

# The Importance of Acute Luminal Diameter in Determining Restenosis After Coronary Atherectomy or Stenting

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**Background.** We evaluated native coronary arteries treated by directional coronary atherectomy or balloon-expandable stent placement in an effort to derive a quantitative geometric model relating the luminal diameter immediately after intervention to that present 6 months later. The minimal luminal diameter of each lesion was measured before and immediately after intervention in 102 single Palmaz-Schatz stents and 134 directional atherectomies, 192 (81%) of which had repeat angiographic measurement of minimal luminal diameter 6 months after the intervention. The immediate enlargement in luminal diameter produced by the intervention (acute gain) and the subsequent reduction in luminal diameter from the time of intervention to 6 months of follow-up (late loss) were calculated.

**Methods and Results.** Luminal diameter: increased from  $0.69 \pm 0.40$  mm to  $3.11 \pm 0.64$  mm (acute gain,  $2.41 \pm 0.64$  mm) after intervention, providing an immediate postprocedure residual stenosis of  $1 \pm 14\%$  relative to a reference diameter of  $3.13 \pm 0.65$  mm. At 6-month follow-up, the late luminal diameter was  $1.97 \pm 0.92$  mm (late loss,  $1.13 \pm 0.89$  mm), yielding a late diameter stenosis of  $36 \pm 26\%$ . The restenosis rate (according to the traditional definition of diameter stenosis  $\geq 50\%$ ) was 30%. Multivariable analysis demonstrated that late luminal diameter ( $p=0.02$ ), late percent stenosis ( $p=0.04$ ), and restenosis (according to a  $> 50\%$  definition,  $p=0.04$ ) were each strongly associated with the luminal diameter present immediately after the procedure. Whereas late luminal diameter was also influenced by reference artery size and the vessel treated (left anterior descending versus right coronary artery), reference vessel size was rejected by the multivariable models of late percent stenosis and binary restenosis after they were adjusted for the effect of postprocedure luminal diameter. Once adjusted for postprocedure luminal diameter, neither late luminal diameter nor late loss was found to be independently determined by which device was used (atherectomy versus stents). Rather, late loss was determined independently by the immediate postprocedure luminal diameter ( $p=0.005$ ) and the postprocedure percent stenosis ( $p=0.02$ ). Although late loss thus increased with acute gain, the net beneficial effect of increased acute gain was maintained: Late loss was only a fraction (0.47) of acute gain, so the ability of a larger postprocedure luminal diameter to reduce the probability of subsequent restenosis was preserved.

**Conclusions.** This quantitative model demonstrates that the late coronary lumen diameter and the probability of restenosis after Palmaz-Schatz stenting or directional atherectomy are influenced strongly by the lumen diameter present immediately after the procedure rather than by the specific device used. Although the influence of a larger acute result on reduced restenosis appears to be well established in this treatment population, the interplay among the multiple other biological influences on restenosis limits the ability to predict the probability of restenosis for the individual patient based on a large acute result alone. Future studies of restenosis, however, can further refine this multivariable quantitative model by adjusting for the effects of other clinical variables, mechanical interventions, or drug therapies in addition to the clear effect of postprocedure luminal diameter. (*Circulation* 1992;86:1827-1835)

**KEY WORDS** • restenosis • stents • atherectomy • lumen diameter

New devices for coronary intervention have been developed to improve upon the immediate and long-term results now obtained with conventional balloon angioplasty.<sup>1-3</sup> Preliminary reports have suggested that some new devices may reduce the incidence of restenosis,<sup>4</sup> but the mechanism of that

reduction remains unclear. It has been demonstrated previously that the luminal diameter and the probability of restenosis 4-6 months after percutaneous transluminal coronary angioplasty (PTCA) are the net result of the acute postprocedure gain in luminal diameter (after any early elastic recoil) produced by the intervention minus any late loss in luminal diameter that occurs due to subsequent intimal hyperplasia<sup>5-10</sup> (Figure 1). Using

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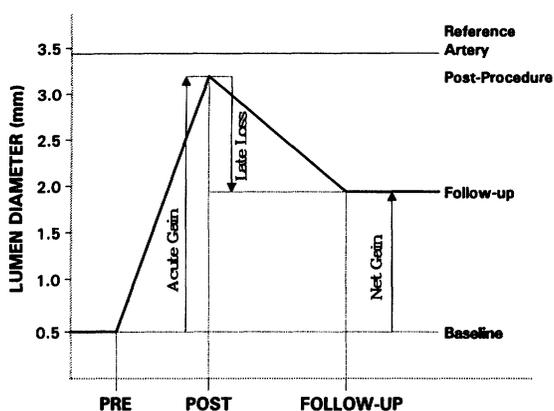


FIGURE 1. Schematic diagram showing changes in luminal diameter over time after coronary intervention. Late procedural outcome is influenced by both the acute gain provided by the intervention (pre→post) and the subsequent late loss that occurs over 4–6 months after the intervention (post→follow-up). The net gain is thus the sum of the offsetting effects of acute gain and late loss.

qualitative description of these geometric parameters and their possible relations to restenosis, we have recently shown that the ability of a newer device to reduce restenosis may be related more to its ability to provide the greatest acute gain in luminal diameter rather than to any ability to reduce subsequent intimal hyperplasia.<sup>11</sup>

Rather than relying exclusively on traditional dichotomous methods (e.g., late diameter stenosis >50%) to compare devices, we sought to develop a continuous analysis relating selected procedure-related angiographic variables and the specific device used to the late luminal diameter. By using this approach to analyze angiograms obtained before, immediately after, and 6 months after directional atherectomy or balloon-expandable stenting, we developed a detailed quantitative model of late lumen diameter that explains observed differences in the probability of restenosis as a direct function of differences in posttreatment lumen diameter rather than any device-to-device differences in subsequent luminal narrowing.

## Methods

### Study Patients

Of 2,136 patients who underwent coronary intervention between June 1988 and January 1991, 290 (13.6%) patients had 306 vascular segments (including 236 native coronaries and 70 saphenous grafts) treated with either a single Schatz-Palmaz stent or directional atherectomy under protocols approved by the Beth Israel Hospital Committee on Clinical Investigation. Results of the first 37 patients who received a stent and the first 111 patients who underwent atherectomy have been reported previously.<sup>4,12</sup> The current analysis also includes these earlier as well as subsequent patients but is limited to 214 patients and 236 native coronary segments treated by atherectomy (116 patients, 134 segments) or stenting (98 patients, 102 segments) during the study period.

All patients were requested to have angiographic follow-up at 6 months, and 192 (81%) underwent such

follow-up by August 1991 (Table 1). Patients who underwent earlier (<4 months) restudy for the evaluation of recurrent symptoms but were found to have ≤70% diameter stenosis were accepted for analysis only if they returned for repeat angiography ≥6 months after the procedure.

### Analysis of Angiographic Results

Angiographic analysis was performed immediately before and after each new intervention and was repeated 6 months after intervention using the view in which the initial stenosis appeared most severe. Coronary arterial dimensions were determined by using caliper measurements made on projected flat images of selected optically magnified cine frames referenced to the known diameter of the filled angiographic catheter. This technique has been used by others<sup>13,14</sup> and has been shown to provide excellent agreement with computerized techniques over a wide range of arterial dimensions,<sup>15–17</sup> and internal comparisons with a well-validated computer system<sup>18</sup> (3% or less variation in determining percent stenosis) also show close agreement. Almost all views for analysis were performed on a magnified “5-inch mode,” with the target lesion and reference guide catheter centered whenever possible, a technique found to reduce or eliminate pincushion distortion.<sup>15,19</sup> Measurements included the minimal luminal diameter of the treated coronary segment and the reference diameter (taken as the mean diameter of the normal-appearing proximal and distal segment) before and after each intervention and at follow-up. Variance estimates on these measurements (Table 1) provide a scale of population variation and measurement error and were similar to other studies using computerized techniques.<sup>9,10,20</sup> Intravenous nitroglycerin (200 μg) was administered immediately before and after intervention.

### Statistical Analysis

All values were reported as the mean±standard deviation. Differences between continuous variables were tested by Student's *t* test, and differences between categorical variables were tested using  $\chi^2$  test. Selected variables were described with their corresponding quartile values (25th, 50th, and 75th percentiles) or 95% confidence intervals (95% CI).

Selected procedural, clinical, and angiographic variables were evaluated as potential determinants of restenosis. Restenosis was defined from the late (6-month) angiogram in one of three ways: as a continuous variable (the late luminal diameter or the late percent stenosis) and as a dichotomous variable (binary restenosis defined as ≥50% diameter stenosis). Explanatory variables included angiographic indexes relating to the initial procedure (reference artery size, postprocedure luminal diameter, acute gain in luminal diameter, and postprocedure percent stenosis), coronary location, the number of diseased coronary arteries (defined as one or more lesions per coronary artery with ≥70% diameter stenosis), the presence of prior restenosis, and the particular device (atherectomy or stent) used.

Associations between continuous or binary outcome variables and various explanatory variables were tested using simple linear or logistic regression techniques, respectively. Independent determinants of each outcome were evaluated by entering all univariable deter-

**TABLE 1. Clinical and Angiographic Characteristics of 236 Coronary Segments Treated by Coronary Atherectomy or Stenting**

	Overall	Stents	Atherectomy	<i>p</i>
Patients ( <i>n</i> )	214	98	116	
Total coronary segments ( <i>n</i> )	236	102	134	
Vessels diseased				
1	154 (65%)	63 (62%)	91 (68%)	
2	54 (23%)	24 (23%)	30 (22%)	
3	28 (12%)	15 (15%)	13 (10%)	0.41
Lesion location (percent)				
Left main artery	2 (1%)	1 (1%)	1 (1%)	
Left anterior descending coronary artery	135 (57%)	32 (31%)	103 (76%)	
Circumflex artery	32 (14%)	15 (15%)	17 (13%)	
Right coronary artery	67 (28%)	54 (53%)	13 (10%)	<0.001
Prior restenosis	124 (52%)	69 (68%)	55 (41%)	<0.001
Immediate results				
Reference diameter (mm)	3.13±0.65	3.26±0.62	3.04±0.66	0.009
Preprocedure luminal diameter (mm)	0.69±0.40	0.73±0.48	0.67±0.34	0.22
Postprocedure luminal diameter (mm)	3.11±0.64	3.40±0.63	2.88±0.55	<0.001
Acute gain (mm)	2.41±0.64	2.67±0.63	2.21±0.58	<0.001
Postprocedure percent stenosis (%)	1±14	-4±12	5±14	<0.001
Follow-up results				
Follow-up coronary segments	192	90	102	
Percent angiographic follow-up (%)	81	88	75	
Time to follow-up (days)	178±51	180±51	176±52	
25th, 50th, 75th percentiles	159, 187, 209	156, 187, 212	160, 185, 207	0.52
Follow-up luminal diameter (mm)	1.97±0.92	2.18±0.92	1.79±0.90	0.004
Late loss	1.13±0.89	1.22±0.90	1.05±0.89	0.20
Follow-up percent stenosis (%)	36±26	33±24	39±27	0.08
Restenosis rate* (%)	30	26	32	0.30

\*Defined as ≥50% reduction in luminal diameter.

minants with values of  $p \leq 0.15$  into the multivariable model. After removal of nonsignificant explanatory variables from the saturated model by the standard “step-down” approach, the independent determinants were evident by final multivariable values of  $p \leq 0.05$ . Analysis of the trend for lower binary restenosis rate with larger luminal dimensions was performed using a logistic regression test of trend.

## Results

### Clinical and Angiographic Characteristics of 236 Coronary Segments Treated by Coronary Atherectomy or Stenting

Of 236 coronary segments treated, intervention in 124 (52%) was for treatment of prior restenosis (68% for stents and 41% for atherectomy,  $p < 0.001$ ); 135 (57%) segments were in the left anterior descending (LAD) coronary artery (31% for stents and 76% for atherectomy,  $p < 0.001$ , Table 1). The overall average reference diameter was  $3.13 \pm 0.65$  mm before intervention,  $3.18 \pm 0.61$  mm immediately after intervention, and  $3.06 \pm 0.65$  mm at 6-month follow-up ( $p = 0.35$  for the difference in reference measurements). The reference diameter for stents was larger ( $3.26 \pm 0.62$  mm) compared with atherectomy ( $3.04 \pm 0.66$  mm,  $p = 0.009$ , Table 1). Acute gain, the increase in luminal diameter from before to after intervention, was  $2.41 \pm 0.64$  mm ( $2.67$  mm for stents and  $2.21$  mm for atherectomy,  $p < 0.001$ ), providing an average postpro-

cedure luminal diameter of  $3.11 \pm 0.64$  mm ( $3.40$  for stents and  $2.88$  for atherectomy,  $p < 0.001$ ) and a postprocedure residual stenosis of  $1 \pm 14\%$  ( $-4\%$  for stents and  $5\%$  for atherectomy,  $p < 0.001$ ).

The mean late loss (the narrowing in luminal diameter from immediately after intervention to 6-month follow-up) was  $1.13 \pm 0.89$  mm ( $1.22$  mm for stents and  $1.05$  mm for atherectomy,  $p = 0.20$ , Table 1), resulting in an average late luminal diameter of  $1.97 \pm 0.92$  mm ( $2.18$  mm for stents and  $1.79$  mm for atherectomy,  $p = 0.004$ ) and a late stenosis of  $36 \pm 26\%$  ( $33\%$  for stents,  $39\%$  for atherectomy,  $p = 0.08$ ). The corresponding restenosis rate (defined as  $\geq 50\%$  diameter stenosis at 6 months) was  $30\%$  ( $26\%$  for stents and  $32\%$  for atherectomy,  $p = 0.30$ ).

### Determinants of Late Outcome

In univariable modeling, larger late (6-month) luminal diameter was associated with the absence of prior restenosis ( $p = 0.05$ ), right coronary artery (RCA) location ( $p < 0.001$ ), and stenting ( $p = 0.004$ , Table 2) as well as with geometric determinants such as larger preprocedure luminal diameter ( $p = 0.03$ ), larger acute gain in luminal diameter ( $p < 0.001$ ), larger reference diameter ( $p < 0.001$ ), and larger immediate postprocedure luminal diameter ( $p < 0.001$ ). Multivariable modeling, however, showed that the independent determinants of late luminal diameter were the reference diameter ( $p =$

**TABLE 2. Univariable and Multivariable Linear Regression Models of the Late (6-Month) Luminal Diameter**

Variable	Univariable*			Multivariable†		
	Intercept	$\beta$	<i>p</i>	$\beta$	95% CI	<i>p</i>
Prior restenosis (0,1)	2.12	-0.27	0.05	...	...	NS
Vessels diseased ( <i>n</i> )	...	...	NS	...	...	...
LAD (0,1)	2.27	-0.53	<0.001	...	...	NS
RCA (0,1)	1.76	0.70	<0.001	0.37	0.08, 0.66	0.01
Cx (0,1)	...	...	NS	...	...	...
Device (0-stent, 1-ath)	2.57	-0.39	0.004	...	...	NS
Reference diameter (mm)	0.18	0.57	<0.001	0.32	0.09, 0.54	0.006
Preprocedure diameter (mm)	1.73	0.34	0.03	...	...	NS
Postprocedure diameter (mm)	0.15	0.59	<0.001	0.28	0.04, 0.52	0.02
Acute gain (mm)	1.00	0.40	<0.001	...	...	NS
Postprocedure % stenosis	...	...	NS	...	...	...

LAD, left anterior descending coronary artery; RCA, right coronary artery; Cx, circumflex artery; ath, atherectomy.

\*Univariable model for late luminal diameter: Late diameter (mm)=intercept+(variable× $\beta$ ).

†Final "step-down" multivariable linear regression model (intercept=0.00): Late diameter (mm)=(0.37×RCA[0 or 1])+(0.32×reference diameter [mm])+(0.28×postprocedure luminal diameter [mm]).

0.006), the postprocedure luminal diameter (*p*=0.02), and RCA location (*p*=0.01, Table 2).

A second univariable model showed that lower late percent stenosis was associated with RCA location (*p*<0.001), larger reference diameter (*p*=0.008), larger acute gain (*p*=0.009), and larger postprocedure luminal diameter (*p*<0.001, Table 3). The corresponding multivariable model showed that the independent determinants of late percent stenosis were RCA location (*p*=0.02) and postprocedure luminal diameter (*p*=0.04). The device type (stent versus atherectomy) was not found to determine late results after adjustment for the postprocedure luminal diameter and coronary location in the independent models of either late luminal diameter and late percent stenosis.

To validate the above models of restenosis relating the acute geometric (continuous variable) results to the late (continuous variable) restenosis results, a third model of the probability of restenosis was developed using logistic regression of binary restenosis (traditionally defined as

≥50% diameter stenosis). This univariable model demonstrated that an increased probability of restenosis was associated with LAD location (*p*<0.001), smaller reference diameter (*p*=0.01), larger postprocedure luminal diameter (*p*=0.002), and larger acute gain (*p*=0.008) but not with the device type (Table 4). The corresponding multivariable model shows that the independent determinants of binary restenosis were LAD location (*p*=0.004) and postprocedure luminal diameter (*p*=0.04, Table 4). After stratification of the postprocedure luminal diameter by its median value (3.0 mm), the independent logistic model demonstrated adjusted relative risks of restenosis of 2.43 (95% CI, 1.24, 4.78) for postprocedure luminal diameter <3.0 mm and 2.93 (95% CI, 1.45, 5.97) for LAD location (Table 5).

*Geometric Determinants of Late Loss*

By univariable modeling, late loss in luminal diameter after intervention was associated with the immediate postprocedure luminal diameter (*p*<0.001), the acute

**TABLE 3. Univariable and Multivariable Linear Regression Models of the Late (6-Month) Percent Stenosis**

Variable	Univariable*			Multivariable†		
	Intercept	$\beta$	<i>p</i>	$\beta$	95% CI	<i>p</i>
Prior restenosis (0,1)	...	...	NS	...	...	...
Vessels diseased ( <i>n</i> )	...	...	NS	...	...	...
LAD (0,1)	30	12	0.002	...	...	NS
RCA (0,1)	40	-14	<0.001	-10	-18, -2	0.02
Cx (0,1)	...	...	NS	...	...	...
Device (0-stent, 1-ath)	26	6	0.08	...	...	NS
Reference diameter (mm)	60	-8	0.008	...	...	NS
Preprocedure diameter (mm)	...	...	NS	...	...	...
Postprocedure diameter (mm)	67	-10	<0.001	-7	-13, -1	0.04
Acute gain (mm)	54	-8	0.009	...	...	NS
Postprocedure % stenosis	...	...	NS	...	...	...

LAD, left anterior descending coronary artery; RCA, right coronary artery; Cx, circumflex artery; ath, atherectomy.

\*Univariable model for late percent stenosis: Late percent stenosis (%)=intercept+(variable× $\beta$ ).

†Final "step-down" multivariable linear regression model (intercept=60): Late percent stenosis (%)=60-(10×RCA[0 or 1])-(7×postprocedure luminal diameter [mm]).

**TABLE 4. Univariable and Multivariable Logistic Regression Models of Binary Restenosis**

Variable	Univariable*			Multivariable†		
	Intercept	$\beta$	<i>p</i>	$\beta$	95% CI	<i>p</i>
Prior restenosis (0,1)	...	...	NS			
Vessels diseased ( <i>n</i> )	...	...	NS			
LAD (0,1)	-1.65	1.25	<0.001	1.05	0.33, 1.77	0.004
RCA (0,1)	-0.57	-1.28	<0.001	...	...	NS
Cx (0,1)	...	...	NS			
Device (0-stent, 1-ath)	...	...	NS			
Reference diameter (mm)	1.15	-0.66	0.01	...	...	NS
Preprocedure diameter (mm)	...	...	NS			
Postprocedure diameter (mm)	1.63	-0.83	0.002	-0.61	-0.02, -1.20	0.04
Acute gain (mm)	0.71	-0.68	0.008	...	...	NS
Postprocedure % stenosis	...	...	NS			

LAD, left anterior descending coronary artery; RCA, right coronary artery; Cx, circumflex artery; ath, atherectomy.

\*Univariable model for binary restenosis (>50% diameter stenosis): Probability of binary restenosis =  $\frac{e^{\text{intercept} + (\text{variable} \times \beta)}}{1 + e^{\text{intercept} + (\text{variable} \times \beta)}}$ .

†Final "step-down" multivariable logistic regression model (intercept=0.31): Probability of binary restenosis =  $\frac{e^{0.31 \times (\text{LAD}[0,1] \times 1.05) + (\text{postproc diameter [mm]} \times -0.61)}}{1 + e^{0.31 \times (\text{LAD}[0,1] \times 1.05) + (\text{postproc diameter [mm]} \times -0.61)}}$ .

gain ( $p < 0.001$ ), and the postprocedure percent stenosis ( $p < 0.001$ ) but not with the coronary location or device type (Table 6). In the multivariable model, acute gain was rejected, leaving the postprocedure luminal diameter ( $p = 0.005$ ) and the postprocedure percent stenosis ( $p = 0.02$ ) as the independent determinants of late loss.

#### Observed Restenosis Rates Stratified by Reference Artery Size or Postprocedure Luminal Diameter

To evaluate how well postprocedure luminal diameter predicted the probability of restenosis observed in the actual data set, we stratified lesions by luminal dimension (Table 3). Restenosis rates were calculated for each stratum of either the reference artery diameter or the postprocedure luminal diameter and showed a significant pattern of decreasing restenosis rates with larger reference artery size ( $p = 0.01$ ) and with larger postprocedure luminal diameter ( $p < 0.001$ ), as predicted by the model.

#### Geometric Models Predicting Late Luminal Diameter and Restenosis

A linear model was developed relating the postprocedure luminal diameter to the late luminal diameter and is displayed in Figure 2. By applying the logistic model of restenosis (defined as >50% diameter stenosis at follow-up) described in Table 4, it was possible to construct a curve (Figure 3) showing the influence of immediate postprocedure luminal diameter to the probability of subsequent restenosis. Superimposed on the curve in Figure 3 is an illustration of how different

immediate results influence the probability of restenosis in a hypothetical 3.5-mm artery.

#### Discussion

By analyzing the immediate and late changes in luminal diameter that take place after coronary atherectomy or stenting, we previously demonstrated that the differences in the late luminal diameter and the restenosis rate between coronary atherectomy and stenting are more the consequence of differences in acute results rather than any device-specific effects in the late loss caused by intimal hyperplasia.<sup>11</sup> Others have reported recently that stratification by acute lumen (e.g., <3.0 versus >3.0 mm) size predicts lower restenosis rates after conventional balloon angioplasty<sup>21</sup> and Palmaz-Schatz stenting.<sup>22</sup>

It is important to understand that the current study was not designed to compare differences in restenosis rates between stenting and atherectomy, given the clear differences in the lesions treated by these two devices; rather, it was undertaken to explore the relation between the acute and late results. To do so, continuous regression models were constructed relating the immediate postprocedure luminal diameter to three different measures of restenosis: Late luminal diameter and late percent stenosis were examined as continuous outcomes using linear regression, whereas binary restenosis (late stenosis  $\geq 50\%$ ) was examined using logistic regression. Clearly, a host of variables other than the acute result also influence restenosis, explaining why there is a substantial patient-to-patient variation in what late lumen diameter is associated with a given immediate postprocedure luminal diameter (Figure 2). Of fundamental importance, however, is that the seemingly random effects of these other variables are superimposed on the platform of the immediate result so that the clear statistical association between the immediate result and both late luminal geometry and the probability of restenosis remained independent of any other tested factor.

#### Value of Continuous Variable Analysis

In their review of 212 published reports on coronary restenosis, Bobbio et al<sup>23</sup> identified 31 methodologically

**TABLE 5. Multivariable Model of Binary Restenosis Using Categorical Variables of LAD Location and Postprocedure Luminal Diameter Dichotomized at Median (3.0-mm Diameter)**

Variable	$\beta$	Relative risk	95% CI (RR)	<i>p</i>
Postprocedure diameter <3.0 mm (0, >3.0; 1, <3.0)	0.89	2.43	1.24, 4.78	0.01
LAD location (0,1)	1.08	2.93	1.45, 5.97	0.003

Intercept for multiple logistic model = -1.13. LAD, left anterior descending coronary artery.

**TABLE 6. Univariable and Multivariable Linear Regression Models of the Late (6-Month) Loss in Luminal Diameter**

Variable	Univariable*			Multivariable†		
	Intercept	$\beta$	<i>p</i>	$\beta$	95% CI	<i>p</i>
Prior restenosis (0,1)	1.00	0.24	0.07	...	...	NS
Vessels diseased ( <i>n</i> )	...	...	NS			
LAD (0,1)						
RCA (0,1)						
Cx (0,1)	...	...	NS			
Device (0-stent, 1-ath)	...	...	NS			
Reference diameter (mm)	...	...	NS			
Preprocedure diameter (mm)	...	...	NS			
Postprocedure diameter (mm)	-0.15	0.41	<0.001	0.31	0.10, 0.52	0.005
Acute gain (mm)	0.28	0.35	<0.001	...	...	NS
Postprocedure % stenosis	0.012	-0.012	<0.001	-0.011	-0.020, -0.002	0.02

LAD, left anterior descending coronary artery; RCA, right coronary artery; Cx, circumflex artery; ath, atherectomy.

\*Univariable model for late loss in luminal diameter: Late loss (mm)=intercept+(variable $\times\beta$ ).

†Final "step-down" multivariable linear regression model (intercept=0.20): Late loss (mm)=0.20+(0.31 $\times$ post-procedure luminal diameter [mm])-(0.011 $\times$ postprocedure percent stenosis [%]).

sound studies that described 61 separate factors related to restenosis. After the 31 studies were pooled for meta-analysis, none of these factors were statistically associated with restenosis. One explanation is that these studies included a wide variety of outcomes (mainly multiple dichotomous angiographic definitions) that were insensitive for restenosis. They also were based on incomplete data collection and incomplete angiographic follow-up and multiple comparisons performed on small data sets ( $\alpha$  or type I error). From a statistical perspective, they lack a standardized approach and do not incorporate more sensitive continuous covariates for either the explanatory and the outcome variables, thus limiting their ability to uncover important linear and nonlinear relations.

In the current study, we evaluated restenosis after Palmaz-Schatz stenting and directional atherectomy from a data set gathered of 236 treated lesions with a high (81%) rate of angiographic follow-up. In doing so, we extended our previous description of restenosis as the result of two offsetting continuous processes (the acute gain in luminal diameter provided by the intervention and the subsequent late loss in luminal diameter at 6-month angiographic follow-up<sup>11</sup>). By using absolute late luminal diameter, the late percent stenosis, and the absolute late loss in luminal diameter as continuous variable surrogates for restenosis, analysis can be performed using linear regression. To eliminate multiple comparison problems, a parsimonious set of explanatory variables was selected. To avoid potential confounding, the influence of other noncontinuous variables (coronary location, prior restenosis, device type) was also evaluated. Logistic regression was used to analyze binary restenosis according to a traditional definition (late stenosis  $\geq 50\%$ ), which helped to establish the validity of the continuous outcome models.

#### *Restenosis is Determined by the Acute Result and Not the Device Type*

In the three models of late (6-month) outcome, the immediate postprocedure luminal diameter was established clearly as an independent determinant of restenosis (Tables 2, 3, and 4). An independent effect of coronary location on restenosis (less restenosis for RCA location compared with LAD location) was also seen and was not surprising because many previous studies have shown similar results.<sup>23,24</sup> The linear relation between the immediate result and the three outcomes of restenosis, however, was independent of coronary location, removing any possibility of confounding between these two variables. The evident variation in late luminal diameter as a function of immediate postprocedure luminal diameter (Figure 2) is merely a reflection that a variety of other variables independently modulate restenosis superimposed on the platform of the acute result. Analysis of larger data sets will probably be required to more completely understand the influence of such variables.

Univariable determinants of the three outcomes of restenosis included device type, prior restenosis, reference diameter, and acute gain. After adjustment of the multivariable models for postprocedure luminal diameter, the other variables dropped out because of their correlation with the stronger independent variables. For example, because stenting provided larger acute gain and consequently larger immediate postprocedure diameters, univariable analysis showed that the device variable (e.g., stent versus atherectomy) determined late luminal diameter ( $p=0.004$ ) and late percent stenosis ( $p=0.08$ ). After multivariable analyses, however, there was no longer any additive effect of the device variable on late luminal diameter, and device type was rejected from the multivariable model. Therefore, the late result was seen in this study to be a function of both the postprocedure luminal diameter provided by the intervention and the coronary location of the treated lesion.

Analysis of binary restenosis offers a demonstration of how acute postprocedure result influences a traditional dichotomous outcome variable, even after adjustment for the effect of coronary location (Table 4). Again, in the final multivariable model, binary restenosis was not affected by the specific device used (Palmaz-Schatz stenting or directional atherectomy). Thus, the advantage of larger late luminal result ( $p=0.004$ ) after

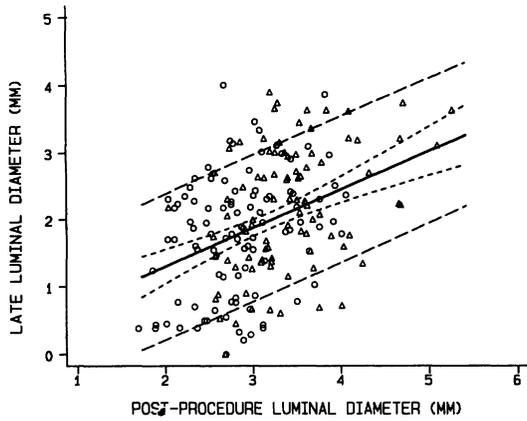


FIGURE 2. Plot of geometric model relating acute postprocedure luminal diameter to late luminal diameter. The absolute late (6-month) luminal diameter is plotted against the corresponding immediate postprocedure luminal diameters for each lesion treated by stent ( $\Delta$ ) and atherectomy ( $\circ$ ). The mean regression line (bold) and the 95% confidence bounds for that regression line (short-dashed lines) shows the tight association between larger postprocedure lumen and larger late lumen. The wider 80% confidence intervals for the treated population (long-dashed lines) show the expected spread of late results about the mean regression line as the consequence of other undetected biological variables that influence the patient-by-patient variability in late loss in luminal diameter. Although it is thus not possible to predict freedom from restenosis for any individual patient based on the acute results alone, late luminal diameter does increase, and the probability of subsequent restenosis decreases with larger postprocedure luminal diameter (see Figure 3).

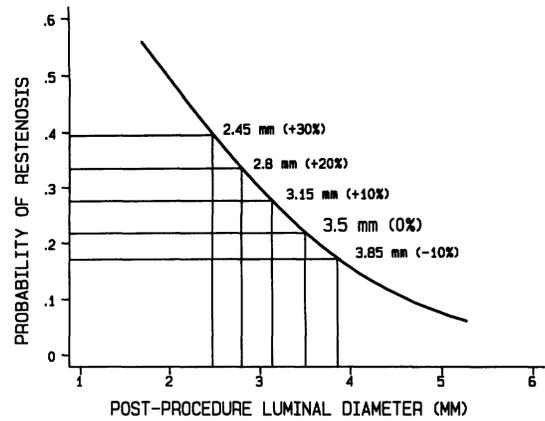


FIGURE 3. Graph illustrating that the probability of restenosis depends on the immediate postprocedure lumen diameter. Applying the geometric model (Figure 2) to a hypothetical 3.5-mm artery yields different probabilities of restenosis depending on the acute lumen diameter and residual stenosis provided by the new coronary intervention. This example is based on the probability model of binary restenosis (defined as  $\geq 50\%$  reduction in reference diameter at 6-month follow-up) described in Table 4 and demonstrates the expected restenosis rate for different acute results. A 2.45-mm diameter (30% residual stenosis) would have a 39% probability of restenosis, whereas a 3.5-mm diameter (0% residual stenosis) would have a 22% probability of restenosis, and an over-dilated 3.85-mm result ( $-10\%$  residual stenosis) would have a 17% probability of restenosis. A restenosis rate  $< 17\%$  would require unobtainably large acute results (less than  $-10\%$  residual) and thus represents a practical lower limit of restenosis for a device that does not also reduce the intimal hyperplastic response.

stenting compared with atherectomy is due to the larger acute luminal result (3.40 mm versus 2.88 mm,  $p < 0.001$ ) and not to the difference in late loss: Late loss actually tends to be somewhat larger for stents (1.22 mm for stents versus 1.05 mm for atherectomy,  $p = 0.20$ , Table 1). Because the effect of larger acute luminal diameter to reduce restenosis is not device specific and appears to operate equally within both groups (Figure 2), stratification of restenosis by the acute result is possible (Table 7). Although there was a tendency for larger vessels (by reference size) in general to have lower restenosis rates ( $p = 0.01$ , Table 7), the acute postprocedure luminal diameter was the best independent determinant of restenosis (Tables 3 and 4) and more strongly influ-

enced the probability of restenosis by stratified luminal diameters ( $p = < 0.001$ , Table 7).

*Late Loss in Luminal Diameter is Ubiquitous and is Not a Function of the Specific Intervention*

Late luminal diameter, late percent stenosis, and binary restenosis are the net result of the acute gain in luminal diameter provided by an intervention and the subsequent late loss in luminal diameter at 6-month angiography. Examination of the determinants of late loss allows it to be analyzed separately from overall restenosis outcomes (Tables 2–4). In the multivariable model (Table 6), the postprocedure luminal result and

TABLE 7. Actual Observed Restenosis Rates Stratified by Reference and Postprocedure Luminal Size

Segment size	Reference diameter		Postprocedure luminal diameter	
	Segments	Restenosis rate†	Segments	Restenosis rate†
$x < 2.5$ mm	24	46%	28	43%
$2.5 \leq x < 3.0$	60	35%	60	42%
$3.0 \leq x < 3.5$	56	29%	52	17%
$3.5 \leq x < 4.0$	32	16%	36	14%
Total*	172		176	
<i>p</i>		0.01		$< 0.001$

\*Total segments do not add up to 192 because categories  $> 4.0$  mm (too few for adequate stratified analysis) were excluded.

†Defined as  $\geq 50\%$  diameter stenosis.

the postprocedure percent stenosis (but not the specific intervention) were independent determinants of late loss. Acute gain in luminal diameter was also a strong univariable determinant of late loss but it was dropped in the multivariable model because acute gain was highly correlated with the stronger postprocedure luminal diameter variable.

The increase in late loss as a function of a larger immediate result might be expected to compromise the potential benefits provided by a larger acute gain. Although late loss is increased by larger postprocedure luminal diameter, the increase late loss is only a fraction of the acute gain provided by the intervention, so that an overall beneficial effect on net gain and late luminal diameter is still present. Thus, each 1-mm increment in acute gain was offset by only a 0.47-mm increment in late loss (average late loss divided by average acute gain, Table 1). From another perspective, if late loss after the intervention is normally distributed,<sup>11</sup> the fraction of any prospective population that will develop significant (>50%) late re-narrowing can be reduced by further improving in the immediate result. This benefit accrues even though late loss was greater (1.1 mm) after these newer interventions than has been reported by Serruys (0.42 mm)<sup>10</sup> and Nobuyoshi (0.39 mm)<sup>9</sup> after conventional PTCA.

#### *A Geometric Model of Restenosis*

The relation described above allow simple models to be constructed that relate either the late luminal diameter or the probability of restenosis to the immediate postprocedure luminal diameter. Graphic display of this model shows that larger postprocedure luminal diameter is associated with a larger late luminal diameter (Figure 2) and a lower probability of restenosis (Figure 3). If greater acute gain can be safely obtained, the larger immediate result tends to offset any increase in late loss and further reduces the probability of subsequent restenosis. The beneficial effect of obtaining maximal acute luminal dimension on minimizing the probability of subsequent restenosis is clear from Figure 3 and would be consistent with the even lower restenosis rates seen after Palmaz-Schatz stenting of large (8-mm) lumen iliac arteries.<sup>27</sup>

Because newer devices for coronary intervention cause luminal enlargement by different mechanisms, these observations do not necessarily apply to conventional PTCA. Unlike conventional PTCA, a stent can be dilated to a 0% postprocedure stenosis (Table 2) without precipitating abrupt closure, whereas a 30% average residual stenosis is what can be anticipated with conventional PTCA.<sup>4,22,26</sup> Similarly, our average acute gain of 2.41 mm with stenting or atherectomy was much larger than the 1.16-mm acute gain reported by Nobuyoshi<sup>9</sup> in his study of 259 conventional angioplasty patients. Although our average reference diameter was also slightly larger than Nobuyoshi's (3.13 versus 2.84 mm), the twofold-greater acute gain that we achieved confirms the superior dilatation mechanics afforded by the newer devices and the fact that these new devices appear to provide a larger immediate lumen diameter compared with conventional balloon angioplasty.

#### *Limitations*

This study has several potential limitations: First, the use of digital calipers rather than computer-aided edge detection might be questioned. Also, reference catheters were analyzed filled with contrast in order to provide consistency for all measurements. Although the consistent use of filled reference catheters does not bias our results, absolute measurements may theoretically be overestimated. Second, measurement of late loss at 6 months assumes that all treated segments have reached their maximal narrowing. Comparison of 6- and 12-month angiograms in stent patients has demonstrated no further reduction in lumen diameter after 6 months,<sup>27</sup> which parallels prior observations in consecutively studied angioplasty patients that show that intimal hyperplasia reaches its final thickness by 4 months.<sup>9,10</sup> Earlier (less than 4 months) restudy of five symptomatic restenosis patients in our study may have truncated their potential late loss by the premature development of clinical symptoms that triggered further intervention but would not significantly alter the overall model.

Third, the conclusion that the late luminal diameter and the probability of restenosis are determined principally by the immediate postprocedure luminal diameter is clearly a preliminary finding. Examination of Figure 2 demonstrates a strong ( $p < 0.001$ ) association and a narrow confidence interval for the mean relation between the acute and late luminal diameters for the study sample. The fact that the individual point spread and confidence intervals for the population are wide does not reflect weakness in this relation but rather reflects the seemingly random interplay of other biological factors that also affect restenosis. Thus, the effect of the immediate postprocedure luminal diameter on the probability of subsequent restenosis may be best viewed as a platform upon which the other multifactorial determinants of restenosis may operate. Although this limits the predictability of the late result for any individual patient, it does not compromise the fact that larger postprocedure luminal diameter decreases the probability of restenosis for any given patient population. We do not intend to suggest that other potentially significant determinants might not be distilled from the study of a larger data set with comparably complete angiographic follow-up. Such potential covariates of late loss might include coronary vessel location (e.g., right versus left coronary artery), demographic variables (smoking, cholesterol, gender), lesion variables (lesion length, morphology), etc. Similarly, clinical determinants of late loss (e.g., other than acute gain) may also become evident in future studies. Finally, extension of this model to saphenous grafts was not done in this study because of the relatively small number of grafts treated.

#### *Conclusions*

The behavior of late luminal diameter and restenosis after coronary atherectomy and stenting can be explained in part by a quantitative model relating acute postprocedural lumen dimensions to the late (6-month) luminal diameter. Specifically, the examination of continuous geometric variables reveals several important associations: First, the 1.1-mm late loss in luminal

diameter is greater than that reported for PTCA (0.4 mm). Second, whereas late loss is positively correlated with increases in acute gain and larger immediate postprocedure lumen diameter, a net benefit is still obtained because the increase in late loss amounts to only a fraction (0.47) of the increase in acute gain. Third, the late luminal diameter, late percent stenosis, and the probability of restenosis rate are strongly determined by the immediate postprocedure luminal diameter but not by which specific device was used to obtain that diameter. Because the choice of device is dictated by other anatomic, clinical, and cost considerations, our results do not argue for the use of one device in preference to another. It does suggest, however, that each device should be used to obtain the largest acute results safely possible if the goal is to minimize the probability of subsequent restenosis. Finally, although the influence of a larger acute result on reduced restenosis appears to be well established for the treatment population, the simultaneous influence of a variety of other biological factors limits the ability to guarantee freedom from restenosis for any individual patient based on a large postprocedure luminal diameter alone.

Statistical analysis of acute and late results after coronary interventions using continuous variables in a quantitative model may allow more precise examination of restenosis compared with the use of traditional dichotomous techniques. Sensitive evaluation of the potentially beneficial effects of promising pharmacological therapy, newer devices, and their combinations may thus be possible through the detection of subtle differences in the component indexes upon which this model is based.

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