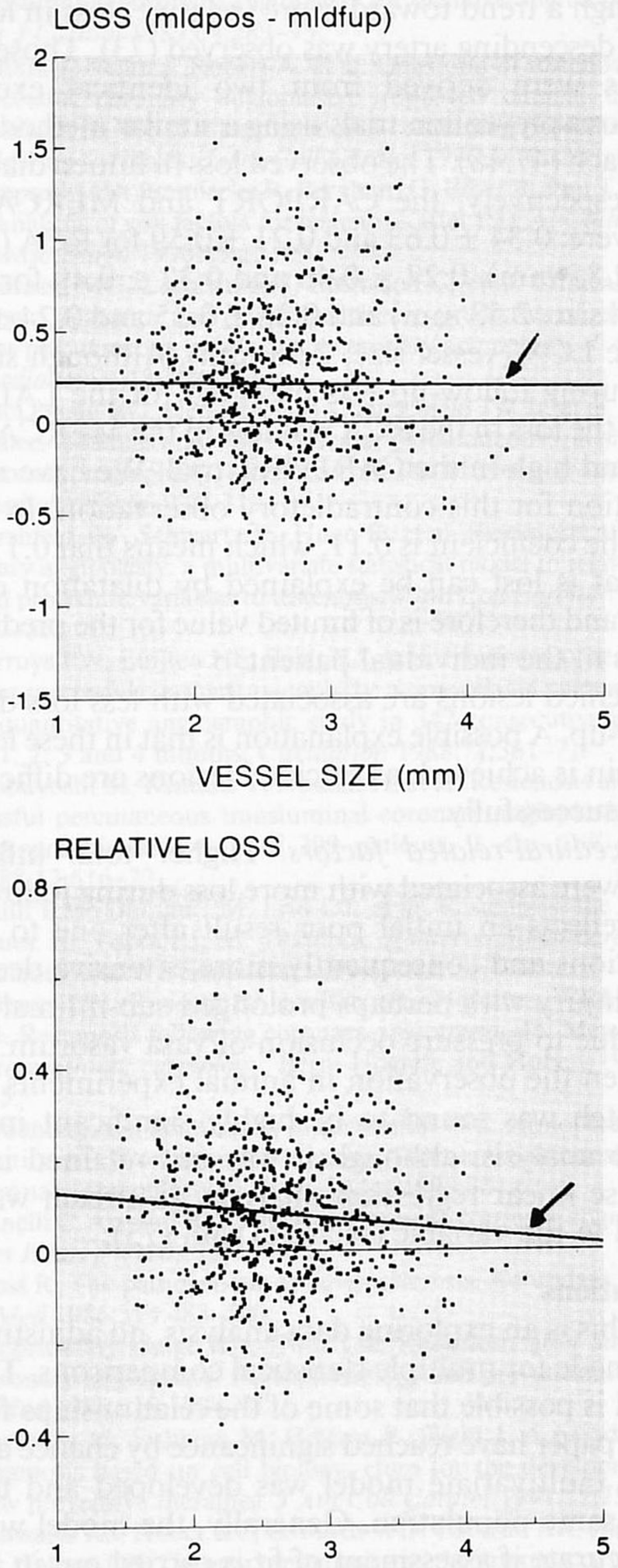

FIG. 4. Scatter plot, with on the x-axis the vessel size, and on the y-axis the loss (**top**) defined as the change in minimal luminal diameter between post-PTCA and follow-up, and relative loss (**bottom**) defined as the change in minimal luminal diameter between post-PTCA and follow-up normalized for the vessel size. The arrow indicates the regression line. PTCA, percutaneous transluminal coronary angioplasty.

1). In present study, univariate analysis shows a greater loss in minimal luminal diameter in the left anterior descending artery (LAD) as compared to the right coronary or left circumflex artery (LCX) (Table 2B). In stepwise linear regression analysis, dilatation of a vessel other than the right coronary artery (RCA) constituted an independent risk factor predictive for loss. This is somewhat surprising, as recently our group has found no statistical significant difference in loss between the three major coronary arteries in 1,452 dilated lesions, although a trend toward more (relative) loss in left anterior descending artery was observed (73). Those 1452 lesions were derived from two identical executed restenosis-prevention trials using a similar methodologic approach (47,48). The observed loss in lumen diameter for, respectively, the CARPORT and MERCATOR trial were: 0.34 ± 0.63 and 0.21 ± 0.59 for RCA (vessel size, 2.85 mm), 0.27 ± 0.46 and 0.32 ± 0.49 for LAD (vessel size, 2.53 mm) and 0.28 ± 0.55 and 0.24 ± 0.47 for the LCX (vessel size, 2.53 mm). Although similar loss during follow-up was observed for the LAD and LCX, the loss in the RCA was low in the MERCATOR trial and high in the CARPORT trial. We have no explanation for this contradictory observation. In addition, the coefficient is 0.11, which means that 0.11 mm of what is lost can be explained by dilatation of the vessel and therefore is of limited value for the prediction of loss in the individual patient.

Calcified lesions are associated with less loss during follow-up. A possible explanation is that in these lesions less gain is achieved, as calcified lesions are difficult to dilate successfully.

Procedural-related factors. Higher total inflation times were associated with more loss during follow-up. This reflects an initial poor result after one to three dilatations and consequently more extensive deep arterial injury with perhaps prolonged sub-intimal ischemia due to pressure occlusion of vasa vasorum. This has been the observation in animal experiments (74).

Stretch was found to be highly significant in univariate analysis, although it was not retained in the stepwise linear regression analysis, as stretch was reflected in the variable (relative) gain (75).

Limitations

As this is an exploring data analysis, no adjustments were made for multiple statistical comparisons. Therefore, it is possible that some of the relationships found in this paper have reached significance by chance alone.

The multivariate model was developed and tested in the same population. Generally, the model will be less accurate if assessment of fit is carried out in a different population. However, the poor fit of the model even if tested in the same population underscores the poor predictability of the restenosis process.

CONCLUSION

Prediction of luminal narrowing with prospectively collected patient, lesion, and procedural factors was shown to be poor. Only three variables were found to be independent determinants of the loss in minimal luminal diameter of the dilated lesions. The most important factors are (a) gain achieved during coronary angioplasty, (b) diameter stenosis post-PTCA, and (c) dilatation of other than the right coronary artery. This finding seems to be a paradox, as every dilatation is aimed to achieve an increase in minimal luminal diameter. However, it seems that the more gain achieved during coronary angioplasty, the more the lesion can and will lose.

Maybe a more meaningful parameter to use in future restenosis-prevention trials or testing of new interventional devices could be the minimal luminal diameter at follow-up, as it is not important for the patient what is lost in diameter as to what is left over.

APPENDIX

Steering Committee: Patrick W. Serruys, M.D. (Chairman), Wolfgang Rutsch, M.D., Nicolas Danchin, M.D., William Wijns, M.D., Hakan Emanuelsson, M.D., François Chappuis, M.D.

MERCATOR Study Group. *Participating Clinics and Investigators:* The following institutions and investigators participated in MERCATOR. The number of patients enrolled at each center are given in parentheses.

The London Chest Hospital, London, England (21): R. Balcon, M.D., Principal Investigator; J. Timmins, M.D., D. C. Springings, M.D., S. J. D. Brecker, M.D., S. W. Davies, M.D. *Hôpital TIMONE, Marseille, France (14):* J. L. Bonnet, M.D., Principal Investigator; F. d'Houdain, M.D. *University Hospital Leiden, Leiden, The Netherlands (41):* B. Buis, M.D., Principal Investigator; A. L. M. Bakx, M.D., M. I. Sedney, M.D. *Ospidale Nuguarda CA'Granda, Milan, Italy (12):* L. Campolo, M.D., Principal Investigator; G. B. Danzi, M.D., A. M. de Biase, M.D. *Hôpital Cantonal, Geneva, Switzerland (20):* F. Chappuis, M.D., Principal Investigator; W. Rutishauser, M.D., P. Urban, M.D., B. Meier, M.D. *CHU Brabois, Vandoeuvre, France (40):* N. Danchin, M.D., Principal Investigator; Y. Juillière, M.D., V. Voilquin-Thomas, M.D. *University of Göteborg, Göteborg, Sweden (44):* H. Emanuelsson, M.D., Principal Investigator; P. Albertsson, M.D., K. Selin, M.D., L. Ekström, M.D. *Medizinisch Klinik, München, Germany (32):* R. von Essen, M.D., Principal Investigator; H. Nebelsieck, M.D., A. Uberreiter, M.D., K. Igerl, M.D. *Onze Lieve Vrouw Ziekenhuis, Aalst, Belgium (44):* G. R. Heyndrickx, M.D., Principal Investigator; P. Nellens, M.D., B. de Bruyne, M.D., M. Goethals, M.D. *Städtisches Krankenhaus Bogenhausen, München, Germany (23):* T. Ischinger, M.D., Principal Investigator; M. Fischer, M.D., K. Coppenrath, M.D. *Albert-Ludwigs-Universität, Freiburg, Germany (18):* H. J. Just, M.D., Principal Investigator; H. Wollschläger, M.D., H. Drexler, M.D., G. Elias, M.D. *Medizinische Poliklinik, Zürich, Switzerland (20):* H. P. Krayenbühl, M.D., Principal Investigator; O. Hess, M.D., F. W. Amann, M.D., R. Schläpfer, M.D., M. Büchi, M.D. *Universität Erlangen, Erlangen, Germany (28):* B. Kunkel, M.D., Principal Investigator; T. Fürste, M.D. *CHRU-Hôpital Cardiologique, Lille, France (40):* J. M. Lablanche, M.D., Principal Investigator; J. M. Joris, M.D., T. Eeman, M.D., M. Henry, M.D. *Kantonsspital Basel, Basel, Switzerland (24):* M. Pfisterer, M.D., Principal Investigator; F. Burkart, M.D.,

W. Kiowski, M.D., E. Straumann, M.D., R. Schäfers, M.D. *Medizinische Hochschule, Hannover, Germany (24):* W. Rafflenbeul, M.D., Principal Investigator; D. Gulba, M.D. *Hôpital Trousseau, Tours, France (12):* P. Raynaud, M.D., Principal Investigator; B. Desvaux, M.D., L. Quillet, M.D. *Freeman Hospital, Newcastle-upon-tyne, England (12):* D. S. Reid, F.R.C.P., Principal Investigator; M. Been, M.D., T. K. Oliver, D.C.R.R., C.H.S.M. *Herzzentrum Hirslanden, Zürich, Switzerland (8):* M. Rothlin, M.D., Principal Investigator; R. Tartini, M.D., U. Dürst, M.D., H. O. Hirzel, M.D. *Universitäts Klinikum Virchow, Berlin, Germany (56):* W. Rutsch, M.D., H. Schmutzler, M.D., Principal Investigators; J. Bott, M.D. *Universitätsklinik, Kiel, Germany (32):* R. Simon, M.D., Principal Investigator; M. Höfig, M.D., G. Herrmann, M.D. *UCL Clinique de Mont-Godinne, Yvoir, Belgium (24):* E. Schroeder, M.D., Principal Investigator; R. Krémer, M.D., B. Marchandise, M.D., P. Chenu, M.D. *Thoraxcenter, Rotterdam, The Netherlands (56):* P. W. Serruys, M.D., Principal Investigator; W. R. M. Hermans, M.D., B. J. Rensing, M.D. *Walsgrave Hospital, Coventry, England (15):* M. Fai Shiu, M.D., Principal Investigator; J. Escaned, M.D., R. Ahmed, M.D. *Medizinische Klinik I, Aachen, Germany (40):* R. Uebis, M.D., Principal Investigator; J. vom Dahl, M.D., C. Stellbrink, M.D., S. Nase-Hüppmeier, M.D. *St. Luc University Hospital, Brussels, Belgium (35):* W. Wijns, M.D., Principal Investigator; J. M. Detry, M.D., J. Col, M.D., J. Cosyns, M.D., C. Hanet, M.D., X. Michel, M.D., J. Renkin, M.D. *Data Coordinating and Analysis:* F. Hoffmann-La Roche Ltd, Basel, Switzerland; SOCAR SA, Givrins, Switzerland. *Angiographic Core Laboratory. Cardialysis/Thoraxcenter, Rotterdam, The Netherlands:* P. W. Serruys, M.D., B. J. Rensing, M.D., W. R. M. Hermans, M.D., J. Pameyer. *Angiographic Assessment Committee:* P. W. Serruys, M.D. (Chairman), W. R. M. Hermans, M.D., R. Balcon, M.D., R. Uebis, M.D., J. M. LaBlanche, M.D., W. Rafflenbeul, M.D. *Study Directors:* Th. Widmann, M.D., F. Hoffmann-La Roche, Ltd., Basel, Switzerland; P. G. Hugenholtz, M.D., Ferme Mont-de-Vaux, Echichens, Switzerland.

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