Influence of Residual Stenosis After Percutaneous Coronary Intervention With Stent Implantation on Development of Restenosis and Stent Thrombosis

Peter Sick, MD, Tobias Hüttl, BS, Josef Niebauer, MD, Holger Thiele, MD, Bernward Lauer, MD, Rainer Hambrecht, MD, Bettina Hentschel, PhD, and Gerhard Schuler, MD

The aim of this study was to assess the effects of residual stenosis after single-stent implantation on the rate of stent thrombosis, as well as restenosis within a 6-month follow-up period. Coronary angiograms of 2,157 patients with 2,523 lesions treated with a single stent were analyzed by quantitative coronary angiography before, immediately after stent implantation, and at a planned 6-month follow-up. Lesions were classified into 4 subgroups according to the degree of residual stenosis after stent implantation: group 1, gross oversizing <−15%; group 2, slight oversizing −15% to <0%; group 3, mild residual 0% to <15%; group 4, moderate residual 15% to <30%. Stent thrombosis rates were not significantly different among the 4 subgroups (group 1: 0 of 60 [0%]; group 2: 2 of 388 [0.5%]; group 3: 8 of 1,370 [0.6%]; group 4: 8 of 705 [1.1%]; p = NS for all). An adequate dosage of ticlopidine (250 mg twice daily) and aspirin (100 mg/day) led to a lower rate of stent thrombosis (6 of 2,189 cases) than inadequate dosages or missing therapy (12 of 343 cases). In 1,882 stenoses with angiographic follow-up (77.7%), gross oversizing of stents lead to a significantly higher increase of percent stenosis (p <0.001) associated with a higher restenosis rate (group 1: 34.7% vs groups 2, 3, and 4: 32.5%, 28.2%, and 29.6%, respectively). A multiple regression analysis was performed. Optimal results with regard to stent thrombosis and restenosis were achieved with mild residual stenoses between 0% and 15% after stent implantation. Oversizing of stents is no longer necessary with an adequate dosage of ticlopidine and aspirin. ©2003 by Excerpta Medica, Inc.

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In the era of conventional anticoagulation therapy without ticlopidine, a balloon-to-vessel ratio >1 was recommended for stent implantation because of a lower rate of stent thrombosis with oversized balloons.[1] With the advent of ticlopidine, stent thrombosis rates became rare.[2,3] However, there are only few data available on the effect of stent oversizing on long term restenosis rates[4−6] in native coronary arteries and on stent thrombosis rates in patients treated with ticlopidine and aspirin. In the present study, we assessed the effects of various degrees of oversizing and residual stenosis after single-stent implantation in a large patient cohort on the rate of stent thrombosis, as well as restenosis within 6 months after the intervention.

METHODS

Study design and patient characteristics: Between September 1996 and February 2000, 2,157 consecutive patients were enrolled in this study. Patients had ≥1 coronary lesions amenable to percutaneous transluminal coronary angioplasty (PTCA), and they underwent implantation of a single stent. Exclusion criteria were multiple stenting in 1 lesion and/or missing follow-up angiography prohibiting the analysis of long-term results; however, stent thrombosis was analyzed in all eligible cases. Further exclusion criteria were lesions in a bypass or in the left main coronary artery. In each patient, quantitative coronary angiography was performed before PTCA, immediately after stenting, and at 6 months (mean follow-up period of 6 ± 1 months) in identical projections. If the recurrence of angina necessitated repeat angiography before 6 months detecting restenosis >50%, no further angiography was performed—otherwise it was carried out as scheduled. Indications for stenting included dissection, recoil, primary recanalization of totally occluded vessels or previous PTCA with restenosis, and elective stenting in de novo lesions.

The primary success of stenting was defined as residual stenosis of <30%. The primary end point for statistical analysis was the increase of percent stenosis between stent implantation and follow-up angiography. Restenosis as a secondary end point was defined as a lumen decrease ≥50% at follow-up. Stent thrombosis within 48 hours after the procedure was classified as acute, and within 28 days after intervention as subacute. Lesions were divided into 4 subgroups according to the residual diameter stenosis (100 − minimal lumen diameter [MLD]/reference diameter × 100 [%]) of the target lesion at the end of the primary procedure: group 1: stent oversizing of <−15%

From the Department of Cardiology, University of Leipzig Heart Center and the Institute for Medical Informatics, Statistics, and Epidemiology, University of Leipzig, Leipzig, Germany. Manuscript received April 8, 2002; revised manuscript received and accepted August 29, 2002.

Address for reprints: Peter Sick, MD, University of Leipzig, Heart Center, Department of Cardiology, Strümpellstraβe 39, 04289 Leipzig, Germany. E-mail: sickp@medizin.uni-leipzig.de.

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(gross oversizing); group 2: stent oversizing of −15% to <0% (slight oversizing); group 3: mild residual stenosis of 0% to <15%; group 4: moderate residual stenosis of 15% to <30%.

Characteristics of stents: The stents used in this trial were: MICRO-stent I and II, as well as GFX (Advanced Vascular Engineering, Düsseldorf, Germany); SITO-stent (Sitomed, Germany, Rangendingen, Germany); Inflow stent (Inflow Dynamic, Munchen, Germany); PURA-Vario-stent (Devon Medical, Hamburg, Germany); Paragon stent (Vascular Therapies, Sunnyvale, California); and MAC-stent (AMG, Handelsgesellschaft für angewandete Medizin-und Gesundheitstecknik mbH, Raesfeld-Erle, Germany). Other stents were used only occasionally (<50 lesions). All stents were 316-L stainless steel, slotted-tube stents except for the Advanced Vascular Engineering stents, which are formed from laser-fused sinusoidal elements. The Paragon stent was covered with nitinol.

Medical treatment: PTCA was usually performed immediately after the diagnostic procedure ("prima vista PTCA"). All patients received 15,000 IU of heparin and aspirin 500 mg. In patients who underwent planned PTCA, ticlopidine was given 1 day before the intervention; in all other patients, it was given immediately after the procedure. Patients who underwent PTCA and stenting between September 1996 and December 1996 received ticlopidine 125 mg twice daily for 3 months; between January 1997 and April 1997 the dosage was increased to 250 mg twice daily, and since April 1997 the loading dose was 500 mg 3 times daily every 12 hours and then 250 mg twice daily for 4 weeks.[7] All patients received aspirin 100 mg/day.

Quantitative coronary angiography: Coronary angiograms were obtained from 2 orthogonal views after intracoronary injections of nitroglycerin 0.2 mg. Quantitative analysis was performed in the view with the highest degree of stenosis. Images were digitally processed using a computer assisted quantitative angiographic system (MEDIS, version 3.0; Medical Imaging Systems, Nuenen, The Netherlands)[8,9] in our core laboratory. The interobserver agreement of measurements of the 2 operators was high, with a correlation coefficient of $r = 0.977$ ($p < 0.0001$) and a regression coefficient of $b = 1.04$ (95% confidence interval (CI) 0.929 to 1.152).

Increase of percent stenosis was defined as the difference between percent stenosis immediately after stent implantation and at follow-up. This parameter was chosen because reference diameters tend to increase after stent implantation as a result of flow-dependent vasodilatation.[4] MLD alone seems to be less valid to compare angiographic results. As for clinical decisions, lumen reduction has to be related to the vessel size. However, MLD is a good parameter to analyze the development of neointima within the stent. Therefore, MLD was analyzed to assess acute gain (MLD after stent implantation − MLD before treatment), late loss (MLD after stent implantation − MLD at follow-up), net gain (acute gain − late loss), and loss index (late loss/initial gain).

Statistical analysis: Baseline characteristics of the 4 patient groups were compared using 1-way analysis of variance, Kruskal-Wallis, and chi-square tests. Normally distributed continuous variables are expressed as mean ± SD. Median and quartiles are shown for not normally distributed continuous variables. To assess the association between residual relative stenosis diameter and increase of percent stenosis, the correlation coefficient was calculated by Pearson's product moment correlation.

A multiple regression model was built to analyze the predictive value of residual relative diameter stenosis on change of percent stenosis using normal rank transformation for change of percent stenosis. For all statistical tests, differences were considered statistically significant at $p < 0.05$. All statistical analyses were performed using SPSS version 10.0.07 (SPSS Inc., Chicago, Illinois).

RESULTS

Baseline characteristics: During the study period 5,795 coronary interventions were performed. In 4,348 (75%) of these PTCA-procedures, a total of 6,468 stents were implanted. Implantation of only a single stent was performed in 2,157 patients with 2,523 lesions. For 592 lesions, follow-up data at 6 months were missing (follow-up angiography rate 77.7%), or they were excluded from analysis due to treatment of left main or bypass (52 cases) or unsuccessful result with a residual stenosis >30% after stent implantation (8 cases); so 1,882 lesions in 1,212 men (75%) and 405 women (25%) with a mean age of 61.8 ± 10.4 years were analyzed for follow-up data. Baseline characteristics for all lesions with follow-up data are listed in Table 1, indications for stent implantation and quantitative coronary angiographic data are listed in Table 2. There were no significant differences among the 4 groups in the distribution of age, degree of coronary artery disease, risk factors, and localization of the lesions. MICRO I and II, SITO, Devon, and Inflow stents were used more often in oversized vessels, whereas the use of GFX stents tended to be for higher residual stenoses ($p < 0.001$). The other stents, as well as indications for stenting, were nearly equally distributed except for elective stenting, which was significantly less in the group with gross oversizing; probably due to more dissections after predilatation.

Stent thrombosis rate: The overall stent thrombosis rate in the cohort of 2,523 treated lesions was 0.7% (18 cases). There was a higher trend for rate of stent thrombosis in patients with residual stenosis (Figure 1) but no statistically significant difference among the 4 groups ($p = 0.434$). In patients who were treated with an adequate dosage of ticlopidine 250 mg twice daily in addition to aspirin 100 mg/day, stent thrombosis occurred in 6 of 2,189 (0.3%). In patients who discontinued the use of ticlopidine due to side effects (or given in a reduced dose in 1 patient who did not take aspirin), stent thrombosis developed in 12 of 343 (3.2%).

TABLE 1 Baseline Characteristics for All Lesions With Angiographic Follow-up

Group	Gross Oversized (group 1) < −15%	Slight Oversized (group 2) −15% to < 0%	Mild Residual Stenosis (group 3) 0% to <15%	Moderate Residual Stenosis (group 4) 15% to <30%	p Value
No. of segments (n = 1,890)	49	309	1,028	497	
Stents					
Micro I and II	17 (34.7%)	90 (29.2%)	170 (16.5%)	39 (7.8%)	<0.001
Sito	11 (22.4%)	62 (20.1%)	156 (15.2%)	52 (10.5%)	
Pure-Vario	7 (14.3%)	38 (12.3%)	100 (9.7%)	42 (8.5%)	
Micro-GFX	3 (6.1%)	74 (24.0%)	365 (35.5%)	196 (39.4%)	
Inflow	8 (16.3%)	33 (10.7%)	105 (10.2%)	51 (10.3%)	
Paragon	1 (2.0%)	0	35 (3.4%)	35 (6.8%)	
MAC	0	0	54 (5.3%)	36 (7.0%)	
Other	2 (4.1%)	11 (3.6%)	43 (4.2%)	48 (9.7%)	
Age (mean ± SD)	62 ± 11	62 ± 10	62 ± 10	61 ± 11	0.273
Gender					
Women	14 (28.6%)	88 (28.6%)	265 (25.8%)	102 (20.5%)	0.044
Men	35 (71.4%)	220 (71.4%)	763 (74.2%)	395 (79.5%)	
Severity of CHD					
1-vessel	18 (36.7%)	125 (40.6%)	445 (43.3%)	212 (42.7%)	0.707
2-vessel	19 (38.8%)	122 (39.6%)	408 (39.7%)	190 (38.2%)	0.956
3-vessel	12 (24.5%)	61 (19.8%)	175 (17.0%)	95 (19.1%)	0.382
Previous interventions					
PTCA	10 (20.4%)	49 (15.9%)	102 (9.9%)	43 (8.7%)	0.001
CABG	4 (8.2%)	11 (3.6%)	36 (3.5%)	17 (3.4%)	0.391
Risk factors					
Hypertension	33 (67.3%)	208 (67.5%)	715 (69.6%)	342 (68.8%)	0.913
Smoker	17 (34.7%)	103 (33.4%)	336 (32.7%)	170 (34.2%)	0.940
Hlp	28 (57.1%)	160 (51.9%)	498 (48.4%)	240 (48.3%)	0.463
Diabetes mellitus	12 (24.5%)	76 (24.7%)	269 (26.2%)	122 (24.5%)	0.893
Localization of stenosis					
LAD	26 (53.1%)	149 (48.4%)	477 (46.4%)	216 (43.5%)	0.387
LC	13 (26.5%)	74 (24.0%)	213 (20.7%)	116 (23.3%)	0.423
Right	10 (20.4%)	85 (27.6%)	338 (32.9%)	165 (33.2%)	0.092

*Chi-square test for nominal variables, analysis of variance for continuous variables.
CABG = coronary artery bypass grafting; CHD = coronary heart disease; Hlp = hyperlipoproteinemia; LAD = left anterior descendent, LC = left circumflex; RD = reference diameter.

Quantitative coronary angiography and restenosis rate: Acute gain, late lumen loss, net gain and loss index, as well as percent stenoses are listed in Table 2. The primary end point increase of percent stenosis was significantly higher in the gross oversized stent group (stent-to-vessel diameter >1.15:1, group 1) in comparison with the other 3 groups[2 to 4] (Figure 2; p <0.001), resulting in a slightly higher restenosis rate. The lowest restenosis rate was found with mild residual stenosis between 0% and 15% (Figure 3).

Regression analysis: To analyze the correlation between residual stenosis and increase of percent stenosis, Pearson's correlation coefficient was calculated. The correlation coefficient of r = −0.33 (p <0.001) demonstrates a negative correlation between these variables, indicating that the greater oversizing of stents resulted in a higher risk of developing neointima, leading to restenosis. To investigate the predictive value of independent factors responsible for the increase of percent stenosis, and thus the development of restenosis, a multiple regression analysis was performed. Variables used in this analysis other than the degree of oversizing or residual stenosis after stent implantation included coronary risk factors like diabetes mellitus, hypertension, smoking, hypercholesterinemia (total cholesterol >200 mg/dl), age, gender, severity of coronary artery disease (1-, 2- or 3-vessel disease), type of lesion, indication for stenting, history of PTCA or coronary bypass grafting, localization of target lesion in the left anterior descendent, right coronary, or left circumflex arteries and proximal versus distal, respectively, reference vessel diameter before stent implantation, emergency versus elective interventions, stent type, and the occurrence of stent thrombosis. The only statistically significant independent predictors for a higher increase of percent stenosis were residual stenosis (r = −0.035, 95% CI −0.04 to −0.031, p <0.001), reference vessel diameter before stent implantation (r = −0.316, 95% CI −0.394 to −0.239, p <0.001), the coronary risk factor diabetes mellitus (r = 0.157, 95% CI 0.059 to 0.254, p = 0.002), emergency interventions (r = 0.108, 95% CI 0.004 to 0.213, p = 0.042), localization of the target lesion in the left anterior descendent compared with the right coronary artery (r = −0.123, 95% CI −0.230 to −0.017, p = 0.023), and type C compared with type A lesions (r = 0.139, 95% CI 0.005 to 0.273, p = 0.042). All other variables were not significant.

TABLE 2 Indications for Stent Deployment, Lesion Types, and Quantitative Coronary Angiographic Data

	Group 1 Gross Oversizing	Group 2 Slight Oversizing	Group 3 Mild Residual Stenosis	Group 4 Moderate Residual Stenosis	p Value
No. of stenoses	49	308	1028	497	
Indications					
Recoil	10 (20.4%)	67 (21.8%)	187 (18.2%)	99 (19.9%)	0.539
Dissection	31 (63.3%)	190 (61.7%)	564 (54.9%)	260 (52.3%)	0.042
Elective	8 (16.3%)	50 (16.2%)	259 (25.2%)	126 (25.4%)	0.005
Other	0	1 (0.3%)	18 (1.8%)	12 (2.4%)	0.111
Lesion type					
A	7 (14.3%)	47 (15.3%)	188 (18.3%)	76 (15.3%)	0.368
B	34 (69.4%)	180 (58.4%)	608 (59.1%)	305 (61.4%)	0.424
C	8 (16.3%)	81 (26.3%)	232 (22.6%)	116 (23.3%)	0.363
Lesion length (without occlusions) (mm)	8.9 ± 4.8	7.8 ± 5.8	8.8 ± 5.8	9.7 ± 6.2	<0.001
Vessel diameter					
RD before	2.7 ± 0.6	2.9 ± 0.5	3.0 ± 0.6	3.0 ± 0.6	0.012
MLD before	0.5 ± 0.4	0.5 ± 0.4	0.5 ± 0.4	0.5 ± 0.4	0.544
MLD at follow-up	1.7 ± 1.0	1.7 ± 0.9	1.7 ± 0.8	1.7 ± 0.8	0.491
Stent length (mm)	16	16	16	16	0.379
Median (quartile)*	(12–16)	(12–18)	(12–18)	(12–18)	
% stenosis before	80.7 ± 11.3	84.0 ± 12.5	83.9 ± 11.5	84.7 ± 11.1	0.105
% stenosis after	−23.2 ± 7.0	−6.2 ± 4.0	8.1 ± 4.2	17.5 ± 2.3	<0.001
% stenosis follow-up	42	33	34	36	
Median (quartile)*	(23–60)	(21–63)	(23–53)	(27–53)	0.002
Acute gain (mm)	2.7 ± 0.5	2.6 ± 0.5	2.4 ± 0.5	2.2 ± 0.5	<0.001
Late lumen loss (mm)	1.6 ± 0.7	1.4 ± 0.8	1.1 ± 0.8	1.0 ± 0.7	<0.001
Net gain (mm)	1.1 ± 0.9	1.2 ± 0.9	1.3 ± 0.8	1.2 ± 0.8	0.495
Increase % stenosis	64.9 ± 29.0	47.7 ± 27.6	33.3 ± 24.6	27 ± 23.3	<0.001
Loss index	0.61 ± 0.3	0.55 ± 0.3	0.48 ± 0.3	0.45 ± 0.3	<0.001

*Due to abnormal distribution, median and first to fourth quartiles are given, all other data were mean ± SD with normal distribution.
Abbreviations as in Table 1.

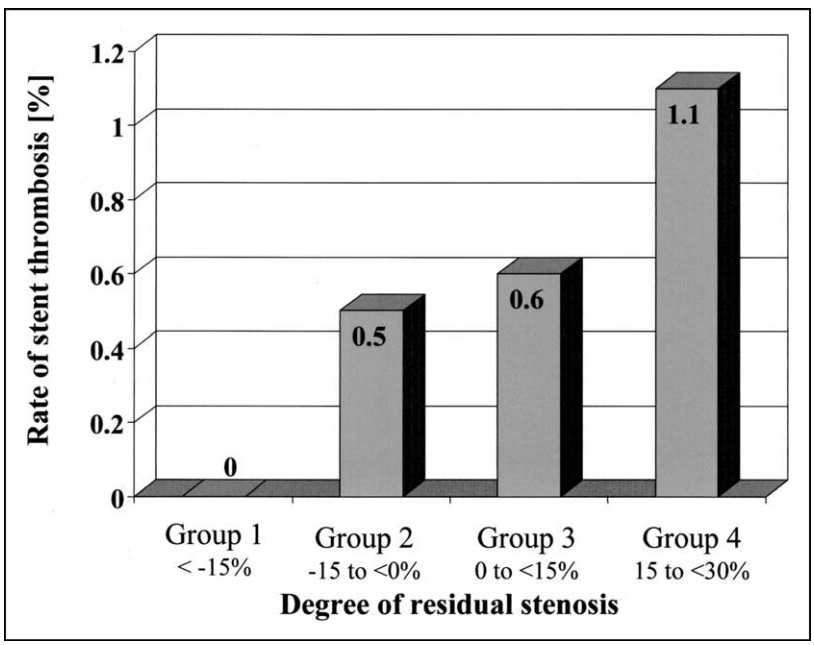

FIGURE 1. Stent thrombosis rate within 28 days after intervention in relation to the initial degree of oversizing or residual stenosis (p = 0.434).

DISCUSSION

Stent thrombosis: The present data of a large patient cohort show that prevention of stent thrombosis is strongly dependent on adequate dosage of ticlopidine and aspirin and is not influenced by the primary angiographic results after stent implantation if residual stenosis is <30%. There was only a trend toward a higher rate of stent thrombosis with a higher degree of residual stenosis. This finding is in line with a study from Schömig et al[3] demonstrating comparable results. However, the overall incidence of stent thrombosis was extremely rare with only 6 patients in the study group in which ticlopidine and aspirin were given in adequate dosages. All other stent thromboses occurred in patients who received ticlopidine in a dosage well below current recommendations or in patients who took neither ticlopidine nor aspirin due to their side effects. The original idea behind decreasing former high rates of acute and subacute reocclusions between 8% and 10%[10–12] came from the notion that oversized high-pressure stenting assisted by intravascular ultrasound coincided with reduced rates of stent thrombosis.[1,13,14] On this basis, anticoagulation therapy could be replaced by platelet inhibiting therapy with ticlopidine and aspirin with less complications.[2,3,15,16] However, the present study shows that medical treatment with adequate dosages of ticlopidine and aspirin is much more relevant for

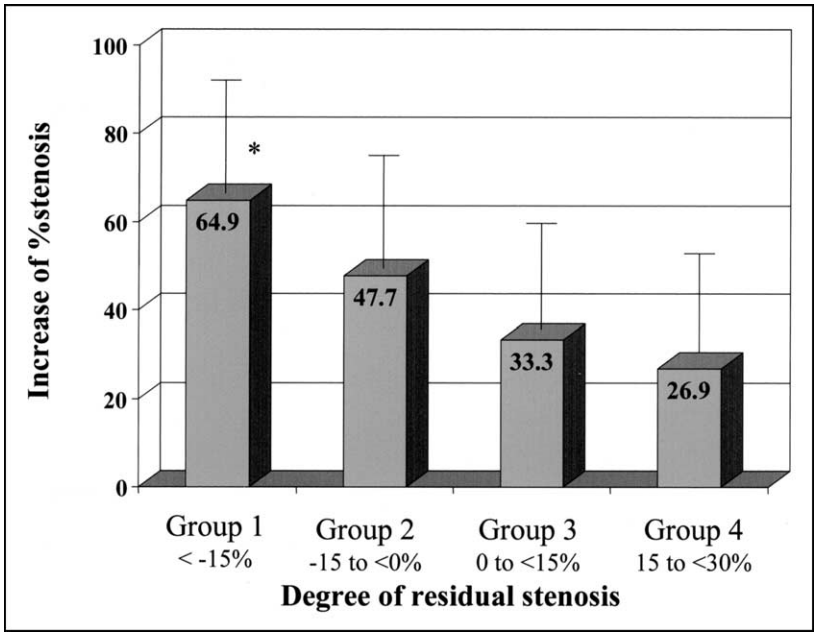

FIGURE 2. Increase of percent (%) stenosis depending on initial degree of oversizing or residual stenosis (mean ± SD). *p <0.001.

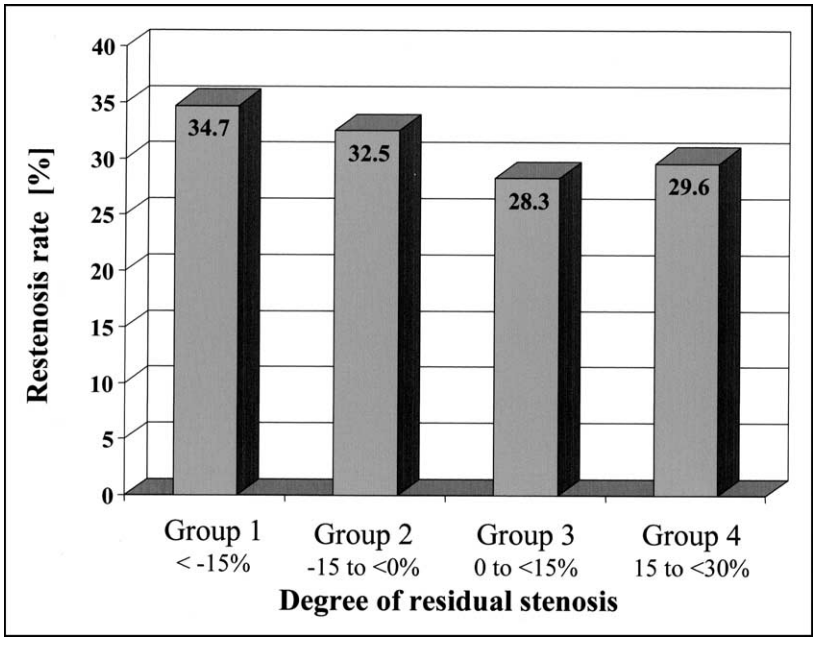

FIGURE 3. Restenosis rate 6 months after stent implantation depending on initial degree of residual stenosis or oversizing.

the decrease of stent thrombosis than the oversizing of stents.

Restenosis: The BENESTENT and STRESS studies have shown that intracoronary stent implantation decreases the restenosis rate compared with PTCA alone due to a higher initial gain despite a higher late lumen loss.[17,18] Because adequate therapy with ticlopidine and aspirin has all but eliminated stent thrombosis, the question remains whether the extent of oversizing or residual stenosis determines long-term results. The data of our study demonstrated that gross oversizing of stents with a stent-to-vessel diameter >1.15:1 (high initial gain) is a powerful stimulant of the restenotic process resulting in a high late lumen loss, whereas slight oversizing ≤1.15:1 and residual stenosis of ≤30% (lower initial gain) resulted in satisfactory long-term results with lower late lumen loss. The best results were achieved with slight residual stenosis between 0% and 15%. This may be explained by the fact that the extent of neointima proliferation after stent implantation is dependent on the extent of damage to the vessel media.[19,20] Additionally, the destruction of the internal elastic lamina due to vessel injury may also enhance smooth muscle cell migration to the neointima.[21] Another consequence of vessel injury is mural thrombus formation with liberation of growth factors like platelet derived growth factor, leading to an increase of smooth muscle cell proliferation. Thrombin also accumulates locally in response to the injury and ongoing thrombotic process and is a chemoattractant for monocytes and other inflammatory cells, thus organizing mural thrombi by connective tissue.[22] All these mechanisms may be enhanced by more severe vessel injury due to roughly oversizing stent diameter.

Multivariate regression analysis: In the present study, the independent predictors of restenosis in a multivariate regression analysis were gross oversizing of stents, reference vessel diameter before stent implantation, diabetes mellitus, localization of target lesion in the left anterior descendent compared with right coronary artery, type C lesions compared with type A lesions, and emergency interventions. This is similar to the results of other studies.[23–26] The variables of hypertension, smoking, hypercholesterinemia, age, gender, severity of coronary artery disease, and previous PTCA or coronary bypass grafting showed no significant influence on increase of percent stenosis, which is in concordance with the results of Foley et al[27] and Bauters et al.[28] Other studies demonstrated additional predictors for in-stent restenosis like multiple stenting,[29] restenotic lesions,[24] and higher percent diameter stenosis after stenting.[24] These results may be due to different study populations, different size of study cohorts, and various inclusion criteria. Foley et al[6] even concluded in a

small study with 80 consecutive patients that more aggressive dilatation within the stented segment with a balloon-to-vessel ratio of 1.33:1 may result in a lower restenosis rate with oversizing of stents particularly in a subset of 22 patients with smaller vessels (<2.5 mm). However, the present study—with a much larger number of patients—could not find that oversizing of stents decreases late restenosis. In contrast, our findings suggest that the oversizing of stents led to increased late lumen loss, even in small vessels.

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