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Impact of Intravascular Ultrasound Guidance in Stent Deployment on 6-Month Restenosis Rate: A Multicenter, Randomized Study Comparing Two Strategies—With and Without Intravascular Ultrasound Guidance

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Objectives. **We aimed to investigate the impact of intravascular ultrasound (IVUS)-guided stent implantation on the 6-month restenosis rate, which has not yet been fully established in randomized trials.**

Background. **The 6-month angiographic restenosis rate was compared in patients with symptomatic ischemic heart disease who were randomly allocated to angioplasty and stent deployment, with versus without IVUS guidance.**

Methods. **After successful stent implantation, patients were randomized into two groups: Group A had no further dilation, and Group B had additional balloon dilation until achievement of IVUS criterion for stent expansion. The study group consisted of 164 patients, assuming a 50% reduction of the restenosis rate in Group B (15% vs. 30%) (alpha = 10%, beta = 20%).**

Results. **We enrolled 155 patients. Overdilation was carried out in 31 (39%) of 79 Group B patients, with the IVUS criterion being achieved in 63 (80%) of 79. No significant difference was observed in the minimal luminal diameter (MLD), but the stent lumen cross-sectional area (CSA) was significantly larger in Group B (mean ± SD) (7.16 ± 2.48 vs. 7.95 ± 2.21 mm^2, p = 0.04). At 6 months, there was no significant difference in the restenosis rate, (28.8% [21 of 73] in Group A vs. 22.5% [16 of 71] in Group B, p = 0.25), but according to the observed difference in the restenosis rate, the power of the study was only 40%. The difference in MLD was also nonsignificant (1.60 ± 0.65 mm in Group A vs. 1.70 ± 0.64 mm in Group B, p = 0.20), whereas the lumen CSA was 20% larger in the IVUS-guided group (4.47 ± 2.59 vs. 5.36 ± 2.81 mm^2, p = 0.03). Lumen CSA was the only predictor of restenosis by multivariate logistic regression analysis.**

Conclusions. **A nonsignificant 6.3% absolute reduction in the restenosis rate and a nonsignificant difference in MLD were observed in this study. Nonetheless, we still cannot rule out a beneficial effect of IVUS guidance, although this may have gone undetected owing to a lack of statistical power. A significant increase was observed in immediate and 6-month lumen size, as detected by IVUS, indicating that ultrasound guidance in stent deployment may be beneficial.**

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Stents are increasingly used because they have been shown to reduce the 6-month restenosis rate (1–3). However, after stent implantation, intravascular ultrasound (IVUS) studies have demonstrated that inadequate stent deployment is not infrequent, despite an apparently adequate angiographic result, and that it can be responsible for acute or subacute stent thrombosis (4–6). It has been shown that it is possible to optimize stent deployment with IVUS-guided overdilations, thanks to bigger balloons or higher inflation pressures. After IVUS-guided overdilation, intrastent lumen cross-sectional area (CSA) and stent minimal lumen diameter (MLD) were shown to increase by as much as 11% to 80% (4,7,8). This made it possible to omit oral anticoagulation and to reduce bleeding complication rates without increasing the stent subacute thrombosis rate (8,9), paving the way for the use of systematic high inflation pressure for stent deployment without IVUS guidance with favorable immediate and 1-month clinical outcomes (10,11). However, it was shown that even after high inflation pressures, suboptimal stent deployment can still be observed with IVUS (6).

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Abbreviations and Acronyms

CSA = cross-sectional area
IVUS = intravascular ultrasound
MLD = minimal lumen diameter
PTCA = percutaneous transluminal coronary angioplasty
QCA = quantitative coronary angiography

The impact of this immediate lumen enlargement on the long-term restenosis rate and on the target lesion revascularization rate (12–15) has been established but not supported by randomized trials. Therefore, we conducted a randomized study comparing two groups of patients who had angioplasty and stent deployment, with or without IVUS guidance, to determine the long-term benefit of IVUS guidance in this setting.

Methods

This was a multicenter, randomized, single-blinded study. Participating centers and investigators were selected on the basis of their experience with coronary angioplasty and IVUS and their involvement in clinical trials. The protocol was approved by the investigators and the Ethics Committee of the University Hospital Saint-Jacques, Besançon, France.

Study design. The study group consisted of patients with symptomatic coronary artery disease with demonstrable ischemia and single-vessel or native multivessel disease with >70% stenosis of the target lesion, who had percutaneous transluminal coronary angioplasty (PTCA) followed by stent implantation for extensive dissection, a suboptimal result or as a primary choice.

The inclusion criteria were 1) single <20-mm long stent deployment with a Palmaz-Schatz stent (Johnson & Johnson), MicroStent (Applied Vascular Engineering), NIR stent (Boston Scientific Corporation) or Freedom stent (Global Therapeutic); 2) balloon/artery ratio for stent placement between 1.0 and 1.2; 3) balloon inflation pressure >12 atm for deployment of a Palmaz-Schatz or NIR stent and >9 atm for deployment of a premounted AVE or Freedom stent; 4) optimal angiographic result after stent implantation, without dissection or residual stenosis >20% as assessed visually or with on-line quantitative coronary angiography (QCA); and 5) written informed consent for participation in the study. The exclusion criteria were 1) vessel diameter <3.0 mm by visual estimation or on-line QCA; 2) coronary lesion >15 mm in length; 3) previous bypass surgery; 4) contraindication to antiplatelet therapy (aspirin or ticlopidine); 5) treatment of acute or chronic total occusion; 6) saphenous vein graft stenosis; and 7) recent (<7 days) acute coronary syndromes.

Randomization into two groups was done after stent implantation, once the angiographic result was judged satisfactory. IVUS imaging was performed in all patients, but no further dilation was performed, irrespective of the IVUS findings in the non-IVUS guidance group (Group A), whereas additional balloon inflations were performed until the criterion for stent expansion on IVUS imaging was reached in the IVUS guidance group (Group B). The ratio of intrastent CSA to the average of the proximal and distal reference lumen CSA, with a cutoff point at 80%, was chosen as the ultrasound criterion for optimal stent deployment.

Ultrasound procedures and measurements. IVUS imaging was done using a 30-MHz mechanical ultrasound transducer (Sonicath, 3.5F Boston Scientific Corporation) and an ultrasound scanner (Sonos 2400A, Hewlett Packard). After optimization of the machine setting, images were recorded on a S-VHS videotape recorder, after an intracoronary bolus injection of 0.5 mg of isosorbide dinitrate and during a slow continuous manual pullback. At 6-month follow-up angiography, IVUS imaging was repeated using the same technique in both groups.

On-line ultrasound assessment was performed in diastole. It was carried out in Group B patients only and repeated after each overinflation, if any, until the criterion for optimal stent deployment was achieved. The lumen CSA at the stent level was assessed by planimetry at the interface of the blood and the stent, at multiple levels (at least three), and the smallest area was chosen. The proximal and distal reference lumen areas were also measured by manual planimetry. The reference segments were selected as the most normal-looking cross section within 10 mm proximal and distal to the stent.

Off-line ultrasound measurements were performed by a single observer using the same technique as for on-line analysis. To reduce the variability, all IVUS measurements were repeated, and the average of the two values was used in the analysis. Reliability of off-line IVUS measurements, which includes image selection variability, was assessed using an average of two measurements by a single observer, with the intraclass correlation coefficient, and the standard deviation of the mean difference from repeat measurements of the lumen CSA in 50 patients. The intraclass correlation coefficient (ratio of interpatient variance to interpatient plus intraobserver variance) of the lumen CSA measurements at the stent level was 0.94 (mean ± SD between two measurements = 0.06 ± 0.8 mm^2) and at the reference level 0.92 (mean ± SD, 0.05 ± 0.9 mm^2).

Angiographic procedure and analysis. Two orthogonal views of the coronary artery segment submitted to balloon angioplasty and stent implantation were taken before and after angioplasty and at 6-month control angiography. QCA was carried out using the empty tip of the 7F guiding catheter for calibration. Angiograms were analyzed off-line using an automated edge detection algorithm (CAAS II, Pie Medical, The Netherlands) by an operator who had no knowledge of the IVUS data. The MLD, proximal and distal reference diameters and percent stenosis were determined for every pair of views and averaged. In addition, the length of diseased segments submitted to balloon angioplasty and stent implantation were determined before angioplasty from QCA measurements.

Postprocedure medication and clinical follow-up. Heparin therapy was stopped within 24 h after angioplasty, and patients

were discharged on day 2 with orders to take a daily dose of aspirin (250 mg) and ticlopidine (500 mg) for 1 month. Clinical outcome was assessed during the hospital stay and up to 6 months later, taking into account major clinical events like death, myocardial infarction (Q or non–Q wave), the need for emergency bypass surgery or repeat angioplasty, recurrent angina, hemorrhagic complications and prolonged hospital stay (>3 days). The definition of these events is the same as used in other studies (11).

Study end points. The primary end point was the 6-month restenosis rate, defined as >50% narrowing at the stent site or 5 mm proximal or distal to the stent, as assessed by QCA. Secondary study end points were the 6-month angiographic MLD and 6-month lumen CSA, as assessed by IVUS.

Statistical methods. Given the complexity, the increased duration and the extra cost of the procedure with the use of IVUS, it was postulated that a reduction of at least 50% of the restenosis rate in the IVUS-guided group would be clinically relevant. Given the restenosis rate observed in the stent group of the STent REStenosis Study (2), we assumed that a 30% restenosis rate would be observed in the control group and 15% in IVUS-guided group. The sample size was calculated accordingly; two groups of 82 patients were needed (alpha 10%, beta 20%, one-sided situation). With such a sample size, the power of the study was 85% for the detection of a 0.2-mm difference in 6-month MLD and 90% for the detection of a 2-mm^2 difference in 6-month lumen CSA. Continuous data were presented as the mean value ± SD and qualitative data as a percentage. Comparisons between the two groups were made: in qualitative data using the Fisher exact probabilities test or the likelihood ratio chi-square test and in quantitative data using the Student *t* test. Intraindividual comparisons were done using the Wilcoxon signed-rank test. Multivariate logistic regression analysis was used to identify predictors of the angiographic restenosis rate (variables with a p value <0.05 by univariate analysis were entered into the multivariate analysis). A p value <0.05 was considered significant. Statistical analysis was performed with BMDP 90 statistical software (University of California, Berkeley). Analysis was done according to the intention-to-treat principle.

Results

Between January 1995 and February 1997, 155 patients were included in the study.

Protocol violations. Four ineligible patients (two in each group) were enrolled. In one patient, the treated lesion was a total occlusion. Three patients had previous bypass surgery, but the target lesion was located on a native artery in all three. Furthermore, three patients from Group A underwent additional stent implantation after randomization. In these patients, IVUS imaging showed incomplete coverage of the lesion at the edge of the stent, with significant residual stenosis, which was not detected angiographically before randomization. These patients were maintained in the control group.

Table 1. Demographic and Clinical Characteristics

Variable	Group A (n = 76)	Group B (n = 79)	p Value
Males	71 (93%)	68 (86%)	0.13*
Mean age (years)	56 ± 12	57 ± 10	0.28†
Previous infarction	48 (63%)	54 (68%)	0.49*
Diabetes	8 (11%)	9 (11%)	0.93*
Cholesterol	52 (68%)	54 (68%)	0.94*
High blood pressure	26 (34%)	24 (30%)	0.67*
Smoker	51 (67%)	55 (70%)	0.94*
CCS functional status			
Silent ischemia	24 (33%)	20 (25%)	0.69‡
Class I	25 (32%)	30 (38%)	
Class II	21 (28%)	19 (24%)	
Class III	5 (6%)	7 (9%)	
Class IV	1 (1%)	3 (4%)	
Lesion site			
LAD	36 (47%)	38 (48%)	0.70‡
LCx	8 (11%)	9 (11%)	
RCA	32 (42%)	32 (41%)	
AHA/ACC lesion type			
A	8 (11%)	5 (6%)	0.43‡
B1	31 (41%)	40 (51%)	
B2	26 (34%)	27 (34%)	
C	11 (14%)	7 (9%)	
Lesion length (min, max)	8.05 ± 4.05 (3.0, 19.2)	7.72 ± 3.53 (3.0, 20.0)	0.59†
Mean LVEF††	51 ± 9	53 ± 13	0.75†

*Result of the Fisher exact probabilities test. †Result of the Student *t* test. ‡Result of the likelihood ratio chi-square test. Data presented are the number (%) of patients or the mean value ± SD. AHA/ACC = American Heart Association/American College of Cardiology; CCS = Canadian Cardiovascular Society; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LVEF = Left ventricular ejection fraction; RCA = right coronary artery.

Comparability of the two groups before randomization. There was no significant difference between the groups in terms of demographic and clinical characteristics (Table 1). Procedural details and angiographic and IVUS measurements before angioplasty and after stent deployment (i.e., before randomization) are given in Table 2. In the whole group, the mean reference diameter was 2.99 ± 0.50 mm. The average MLD was 0.99 ± 0.40 mm before angioplasty and increased to 2.47 ± 0.44 mm after angioplasty. There was no significant difference between the groups in terms of stent type, balloon size, balloon/artery ratio and angiographic details before PTCA or in terms of angiographic and IVUS details after stent implantation.

Feasibility, safety and results of IVUS guidance in stent deployment. Seventy-nine patients were randomly allocated to Group B. IVUS imaging was not available because of technical failure in five patients. On-line analysis showed that the IVUS criterion was not reached in 31 (39%) of 79 patients who were subjected to further inflations within the stent. Actually, off-line measurements showed that 8 of 31 patients submitted to overdilation had already reached the IVUS criterion before overdilation was undertaken, and that 5 of 43 patients not

Table 2. Procedural, Angiographic and Intravascular Ultrasound Data, Before Angioplasty and After Stent Implantation (i.e., Before Randomization)

Variable	Group A (n = 76)	Group B (n = 79)	p Value
Type of stent			
Palmaz-Schatz	32 (42%)	42 (53%)	0.48*
AVE MicroStent	18 (24%)	18 (23%)	
NIR Scimed	21 (28%)	16 (20%)	
Freedom Global Therapeutic	5 (7%)	3 (4%)	
Mean length of stent (mm)	15.4 ± 5.6	15.8 ± 4.9	0.42†
Balloon size (mm)			
3.0 mm	37 (49%)	35 (44%)	0.29*
3.5 mm	31 (41%)	40 (51%)	
4.0 mm	8 (11%)	4 (5%)	
Mean	3.30 ± 0.33	3.30 ± 0.29	0.93†
Balloon/artery ratio	1.14 ± 0.15	1.13 ± 0.16	0.99†
Mean balloon pressure (atm)	11.72 ± 2.09	11.67 ± 3.03	0.85†
Angiography before PTCA			
Proximal reference diameter (mm)	3.06 ± 0.59	2.94 ± 0.57	0.38†
Distal reference diameter (mm)	2.88 ± 0.58	2.90 ± 0.49	0.56†
%Stenosis	64 ± 12	65 ± 11	0.51†
MLD (mm)	1.02 ± 0.44	0.96 ± 0.37	0.39†
Angiography after stent implantation			
Proximal reference diameter‡ (mm)	2.94 ± 0.51	3.02 ± 0.49	0.37†
Distal reference diameter§ (mm)	2.77 ± 0.56	2.85 ± 0.49	0.36†
%Stenosis	19 ± 9	19 ± 10	0.92†
MLD (mm)	2.46 ± 0.46	2.48 ± 0.43	0.73†
IVUS after stent implantation			
Proximal reference diameter lumen CSA‖ (mm^2)	8.72 ± 2.51	8.62 ± 2.62	0.75†
Distal reference diameter lumen CSA¶ (mm^2)	7.96 ± 2.66	8.45 ± 3.03	0.44†
Stent lumen CSA# (mm^2)	7.16 ± 2.48	6.89 ± 2.71	0.35†

*Result of the likelihood ratio chi-square test. †Result of the Student t test. MLD = minimal luminal diameter (assessed by quantitative coronary analysis [QCA]). ‡Proximal reference diameter = lumen diameter of the reference segment proximal to the stent (assessed by QCA). ‡Distal reference diameter = lumen diameter of the reference segment distal to the stent (assessed by QCA). ¶Proximal reference diameter lumen CSA = lumen cross-sectional area of the reference segment proximal to the stent (assessed by IVUS). ‖Distal reference diameter lumen CSA = lumen cross-sectional area of the reference segment distal to the stent (assessed by IVUS). #Stent lumen CSA = minimal intrastent lumen cross-sectional area (assessed by IVUS). Quantitative values normally distributed and non-normally distributed are expressed as the value ± mean SD. Other data are expressed as the number (%) of patients. CSA = cross-sectional area; IVUS = intravascular ultrasound; MLD = minimal lumen diameter; PTCA = percutaneous transluminal coronary angioplasty.

submitted to overdilation had a lumen ratio <0.8. Overdilation was carried out with a bigger noncompliant balloon (+0.5 mm in diameter) in seven patients, with the same noncompliant balloon as used for stent deployment but at a higher pressure in eight patients and with the same compliant balloon as used for stent deployment but at a higher pressure in 16 patients. In 10 patients, a second overdilation was necessary after a first attempt failed to achieve the criterion for optimal stent deployment.

In 7 of 31 patients, the procedure was stopped even though the IVUS criterion was not reached. The cause was angiographic evidence of overexpansion of the stent in four patients. In three other patients with a Palmaz-Schatz stent, the smallest lumen area was measured at the central articulation of the stent, so that overdilation with larger balloons did not result in lumen enlargement and did not allow achievement of the IVUS criterion.

No major complication was induced by overdilation. Three cases of coronary nonocclusive dissection (type C) distal to the stent occurred and was treated by additional prolonged balloon inflation in one patient and by additional stent implantation in two patients.

In patients submitted to overdilation, significant enlargement was observed, both in MLD (from 2.31 ± 0.45 to 2.62 ± 0.42 mm, mean difference 0.31 ± 0.30 mm, $p < 0.001$) and in IVUS stent lumen CSA (from 6.90 ± 1.81 to 7.49 ± 1.61 mm^2, mean difference 0.59 ± 0.68 mm^2, $p < 0.003$) (Table 3).

After completion of the procedure, a significant difference appeared between the two groups at the highest balloon pressure used (11.7 ± 2.1 vs. 13.2 ± 2.3 atm, $p = 0.04$) (Table 4), but without a significant difference in the balloon/artery ratio. No significant difference was observed in MLD or residual stenosis, but acute angiographic gain was significantly higher in Group B (1.45 ± 0.53 mm in group A vs. 1.62 ±

Table 3. Angiographic and Intravascular Ultrasound Data From 31 Patients Submitted to Overdilation (n = 31)

Variable	Before Angioplasty (a)	Randomization (b)	Final Result (c)	p Value* (a) vs. (b)	p Value* (b) vs. (c)
Proximal reference diameter (mm)	3.01 ± 0.61	2.97 ± 0.52	3.00 ± 0.44	0.85	0.37
Distal reference diameter (mm)	2.98 ± 0.50	2.88 ± 0.52	2.94 ± 0.41	0.43	0.20
MLD (mm)	0.91 ± 0.31	2.31 ± 0.45	2.62 ± 0.42	<0.001	0.001
%Stenosis	65 ± 10	22 ± 9	16 ± 9	<0.001	0.008
Proximal reference diameter lumen CSA (mm^2)	No data	9.31 ± 2.94	9.56 ± 2.68		0.58
Distal reference diameter lumen CSA (mm^2)	No data	9.17 ± 3.56	9.38 ± 3.94		0.41
Stent lumen CSA (mm^2)	No data	6.90 ± 1.81	7.49 ± 1.61		0.003

*Result of the Wilcoxon signed-rank test. Data presented are the mean value ± SD. Abbreviations as in Table 2.

0.43 mm in Group B, p = 0.04). Stent lumen CSA was also significantly larger in Group B than in Group A (7.16 ± 2.48 vs. 7.95 ± 2.21, p = 0.04). In Group B, 63 (80%) of 79 patients had reached the IVUS criterion at the end of the procedure, as compared with 45 (59%) of 76 patients in Group A, without IVUS-guided overdilation (p < 0.01).

Six-month follow-up. Six-month clinical follow-up was completed for all patients. Two died during the follow-up period—one from noncardiac death (Group B) and one from a massive pulmonary embolism 4 months after stent implantation (Group A). Nine patients refused angiographic follow-up. None had recurrence of angina, and an exercise stress test was negative in four. Recurrent chest pain requiring early angiographic control (between 12 and 20 weeks after angioplasty) occurred in 12 patients. Four had intrastent restenosis (including one occlusion). Eight had no restenosis, four of whom underwent a second control angiography at 6 months. Control angiography was obtained in 144 patients (93%) between 5 and 7 months after stent implantation (Table 4). The restenosis rate was not significantly different between the two groups—28.8% (21 of 73) in Group A versus 22.5% (16 of 71) in Group B (p = 0.25). There was no significant difference in MLD, average percent stenosis, late loss or net gain between the two groups.

IVUS images were available in 137 of 144 patients with angiographic follow-up (69 patients in Group A and 68 in Group B). In four patients with >70% angiographic restenosis (two in each group), the IVUS transducer failed to cross the lesion, and a value of 1 mm^2 was assigned as 6-month stent lumen CSA. There was a significantly larger FU stent lumen CSA in Group B—4.47 ± 2.59 versus 5.36 ± 2.81 mm^2 (p = 0.03). Bivariate regression analysis showed a significant correlation between the two measurements of lumen CSA at the stent level (r = 0.55, p < 0.001). Cumulative distribution curves of MLD and lumen CSA before and after stent implantation and at follow-up are presented in Figures 1 and 2.

Univariate analysis was carried out to compare patients with and without restenosis on angiography. A significant difference was observed with regard to lesion site, postprocedure in-stent lumen size (MLD or stent lumen CSA), prepro-

Table 4. Angiographic and Intravascular Ultrasound Results at End of Procedure and at 6 Months

Variable	Immediate Results: Group A (n = 76)	Immediate Results: Group B (n = 79)	Immediate Results: p Value	6-Month Results: Group A (n = 73)	6-Month Results: Group B (n = 71)	6-Month Results: p Value
Balloon/artery ratio	1.17 ± 0.12	1.22 ± 0.13	0.45*	—	—	
Inflation pressure (atm)	11.7 ± 2.1	13.2 ± 2.3	0.04*	—	—	
Angiographic result						
Proximal reference diameter (mm)	2.94 ± 0.51	3.00 ± 0.46	0.59*	2.82 ± 0.46	2.74 ± 0.49	0.29
Distal reference diameter (mm)	2.77 ± 0.56	2.88 ± 0.41	0.24*	2.62 ± 0.52	2.72 ± 0.51	0.22*
MLD (mm)	2.46 ± 0.46	2.57 ± 0.41	0.11*	1.60 ± 0.65	1.70 ± 0.64	0.20*
%Stenosis	19 ± 9	16 ± 10	0.35*	42 ± 18	38 ± 20	0.13*
Early gain (mm)	1.45 ± 0.53	1.62 ± 0.43	0.04*	—	—	
Net gain (mm)	—	—	—	0.60 ± 0.70	0.74 ± 0.65	0.85*
Late loss (mm)	—	—	—	0.86 ± 0.57	0.87 ± 0.57	0.85*
Restenosis rate (%)	—	—	—	28.8 (21/73)	22.5 (16/71)	0.25†
IVUS result						
Proximal reference diameter lumen CSA (mm^2)	8.72 ± 2.51	8.80 ± 3.08	0.85*	8.24 ± 2.86	8.49 ± 2.69	0.85*
Distal reference diameter lumen CSA (mm^2)	7.96 ± 2.66	8.54 ± 3.15	0.23*	8.20 ± 3.8	8.41 ± 2.72	0.43*
Stent lumen CSA (mm^2)	7.16 ± 2.48	7.95 ± 2.21	0.04*	4.47 ± 2.59	5.36 ± 2.81	0.03*
%IVUS criteria achieved	45 (59%)	63 (80%)	0.001†			

*Result of the Student *t* test. †Result of the Fisher exact probabilities test. Data presented are the mean value ± SD or as the number (%) of patients. Abbreviations as in Table 2.

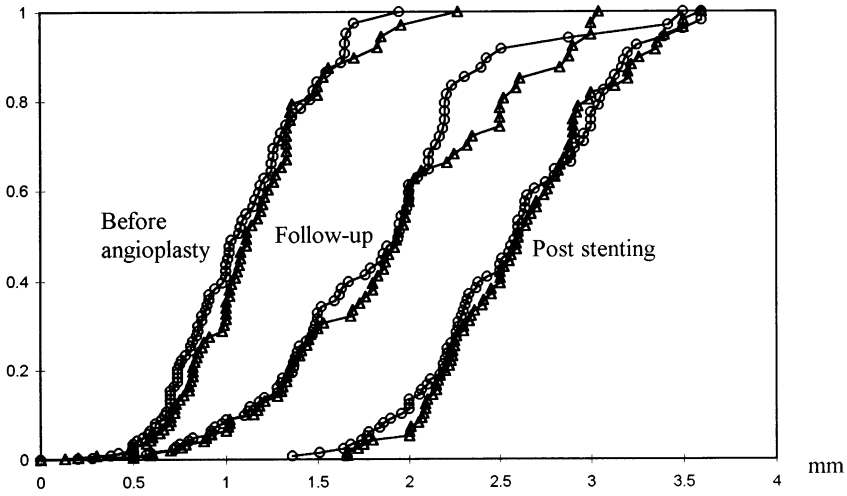

Figure 1. Cumulative distribution curves of angiographic MLD (**horizontal axis**, in mm) before angioplasty, after stent deployment and at follow-up in the two groups. **Open circles** = Group A; **open triangles** = Group B.

cedure vessel size (angiographic distal reference diameter) before angioplasty and balloon size (Table 5). These variables were entered into a logistic regression model, as well as group assignment and age, which were forced into the model despite being nonsignificant. The only independent predictor of restenosis was postprocedure lumen CSA at the stent level (OR 0.70 per additional mm^2 in stent lumen CSA, 95% confidence interval 0.47 to 0.93) (Table 6).

Discussion

The main findings of this study are: 1) despite the use of high inflation pressures for stent implantation, the IVUS criteria for optimal stent deployment were not achieved in ~60% of the patients even with an adequate angiographic appearance of the stented lesion; 2) IVUS-guided overinflation led to a significant early increase in MLD and lumen CSA, resulting in the whole group in a significant increase in lumen CSA, but a nonsignificant increase in MLD; 3) a nonsignificant, 6-month absolute 6.3% reduction in the restenosis rate at 6 months and a nonsignificant 6-month 0.1-mm increase in MLD; and 4) a significant 19.9% increase in lumen CSA.

These results were obtained in patients routinely submitted to PTCA and stent implantation whose indication was based on the currently admitted indications (i.e., extensive dissection, suboptimal results or as a primary choice in arteries ≥3 mm in diameter) (1,2). Moreover, the clinical status, types of stent used, indication for stent implantation, balloon/artery ratio and balloon inflation pressure were identical to those used in our daily practice, so that we can assume that there was no major difference between the study patients and patients routinely submitted to PTCA and stent implantation in the institutions participating in the trial but not included in the study.

In addition, the study design guaranteed the comparability of the two groups, as randomization took place only after the optimal post-stent angiographic result was obtained. Lastly, the use of high inflation pressures and balloon/artery ratio >1.1 for stent implantation guaranteed that the stents were not systematically underexpanded before IVUS imaging—this be-

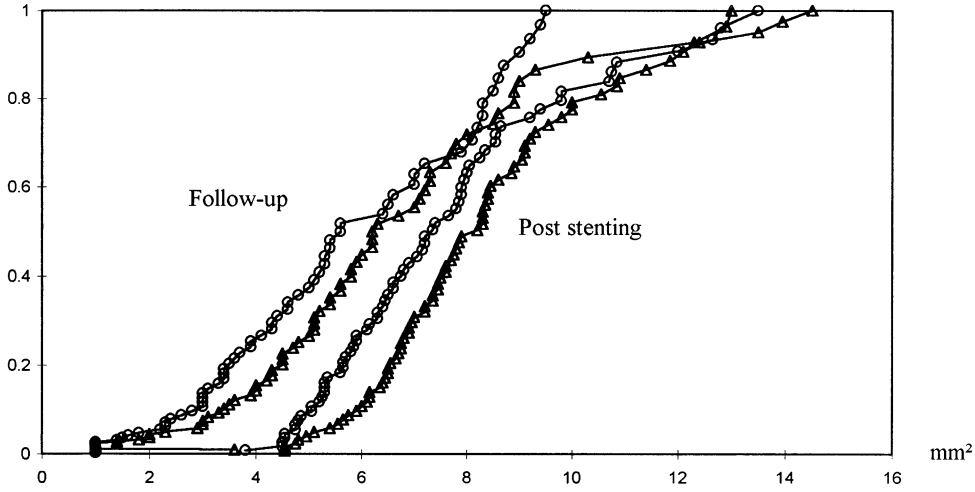

Figure 2. Cumulative distribution curves of minimal lumen CSA (**horizontal axis**, in mm^2), as assessed by IVUS, after stent deployment and at follow-up in the two groups. **Open circles** = Group A; **open triangles** = Group B.

Table 5. Univariate Analysis: Comparison of Patients With Versus Without Restenosis

Variable	Patients With Restenosis (n = 37)	Patients Without Restenosis (n = 107)	p Value
Age (years)	59 ± 11	55 ± 11	0.06*
Male	34 (92%)	94 (88%)	0.71†
Diabetes	5 (13%)	11 (10%)	0.80†
Cholesterol	23 (62%)	75 (70%)	0.28†
High blood pressure	15 (41%)	32 (30%)	0.30†
Smoker	27 (73%)	69 (64%)	0.40†
Lesion site			
LAD	25 (67%)	44 (41%)	0.02‡
LCx	3 (8%)	12 (11%)	
RCA	9 (24%)	51 (48%)	
AHA/ACC lesion type			
A	5 (14%)	8 (7%)	0.60‡
B1	15 (41%)	49 (46%)	
B2	12 (32%)	38 (36%)	
C	5 (14%)	12 (11%)	
Lesion length (mm)	7.91 ± 4.08	8.08 ± 3.78	0.85*
Balloon size (mm)	3.18 ± 0.32	3.34 ± 0.31	0.01*
Balloon/artery ratio	1.22 ± 0.14	1.18 ± 0.14	0.13*
Proximal reference diameter (mm) before PTCA	2.89 ± 0.48	3.04 ± 0.62	0.17*
Distal reference diameter (mm) before PTCA	2.69 ± 0.40	2.97 ± 0.56	0.007*
MLD before PTCA (mm)	0.90 ± 0.38	1.00 ± 0.39	0.20*
%Stenosis before PTCA	66 ± 12	64 ± 12	0.27*
Stent type			
Palmaz-Schatz	17 (46%)	54 (50%)	0.97‡
AVE	9 (24%)	24 (22%)	
NIR	9 (24%)	24 (22%)	
Freedom	2 (5%)	5 (5%)	
MLD after procedure (mm)	2.35 ± 0.40	2.56 ± 0.45	0.01*
%Stenosis after stent	19 ± 11	17 ± 9	0.32*
Stent lumen CSA (mm^2) after procedure	6.34 ± 1.40	7.90 ± 2.50	0.0002*
Early gain (mm)	1.45 ± 0.49	1.57 ± 0.48	0.21*
Late loss (mm)	0.66 ± 0.42	1.47 ± 0.50	<0.0001*
Net gain (mm)	0.91 ± 0.55	0.02 ± 0.50	<0.0001*
IVUS guidance	16 (43%)	55 (51%)	0.45†
%IVUS criterion achieved	26 (70%)	72 (67%)	0.83†

*Result of the Student *t* test. †Result of the Fisher exact probabilities test. ‡Result of the likelihood ratio chi-square test. Data are presented as mean value ± SD or number (%) of patients. Abbreviations as in Tables 1 and 2.

ing a known bias capable of influencing the need for subsequent overexpansion (8).

Finally, these results were obtained using a simple IVUS criterion for optimal stent deployment, which has previously been shown to be associated with an acceptable benefit to risk ratio and which is currently widely accepted (12,16,17,18). This IVUS criterion, compared with more complex criteria, led to a reduction in discrepancies between on-line and off-line analysis, which depend on the reliability of IVUS measurements (satisfactory in our experience) (17,18).

Impact of IVUS guidance on immediate results. According to our IVUS criteria, 31 (39%) of 79 Group B patients needed overdilation, which resulted in a lower than expected increase in intrastent lumen size, 13% in MLD and 8.5% in stent lumen CSA. Nonetheless, this was sufficient to significantly increase angiographic early gain and stent lumen CSA in the whole group. A preliminary report of a randomized trial using another IVUS criterion showed that 29% of patients needed overdilation, resulting in a 24.3% increase in lumen CSA and a 0.32-mm increase in MLD (19).

The fact that, in our study, the IVUS criterion was not achieved in a small but sizeable proportion of patients (7 of 31) despite high overdilation pressure and balloon/artery ratio >1.15 may have contributed to the rather modest increase in intrastent lumen size. This fact is consistent with the findings of a preliminary report from another randomized trial in which the IVUS criteria were achieved in only 68% of cases after IVUS guidance (20). The inability to achieve the IVUS criterion may depend on the criterion chosen and also on the type of stent used, coil stents being more prone to recoil than tubular slotted stents; plaque prolapse at the central articulation of Palmaz-Schatz stents can also prevent achievement of the target lumen size despite bigger balloons and higher inflation pressure (16).

Table 6. Multivariate Predictors of Angiographic Restenosis at 6 Months (Logistic Regression)

Variable	Odds Ratio	95% Confidence Interval	p Value
IVUS guidance	0.94	0.38–2.30	0.89
Age (/yr)	1.03	0.99–1.07	0.15
Site: LCx vs. LAD	0.57	0.13–2.50	0.12
Site: RCA vs. LAD	0.65	0.23–1.87	0.12
Average reference diameter* (/mm)	0.82	0.40–1.70	0.59
MLD before PTCA (/mm)	0.98	0.26–3.71	0.97
MLD after stent (/mm)	0.79	0.19–3.19	0.73
Stent lumen CSA (/mm^2)	0.70	0.47–0.93	0.007

*Average reference diameter defined as the average of proximal and distal reference diameter. Abbreviations as in Tables 1 and 2.

Higher gains in lumen area or MLD have been previously reported, but with very different stenting policies and IVUS criterion. Nakamura et al. (4), in a first report, showed that 88% of patients in their series needed overdilation, which resulted in an average 30% increase in intrastent lumen CSA. A further report on a larger series by the same group (8) confirmed that an average 35% increase in intrastent lumen CSA was obtained by overdilation. However, these results were achieved with very aggressive criteria for optimal stent deployment, which led to an aggressive overdilation strategy, resulting in negative residual stenosis ($-9 \pm 15\%$) (i.e., intrastent MLD oversized with regard to the diameter of the reference segment), and a 5.7% procedural complication rate and 1.2% coronary artery rupture. With increasing experience, less aggressive criterion for optimal stent deployment and more appropriate balloon sizing (1.05 ± 0.14 average balloon/artery ratio), the procedural complication rate was reduced to 1% (0% artery rupture), with 1% average final residual stenosis (8). Following these initial reports, stenting policy and criterion for optimal stent deployment have changed, with the ratio of intrastent to reference lumen CSA with a cutoff point of 0.8 to 0.9 being now broadly adopted (12,19,21). As a result of this modified IVUS guidance strategy, the IVUS criterion can be achieved in the majority of patients relying only on the angiographic appearance of the stented segment (19,21), so that the anticipated gain obtained by IVUS-guided overdilation is potentially reduced.

Impact on 6-month angiographic and IVUS end points. A nonsignificant reduction in the restenosis rate was found in Group B compared with Group A (22.5% vs. 28.8%, respectively) (absolute difference $6.3 \pm 12\%$). However, the 95% confidence interval was -6% to 18%, so that the hypothesis of the study cannot be ruled out. Retrospective calculation of the power of the study with regard to the primary end point confirmed the lack of power with a beta risk of 60%.

There was a trend toward a larger MLD in Group B; however, the difference was not significant. However, the lumen size assessed using lumen CSA was significantly larger in Group B at 6 months. Such angiographic and IVUS results were also observed after stent implantation (a larger stent lumen CSA was observed in Group B, without a significant difference in MLD). This confirms the higher sensitivity of IVUS measurements in assessing lumen size. At 6-month follow-up, a 20% difference in lumen CSA was observed between both groups (4.47 ± 2.59 mm^2 in Group A vs. 5.36 ± 2.81 mm^2 in Group B, $p = 0.03$).

Predictors of 6-month restenosis. Postprocedure intrastent MLD, lumen CSA, lesion site and reference diameter were shown to be predictors of 6-month restenosis by univariate analysis. By multivariate logistic regression analysis, lumen CSA was shown to be the only independent predictor of 6-month restenosis (OR 0.70 ± 0.23, $p = 0.007$). This finding is consistent with previous observations showing that lumen CSA was a predictor of 6-month angiographic results and target lesion revascularization rate (12–14,21). Moreover, postprocedure lumen CSA was significantly correlated with the 6-month intrastent lumen CSA. Based on this observation, and on the larger postprocedure lumen CSA observed in Group B, one can reasonably assume that the IVUS guidance might favorably affect the 6-month results.

Study limitations. The sample size was calculated according to the hypothesis that there would be an absolute 15% difference in the restenosis rate between the two groups (30% vs. 15%), despite the fact that there was no evidence in previous studies to suggest that such a difference between the two groups could be expected. However, it was deemed necessary by the investigators to adopt such a large difference to compensate for the increased complexity and cost of the procedure and to justify the routine use of this technique. The main disadvantage of such an approach is the lack of statistical power.

The other limitation of this study was that four different types of stents were used, each with a different design and a different recommended implantation pressure. However, neither univariate nor multivariate analysis showed any evidence that stent type had an influence on the immediate or long-term results.

Clinical implications. The 19.9% increase in late lumen CSA, obtained with IVUS-guided stent implantation compared with the angiography-based stenting strategy, may be offset by the extra cost induced by the use of IVUS (22). However, given the increasing rate of stenting, one can anticipate encountering in the near future a growing rate of intrastent restenosis, which to date is one of the most challenging problems in interventional cardiology (23). IVUS-guided overdilation might then be worth considering, whatever the magnitude of the gain that can be anticipated with this technique.

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