Original articles
Coronary stenting beyond standard indications. Immediate and follow-up results

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Key words:
Coronary artery; Indications; Long-term clinical results; Stents.

Background. **Coronary stent has become an accepted treatment modality for selected indications. However, the literature shows diverse results when indications for coronary stenting are different from those tested in large randomized trials. The purpose of this study was to determine immediate and follow-up clinical and angiographic results in patients treated with coronary stenting for indications not specifically tested in large randomized trials.**

Methods. **Coronary stents were implanted in a total of 2060 lesions (1757 patients) in seven groups with expanded indications: left main coronary lesions, calcified lesions, small vessels (< 3 mm in size), small vessels with diffuse disease, large vessels with diffuse disease, and bifurcation lesions treated with stents in both branches or with one stent implanted only in the major branch. Stents were implanted using high balloon pressure for final inflation and in most cases with intravascular ultrasound. Clinical follow-up was achieved in 96% of patients at a mean time of 12 ± 7 months.**

Results. **Primary success (range 89-96%) and acute complications (range 5.7-13%) were comparable in all groups. At follow-up, the mortality rate was highest in the group of left main stenting (12.5%) but 20% of these patients had coronary stenting on non-elective basis. The restenosis rates ranged between 16-43%. The restenosis rate was highest in the group of bifurcation lesions with stent implantation in both vessels leading to a major adverse cardiac event (MACE) rate of 62% in this group. However, the survival rate at 1 and 2 years in the overall study group was 97 and 96%, and the event free survival was 76 and 74%, respectively. The procedure-related predictors of MACE were: final intravascular ultrasound result, use of stents with non-slotted tube morphology, final stent percent stenosis, and vessel size.**

Conclusions. **Coronary stenting beyond standard indications is feasible, with acceptable primary success and complication rates. However, the overall MACE rates were relatively high (34-62%), in particular for the indication of bifurcation lesions with stents implanted in both vessels.**

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Introduction

Coronary stenting has become an accepted treatment for selected patients with coronary artery disease. The recognized indications for stent implantation include *de novo* or restenotic short proximal lesions in vessels of ≥ 3 mm in size[1]. The primary and long-term results have been explored for the last 10 years and have been found to be satisfactory[2,3]. However, in clinical practice the operator is often confronted with patient selection and lesions with characteristics quite different from the ones used in large randomized studies[3,4]. In our institution coronary stenting has been performed since 1989. We used stents not only for standard indications but also for other indications such as in vessels of < 3 mm in size, in long and calcified lesions, in lesions involving a bifurcation or in selected lesions in the left main coronary artery. The purpose of this article was to analyze the immediate and long-term results of coronary stenting performed in this unselected group of patients.

Methods

Patients, lesions, groups and subgroups. The study population consisted of 1757 patients with 2060 lesions selected from a total population of 3440 patients who had undergone stent implantation in our institution from March 1993 to December 1997 (Fig. 1). Patients were excluded if they had lesions < 15

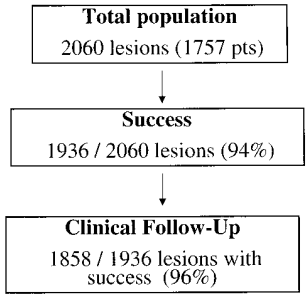

Figure 1. *Flow-chart of the study population.*

mm and located in a vessel ≥ 3 mm, unless the lesion met the inclusion criteria for a specific subgroup. The enrollment of patients in this study stopped at the end of 1997 in order to allow sufficient clinical follow-up. We selected from our database all patients who underwent coronary stent implantation for the following indications: left main coronary artery, calcified lesions, small vessels (size < 3 mm), diffuse disease (lesion length > 15 mm), and bifurcation lesions. The diffuse disease group was divided into two subgroups: one subgroup with the reference vessel size < 3 mm and the other subgroup with the reference vessel size ≥ 3 mm. Lesions located on a bifurcation were divided into two subgroups according to the stenting technique used. One subgroup included bifurcations treated with stents in both branches and another subgroup included bifurcations treated with one stent implanted only in the major branch (Table I).

Definitions.

- Critical stenosis = a narrowing > 70% in luminal reduction by quantitative coronary analysis (QCA);
- small vessel = vessel of < 3 mm in size by QCA;
- calcified lesion = presence of calcium at the site of the lesion on angiography immediately before contrast injection;
- diffuse disease = a lesion of > 15 mm in length by QCA;
- bifurcation lesion = a lesion involving the origin of two branches.

Indications for stenting were considered on the intention-to-treat basis:

- elective = stent implantation planned before starting the intervention;
- acute = stenting performed following coronary angioplasty;
- stent success = stent implantation in the target lesion with < 30% residual stenosis based on angiography and with the patient leaving the catheterization laboratory free from any of the following events: death, Q wave myocardial infarction or emergency bypass surgery.

The events analyzed in this study were: death, bypass surgery, myocardial infarction (Q wave or non-Q wave), emergency coronary angioplasty, and vascular complications. Death was defined as any death irrespective of the cause. These events were reported for the hospital stay as well as for the follow-up analysis:

- Q wave myocardial infarction = a new pathological Q wave present on ECG in association with an elevation of total creatine kinase (CK) enzyme twice the normal value with a positive MB band;
- non-Q wave myocardial infarction = an elevation of total CK enzyme twice the normal value with a positive MB band without any new Q waves on the ECG;
- emergency coronary bypass surgery = surgical revascularization performed after immediate transfer of the

Table I. Patient characteristics.

	Left main	Calcified	Small (< 3 mm)	Diffuse disease		Bifurcation		p
				Large	Small	Both vessel stent	Single vessel stent	
No. patients	36	256	896	237	196	45	91	
Age (years)	63 ± 11	61±10	58 ± 10	59 ± 10	59 ± 11	58 ± 11	58 ± 10	NS
Male	26 (72%)	227 (89%)	752 (84%)	215 (91%)	152 (78%)	44 (96%)	90 (85%)	< 0.01
Risk factors*								
Hypertension	22 (61%)	102 (40%)	394 (44%)	104 (44%)	78 (40%)	21 (47%)	49 (54%)	NS
Hypercholesterolemia	22 (61%)	140 (62%)	493 (55%)	130 (55%)	109 (56%)	30 (68%)	56 (62%)	NS
Diabetes	6 (17%)	36 (16%)	125 (14%)	31 (13%)	33 (17%)	10 (23%)	11 (12%)	NS
Current smokers	7 (19%)	63 (28%)	250 (28%)	73 (31%)	53 (27%)	9 (21%)	22 (24%)	NS
Family history	15 (42%)	100 (44%)	394 (44%)	104 (44%)	88 (45%)	23 (51%)	35 (38%)	NS
Prior myocardial infarction	11 (31%)	106 (47%)	412 (46%)	102 (43%)	84 (43%)	24 (53%)	47 (52%)	NS
Previous angioplasty	3 (8%)	18 (8%)	107 (12%)	33 (14%)	27 (14%)	5 (11%)	11 (12%)	NS
Previous coronary bypass	14 (39%)	36 (16%)	98 (11%)	28 (12%)	21 (11%)	8 (19%)	2 (2%)	NS
LVEF (%)	55 ± 12	57 ± 11	58 ± 11	57 ± 11	57 ± 11	59 ± 14	60 ± 10	NS
Unstable angina	14 (39%)	66 (29%)	242 (27%)	78 (33%)	62 (32%)	15 (32%)	24 (27%)	NS
Multivessel disease	36 (100%)	15 (66%)	573 (64%)	144 (61%)	137 (70%)	35 (79%)	54 (60%)	< 0.05
Antiplatelet therapy								
Ticlopidine + aspirin	33 (92%)	195 (86%)	753 (84%)	182 (77%)	157 (80%)	41 (96%)	91 (88%)	NS
Aspirin alone	3 (8%)	32 (14%)	143 (16%)	54 (23%)	39 (20%)	4 (4%)	11 (12%)	NS

LVEF = left ventricular ejection fraction. * not mutually exclusive.

patient from the cardiac catheterization laboratory to the operating room or within 24 hours of the procedure;
- elective coronary bypass surgery = surgical revascularization performed 24 hours after stenting or attempted stenting in the absence of clinical or ECG signs of acute ischemia;
- acute stent thrombosis = stent occlusion or the finding of TIMI flow 1 or 2 associated with an intraluminal filling defect occurring within 24 hours of stent implantation;
- subacute stent thrombosis = stent occlusion or the finding of TIMI flow 1 or 2 associated with an intraluminal filling defect occurring after 24 hours from stent implantation;
- emergency coronary angioplasty = any percutaneous intervention performed for ongoing ischemia following the stenting procedure and with flow impairment at the stent site;
- repeat coronary angiography = a new percutaneous intervention performed for the treatment of stent restenosis;
- new coronary angioplasty = a new percutaneous intervention performed for the treatment of coronary artery disease progression;
- vascular complications = bleeding or hematoma formation at the puncture site associated with the need for transfusion, vascular repair or prolonged external compression following initial successful sheath removal;
- stent restenosis = a 50% or more luminal reduction occurring at the stent site or immediately proximal or distal and demonstrated at the follow-up angiogram irrespective of clinical symptoms of the patient;
- target lesion revascularization = performance of a new revascularization procedure (coronary angioplasty or bypass surgery) at the stented lesion;
- major adverse cardiac events (MACE) = cumulative number of percutaneous or surgical revascularization for restenosis or disease progression, myocardial infarction, or death.

The patients in the group treated with left main stenting were divided into two subsets with "optimal" or "suboptimal" indication for surgical revascularization using a scoring scale previously published (Table II)[5]. An "optimal" indication had a score of < 3 points.

Stenting procedure. Stents were placed according to the operator technique at the given time. The intravascular ultrasound (IVUS) guide for stent deployment and high balloon pressure inflations for final stent dilation were used to obtain an optimal immediate result in every case as described previously[6]. In our patient population the use of GP IIb/IIIa antagonists was very limited due to the fact that patient recruitment for this study ended in December 1997. Angiographic follow-up was solicited and scheduled at 6 months for most patients.

Table II. Preoperative risk factors for adverse outcome in patients undergoing cardiac surgery: a clinical severity scoring system[5].

Preoperative risk factor	Score
Emergency case	6
Serum creatinine 1.6-1.9 mg/dl; > 1.9 mg/dl	1; 4
Severe left ventricular dysfunction (EF < 45%)	4
Reoperation	3
Operative mitral insufficiency	3
Age > 65 years	3
Prior vascular surgery	2
Chronic obstructive pulmonary disease	2
Anemia (hematocrit < 0.34)	2
Operative aortic valve stenosis	2
Weight < 65 kg	1
Diabetes on oral or insulin therapy	1
Cerebrovascular disease	1

EF = ejection fraction.

Quantitative coronary and intravascular ultrasound analyses. Coronary angiograms were quantitatively analyzed (QCA) by personnel not involved in the stenting procedure and without knowledge of the IVUS or clinical results. The CMS QCA system (Nuenen, The Netherlands) was used. Minimal lumen diameter and percent stenosis were obtained from baseline, final and follow-up angiograms. The mean reference lumen was calculated as the average of the proximal and distal reference lumens or as the interpolated reference. Lesion length was measured as the distance from the shoulders of the lesion. Lesions were characterized according to the American College of Cardiology/American Heart Association classification[7]. Long lesions were defined as a single continuous narrowing > 15 mm in length. IVUS evaluations were carried out utilizing a 3.9 monorail system with a 25 MHz transducer tipped catheter (Interpret Catheter InterTherapy/CVIS, Boston Scientific Corporation, Sunnyvale, CA, USA). A cardiovascular imaging system with a 2.9 F imaging catheter was used during the early stages of this study. The detailed description of IVUS analysis has been published previously[8].

Follow-up. Clinical follow-up was performed by the primary physician or at our institution when the follow-up angiogram had been done, and consisted of an interview and a stress test if indicated. The mean follow-up time was 12 ± 7 months (range 1-34 months). A minority of patients had a telephone interview. Angiographic follow-up was done on a routine basis at 6 months or when indicated earlier in patients that had angina recurrence. Eligibility of patients for follow-up angiogram was based on at least a 4-month time interval after successful stenting. All data were introduced in a dedicated database.

Statistical analysis. Values are presented as mean ± 1 SD, or SE. For the statistical analysis, comparison between two groups was made using Student's t-test for

paired or unpaired data as appropriate. The χ^2 test was used to test categorical variables. Comparison between three or more groups was made by ANOVA. The univariate, multivariate analysis, as well as logistic regression analysis were used. The variables were analyzed per lesion or per patient. For example restenosis was calculated per lesion, while MACE were analyzed per patient. To establish the predictors of restenosis and MACE we constructed a classification and regression tree for binary outcomes. The variables to be included in the tree analysis were first selected from the ones significant on univariate and multivariate analysis. The cut-off point for the numerical value for each variable was taken at the site where the strongest statistical difference was found within the group. This statistical technique is close to the cluster analysis already used for similar purposes[9]. The following statistical programs were used: SAS Logistic Regression Statistic, Microsoft Excel and Stat-View 4.5. A probability value of < 0.05 was considered statistically significant.

Results

Patient and lesion characteristics. Baseline patient characteristics are shown in table I. There was a significant difference in the extent of multivessel coronary artery disease in the groups with left main stenting and bifurcation lesion with stenting of both vessels compared to other groups. The higher incidence of male patients was observed in the group with calcified lesions (89%), in the group of large vessels with diffuse disease and in the group with small vessels (91% and 84%, respectively). There were no other significant differences in patient characteristics between the groups.

The incidence of unplanned stenting did not differ significantly between the groups (Table III). However, vessel distribution was different, with a high incidence of treatment of the left coronary artery in the groups with left main and bifurcation lesion stenting. In these groups slotted tube stents were used significantly more often (Table IV). In the group with left main stenting, 7 patients (20%) had stenting on a non-elective basis and 14 patients (39%) had prior surgery. The rotablator was used more often in the calcified lesion group (33%) as compared to other groups. Multiple stenting was performed more frequently in the group with bifurcation lesion and in the group of large vessels with diffuse disease (54%) than in the other groups (17-44%, $p < 0.01$). The final balloon to vessel ratio was highest in the group of small vessel showing the operator's attitude towards achieving the optimal final stent result. Quantitative angiographic measurements revealed a difference in vessel size, lesion minimal lumen diameter and percent stenosis before and after stenting between the groups (Table V). The group with left main stent had the highest minimal lumen diameter after stenting (3.66 ± 0.62 mm) and at follow-up (2.69 ± 0.92 mm) that influenced derived indexes of acute gain (2.42 ± 0.71 mm) and loss index (0.31 ± 0.27). On the other hand, the bifurcation group with stent placement in both branches had the smallest minimal lumen diameter at follow-up (1.55 ± 0.93 mm).

Table III. Indication for stenting and angiographic characteristics.

	Left main	Calcified	Small (< 3 mm)	Diffuse disease		Bifurcation	
				Large	Small	Both vessel stent	Single vessel stent
No. lesions	36	319	1108	248	209	47	93
Indication for stenting							
Elective	29 (80%)	260 (82%)	886 (80%)	188 (76%)	155 (76%)	39 (84%)	78 (84%)
Acute	7 (20%)	24 (8%)	122 (12%)	23 (9%)	23 (9%)	3 (6%)	8 (9%)
Total occlusion	0	35 (11%)	100 (9%)	37 (15%)	31 (15%)	5 (10%)	7 (8%)
Stented vessel (%)							
LAD	0	180 (56%)	623 (56%)	116 (47%)	119 (57%)	25 (54%)	68 (72%)
RCA	0	70 (22%)	215 (19%)	92 (38%)	45 (22%)	7 (15%)	8 (9%)
LCx	0	56 (18%)	245 (22%)	32 (13%)	42 (20%)	15 (32%)	17 (19%)
Left main	36 (100%)	13 (4%)	4 (0.36%)	0	1 (0.5%)	0	0
Vein graft	0	0	22 (2%)	7 (3%)	2 (1%)	0	0
IMA	0	0	1 (0.09%)	1 (0.4%)	0	0	0
Modified ACC/AHA lesion type (%)							
A	3 (8%)	3 (1%)	46 (4%)	0	0	0	0
B1	3 (8%)	26 (8%)	325 (29%)	47 (19%)	29 (14%)	2 (4%)	5 (5%)
B2	23 (64%)	191 (60%)	504 (45%)	103 (42%)	92 (44%)	33 (69%)	69 (74%)
C	7 (19%)	99 (31%)	233 (21%)	98 (40%)	88 (42%)	12 (27%)	19 (20%)

ACC/AHA = American College of Cardiology/American Heart Association; IMA = internal mammary artery; LAD = left anterior descending coronary artery; LCx = left circumflex artery; RCA = right coronary artery.

Table IV. Procedural characteristics.

	Left main	Calcified	Small (< 3 mm)	Diffuse disease		Bifurcation	
				Large	Small	Both vessel stent	Single vessel stent
DCA prior to stenting (%)	4 (11%)	22 (7%)	33 (3%)	17 (7%)	4 (2%)	66 (14%)	9 (10%)
RTCA prior to stenting (%)	10 (28%)	105 (33%)*	121 (11%)	22 (9%)	29 (14%)	7 (16%)	13 (14%)
Type of stent used (%)							
Slotted tube type	83*	73	61	63	76	60	73
Coil type	0	8	11	7	19	13	15
Ring type	17	8	9	4	11	21	11
Other (self-expanding, etc.)	0	2	9	14	7	0	0
Combination of stents	6	9	10	12	11	6	2
Stents/lesion	1.2 ± 0.4	1.6 ± 1.1	1.6 ± 1.0	1.9 ± 1.2	1.8 ± 1.1	NA	NA
Multiple stents (%)	6 (17%)	121 (38%)	365 (33%)	133 (54%)*	92 (44%)	NA	NA
Final balloon size (mm)	3.96 ± 0.58*	3.61 ± 0.49	3.35 ± 0.40	3.70 ± 0.47	3.33 ± 0.40	3.35 ± 0.35	3.47 ± 0.41
Final B/V ratio	1.09 ± 0.17	1.18 ± 0.18	1.29 ± 0.19*	1.09 ± 0.12	1.28 ± 0.17*	1.21 ± 0.20	1.19 ± 0.18
Maximal inflation pressure (atm)	16.6 ± 3.4	16.1 ± 3.3	16.0 ± 3.4	16.6 ± 3.2	16.1 ± 3.2	14.6 ± 3.5	15.8 ± 4.0

B/V = balloon/vessel ratio; DCA = directional coronary atherectomy; NA = not applicable; RTCA = rotational coronary atherectomy. * $p < 0.05$.

Table V. Quantitative angiographic results.

	Left main	Calcified	Small (< 3 mm)	Diffuse disease		Bifurcation		p
				Large	Small	Both vessel stent	Single vessel stent	
Before the procedure								
Reference vessel diameter (mm)	3.75 ± 0.80	3.09 ± 0.52	2.63 ± 0.29	3.41 ± 0.38	2.63 ± 0.26	2.83 ± 0.49	2.96 ± 0.46	< 0.01
Minimal lumen diameter (mm)	1.32 ± 0.69	0.85 ± 0.52	0.74 ± 0.39	0.85 ± 0.54	0.70 ± 0.41	1.06 ± 0.77	0.86 ± 0.47	< 0.01
% stenosis	65 ± 14	73 ± 15	72 ± 15	75 ± 15	73 ± 16	64 ± 24	71 ± 15	NS
Lesion length (mm)	7.0 ± 5.2	11.4 ± 7.5	10.6 ± 7.0	22.0 ± 7.3	21.6 ± 6.3	8.7 ± 6.0	11.0 ± 7.4	NS
After stenting								
Reference vessel diameter (mm)	3.90 ± 0.79	3.21 ± 0.51	2.80 ± 0.35	3.41 ± 0.40	2.83 ± 0.37	2.98 ± 0.44	3.08 ± 0.44	< 0.01
Minimal lumen diameter (mm)	3.66 ± 0.62*	3.13 ± 0.60	2.82 ± 0.48	3.19 ± 0.50	2.76 ± 0.49	2.77 ± 0.66	2.90 ± 0.57	< 0.01
% stenosis	4 ± 10	2 ± 15	-1 ± 15	6 ± 11	2 ± 15	7 ± 18	6 ± 11	< 0.01
At follow-up								
Reference vessel diameter (mm)	3.60 ± 0.42	3.03 ± 0.53	2.74 ± 0.42	3.15 ± 0.50	2.79 ± 0.44	2.83 ± 0.54	2.88 ± 0.46	< 0.01
Minimal lumen diameter (mm)	2.69 ± 0.92*	1.99 ± 0.98	1.72 ± 0.89	2.02 ± 1.00	1.58 ± 0.92	1.55 ± 0.93	1.93 ± 0.90	< 0.01
% stenosis	26 ± 23	35 ± 28	38 ± 30	36 ± 29	44 ± 31	46 ± 27	35 ± 25	< 0.05
Indexes								
Acute lumen gain (mm)	2.42 ± 0.71	2.29 ± 0.69	2.07 ± 0.58	2.33 ± 0.72	2.06 ± 0.61	1.71 ± 0.91*	2.04 ± 0.62	< 0.01
Late lumen loss (mm)	1.00 ± 1.01	1.16 ± 0.91	1.11 ± 0.87	1.19 ± 0.96	1.21 ± 0.89	1.22 ± 0.89	0.91 ± 0.69	NS
Loss index	0.31 ± 0.27*	0.51 ± 0.41	0.55 ± 0.46	0.53 ± 0.50	0.61 ± 0.45	0.69 ± 0.49	0.43 ± 0.35	< 0.01

Immediate and follow-up results. The primary success and the in-hospital complication rates did not differ significantly (Table VI). Angiographic follow-up was done in 69-84% of patients and was not significantly different between the groups. However, angiographic restenosis was different between the groups.

A 42% angiographic restenosis rate was found in the group of bifurcation with stent placement in both branches and in the group of small vessels that was significantly higher than the restenosis rate of 16% in the group with left main stenting. The difference compared to the restenosis rates in the groups with calcified lesions, small vessels and large vessels with diffuse disease was not statistically significant. The target lesion revascularization rates reflect the difference in restenosis rates in the different groups (Table VI).

In patients with left main stenting, acute and follow-up events occurred almost exclusively in those who were classified as "suboptimal" surgical candidates (Table VII).

During clinical follow-up a MACE rate was observed in 34-64% of patients in the whole group (Fig. 2). The highest rate occurred again in the group of bifurcation lesion with stents implanted in both vessels. The predictors of MACE are shown in figure 3. The Kaplan-Meier survival curves for the entire study group at 1 and 2 years showed a survival rate of 97 and 96%, and the event free survival of 76 and 74%, respectively (Fig. 4).

Table VI. Procedural outcomes and clinical follow-up events.

	Left main	Calcified	Small (< 3 mm)	Diffuse disease		Bifurcation		p
				Large	Small	Both vessel stent	Single vessel stent	
No. lesions	36	319	1108	248	209	47	93	
No. patients	36	256	896	237	196	45	91	
Procedural success (%)	32 (89%)	296 (93%)	1052 (95%)	235 (95%)	190 (91%)	42 (89%)	89 (96%)	NS
Angiographic success (%)	36 (100%)	312 (98%)	1096 (99%)	243 (98%)	205 (98%)	46 (99%)	91 (98%)	NS
Procedural MI (%)	1 (2.7%)	6 (1.9%)	17 (1.9%)	6 (2.8%)	8 (3.8%)	2 (4.4%)	0	NS
Procedural CABG (%)	3 (8.3%)	8 (3.1%)	15 (1.7%)	4 (1.6%)	6 (2.9%)	1 (2.1%)	0	NS
Procedural death (%)	0	1 (0.6%)	1 (0.1%)	3 (1.2%)	1 (0.5%)	1 (2.1%)	0	NS
Acute thrombosis (%)	0	3 (0.9%)	6 (0.6%)	2 (0.8%)	3 (1.4%)	1 (2.1%)	0	NS
Subacute thrombosis (%)	0	4 (1.3%)	12 (1.1%)	2 (0.8%)	3 (1.4%)	1 (2.1%)	0	NS
Total complication (%)	4 (11%)	22 (8.5%)	51 (5.7%)	17 (7.1%)	21 (10%)	6 (13%)	0	
Follow-up angiography (%)	25 (78%)	267 (90%)	930 (88%)	188 (80%)	171 (90%)	35 (83%)	69 (76%)	NS
CABG at follow-up	1 (2.7%)	10 (3.4%)	38 (4.2%)	6 (2.5%)	8 (3.4%)	1 (2.1%)	2 (2%)	NS
Death at follow-up	4 (12.5%)*	10 (3.4%)	22 (2.0%)	53 (28%)	8 (4%)	1 (2.1%)	1 (1%)	< 0.01
Restenosis	4 (16%)	73 (27%)	255 (27%)	12 (5%)	71 (42%)	15 (43%)*	20 (29%)	< 0.002
New PTCA for lesion prog.	0	17 (6.6%)	62 (7%)	12 (6%)	62 (32%)	0	4 (4%)	NS
Redo PTCA for restenosis	4 (16%)	55 (22%)	244 (27%)	47 (20%)	62 (32%)	14 (31%)	19 (21%)	NS
TLR at follow-up	5 (14%)	65 (20%)	282 (25%)	65 (26%)	70 (33%)	16 (37%)*	22 (24%)	< 0.05
MACE (acute + follow-up)	14 (38%)	108 (42%)	349 (39%)	80 (34%)	86 (44%)	28 (62%)	33 (37%)	= 0.05

CABG = coronary artery bypass grafting; MACE = major adverse cardiac events; MI = myocardial infarction; TRL = target lesion revascularization. * per lesion with procedural success.

Table VII. Results in patients with left main stenting divided into optimal or suboptimal surgical candidates.

	Optimal (n=12)	Suboptimal (n=24)
Acute complications	0	4 (16%)
Myocardial infarction	0	1
Emergency CABG	0	4
Follow-up		
Death	0	4 (16%)
TLR	1 (8%)	4 (16%)
Redo PTCA	0	4
CABG	1	0
Total MACE*	1 (8%)	12 (50%)

PTCA = percutaneous transluminal coronary angioplasty. Other abbreviations as in table VI. * p = 0.001.

Predictors of major adverse cardiac events. Statistical analysis identified the following variables (ranked according to their strength) as predictors of MACE: final IVUS minimal lumen diameter < 3.2 mm, non-slotted tube stent morphology, stent final stenosis > 9.25%, reference vessel size by IVUS < 4.6 mm, and final IVUS minimal diameter < 2.45 mm (Fig. 3, Tab. VIII).

Discussion

The results of our study show the feasibility of coronary stent implantation beyond standard indications. However, the specific groups demonstrate important

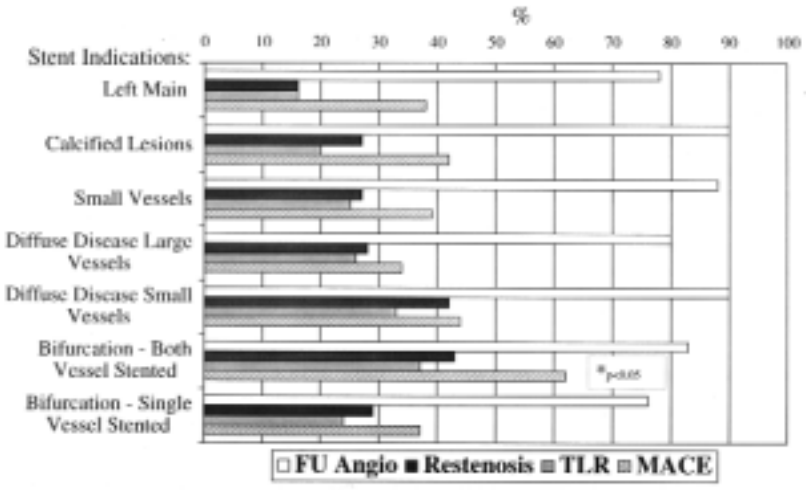

Figure 2. *Follow-up (FU) results in stent groups with different indications. MACE = major adverse cardiac events; TLR = target lesion revascularization.*

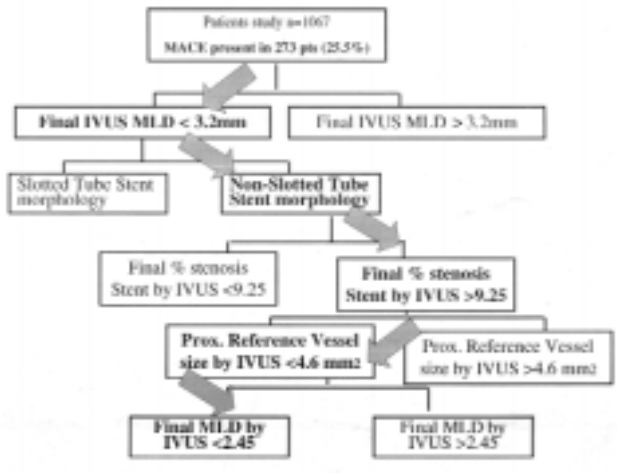

Figure 3. *Angiographic and procedural predictors of major adverse cardiac events (MACE). Lesion and procedural predictors of MACE are ranked according to their strength. In this "answering tree analysis" each variable has a p < 0.001. The fact that a specific variable such as final intravascular ultrasound (IVUS) minimal lumen diameter (MLD) comes before "non-slotted tube stent morphology" means that the first variable is more powerful in explaining MACE occurrence than the second one.*

differences in terms of mid-term angiographic results and restenosis rate. We will discuss the specific differences for each group as well as possible future improvements.

Left main stenting. Percutaneous interventions on the left main coronary artery have been considered unsuitable for many years in particular because of periprocedural complications and unacceptably high early mortality rate[9-12]. With the introduction of coronary stent implantation and directional atherectomy, protected as well as unprotected left main coronary arteries have been attempted[9-13]. In our patient group (Tables VI and VII), the acute complications occurred in 4 patients (11%, 1 patient had two complications), and target lesion revascularization rate was 14% with a late mortality rate of 12.5%. This is in accordance with the 18% mortality rate in the Ellis study[13]. We should point out that 7 patients (20%) had stenting on a non-elective basis and 14 patients (39%) had prior surgery. Surgeons referred many patients

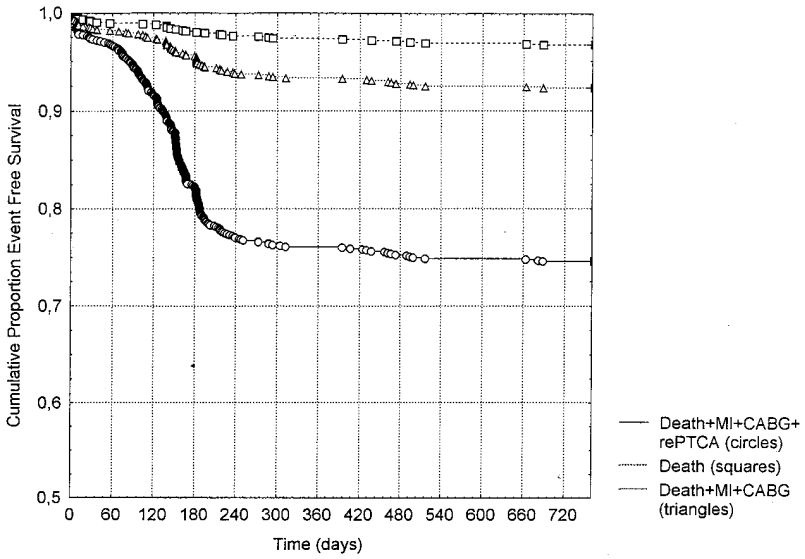

Figure 4. *Kaplan-Meier curves of the event free survival at follow-up. CABG = coronary artery bypass grafting; MI = myocardial infarction; re-PTCA = percutaneous intervention for restenosis.*

Table VIII. Specific data of variables shown in figure 3.

Variable	Present	Absent	Total
MACE	273 (25.5%)	794 (74.5%)	1067 (100%)
Final IVUS MLD < 3.2 mm	231 (27.5%)	685 (72.4%)	916 (85.5%)
Final IVUS MLD > 3.2 mm	112 (9.9%)	109 (90%)	221 (20.7%)
Slotted tube stent morphology	144 (23.6%)	464 (76.3%)	608 (56.9%)
Non-slotted tube stent morphology	117 (34.7%)	221 (65.3%)	338 (31.8%)
Final % stenosis stent by IVUS	50 (50.5%)	49 (49.5%)	99 (9.3%)
Proximal reference vessel size by IVUS < 4.6 mm^2	42 (56.7%)	32 (43.2%)	74 (6.9%)
Final MLD by IVUS < 2.45	279 (65.8%)	14 (34.1%)	293 (27.4%)

IVUS = intravascular ultrasound; MACE = major adverse cardiac events; MLD = minimal lumen diameter.

with left main stenting to us, because they were not considered good surgical candidates. In fact, when a risk stratification scoring system is applied (Table VIII), only 14 of our patients were considered good surgical candidates. In a recent article Wong et al.[14] reported an 80% asymptomatic status in 61 patients at a mean time of 16 months after coronary stenting of the left main coronary artery, a finding that was not uniformly present in previous reports. The long-term survival could probably be improved by a very careful patient selection, such as treating only patients with preserved ventricular function[15].

Calcified lesions. Calcifications in coronary lesions can limit the optimal stent expansion[16,17]. The new approach to treat these lesions was based on the theory of performing lesion modification using rotational atherectomy prior to stent implantation[18,19]. Of 319 lesions in our study, rotational atherectomy was done in 33% of the lesions with only 7% usage of directional atherectomy. The restenosis rate in this group was 27%, which was a relatively high value but lower than the one reported with rotablator alone or stent alone in a similar patient population[20]. Future efforts should be directed to develop better debulking devices.

Small vessels. The American College of Cardiology guidelines[1] do not recommend stenting in vessels of < 3 mm in size. Several recent reports using IVUS and high balloon pressure for final stent deployment have shown a low incidence of immediate complications in small vessels. In spite of this, the long-term results are disappointing with a restenosis rate as high as 40% especially when the lesion located in the small vessel is > 15 mm[9,21]. The study by Elezi at al.[21] identified subgroups with increased risk for restenosis in patients with small vessels: 53.5% in patients with diabetes and complex lesions compared to 29.6% in patients without additional risk factors. Unfortunately other treatment modalities such as surgery, coronary angioplasty or rotational atherectomy are not superior to coronary stenting for this indication. The use of radiation to prevent in-stent restenosis could be advocated in small vessels with long lesions, but further data are needed.

Bifurcation lesions. The percutaneous treatment of bifurcation lesions remains a technical challenge for the interventional cardiologist. Even with an optimal immediate result, the long-term outcome is still unsatisfactory. Summarizing results of 654 patients from 9 major published series on bifurcation stenting, Di Mario at al.[22] found a mean restenosis rate of 37.5%, with a target lesion revascularization rate of 24%. The presence of a substantial amount of plaque material in both branches involved in a bifurcation lesion, results in a plaque "shifting" from one side to the other and "bifurcation remodeling" after each balloon inflation. In our study the group with stent implantation in both vessels had a particularly high restenosis rate (43%) leading to a MACE rate of 62%. Even in situations where stents were correctly deployed in the bifurcation of each vessel using different "kissing" stent techniques and "excellent" immediate angiographic and optimal ultrasound results were obtained, the long-term results did not meet the expectations. New stent types and models may find a dedicated application in this setting[23-25] by facilitating the achievement of a good immediate result. A possible improvement on the long-term outcome has not been demonstrated yet[26].

Predictors of major adverse cardiac events. The statistical model used in our study depicted also procedural variables that played a role in the development of MACE (Fig. 3) demonstrating the importance of achieving an optimal IVUS and angiographic immediate result of coronary stenting[27,28]. In the study by de Feyter at al.[29] using IVUS, the expected 6-month in-stent restenosis rate after stent implantation for short lesions in relatively large vessels could be predicted by the use of in-stent minimal area (which is inversely related to restenosis) and stent length (which is directly related to restenosis). This finding is in accordance with the data from our study. Diabetes mellitus was not found to be a predictor of MACE. This fact can be explained on the basis of the relatively small number of patients with diabetes in our study (12-23%).

Study implications. The implications of our results for the future of coronary interventions are not only technical but also conceptual. Stenting in vessels of small diameter should be used with parsimony. It may be possible that the introduction of new dedicated stents specifically manufactured for vessels of small diameter may change the above statement. Until results of specifically designed randomized trials are available, the interventional cardiologist will need to limit stent usage to small vessels. At present the results of three large trials addressing stenting versus coronary angioplasty in small vessels (Intracoronary Stenting in Small Arteries-ISAR; Stenting in Small Arteries-SISA; Be-Stent in Small Arteries-BESMART) have been presented at the "Late-Breaking Clinical Trials in Interventional Cardiology" section 72 of the 49th Annual Scientific Session of the American College of Cardiology held in 2000 in Anaheim (www.acc.org/session2001/late/besmart.htm).

Two of these trials showed no difference in the outcome of stenting versus coronary angioplasty while a third one reported superior results with stenting.

Another area of concern is in the usage of long stents. Multiple or long stent implantation should probably not be performed on an elective basis on small vessels especially if the lesion is long, due to the associated high restenosis rates with increased subsequent target lesion revascularization. We investigated the pos-

sibility of reducing stent length in vessels with diffuse disease by combining coronary angioplasty with "spot" stenting. This means single stent implantation at the most severe site of the lesion with optimal angioplasty, eventually guided by IVUS or Doppler flow measurements[30]. Debulking prior to stent implantation may be important not only for calcified lesions but possibly also for bifurcational lesions. The use of debulking techniques will depend on the availability of improved debulking devices and on the results of the two randomized trials which compared directional atherectomy prior to stenting with stenting alone (Atherectomy and Multilink Improve Gain and Outcome-AMIGO, Debulking and Stenting in Restenosis Elimination-DESIRE). The use of GP IIb/IIIa antagonists in this patient subset with complex lesions might improve the short and long-term outcome.

Study limitations. The limitations of our study include its retrospective nature, evidently without any group for comparison. However there are a number of randomized studies which evaluate stenting in more simple lesions which could be used for comparison. The procedures have been performed over several years during which a definite change in stenting strategy has occurred. This fact could have influenced some of the results. Finally, the incomplete angiographic follow-up could bias the restenosis rate towards a higher incidence due to the fact that only the most symptomatic patients returned for the angiographic control.

In conclusion, coronary stenting beyond standard indications is feasible with good immediate results. However, the overall MACE rates were relatively high (34-62%). The follow-up mortality rate in patients with a stent in the left main coronary artery and high restenosis rate in small vessels with long lesions or in bifurcation vessels are limiting factors. Future developments are necessary before recommending the liberal use of stent in these patient groups.

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