

# Angiographic Patterns of In-Stent Restenosis Classification and Implications for Long-Term Outcome

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**Background**—The angiographic presentation of in-stent restenosis (ISR) may convey prognostic information on subsequent target vessel revascularizations (TLR).

**Methods and Results**—We developed an angiographic classification of ISR according to the geographic distribution of intimal hyperplasia in reference to the implanted stent. Pattern I includes focal ( $\leq 10$  mm in length) lesions, pattern II is  $\text{ISR} > 10$  mm within the stent, pattern III includes  $\text{ISR} > 10$  mm extending outside the stent, and pattern IV is totally occluded ISR. We classified a total of 288 ISR lesions in 245 patients and verified the angiographic accuracy of the classification by intravascular ultrasound. Pattern I was found in 42% of patients, pattern II in 21%, pattern III in 30%, and pattern IV in 7%. Previously recurrent ISR was more frequent with increasing grades of classification (9%, 20%, 34%, and 50% for classes I to IV, respectively;  $P=0.0001$ ), as was diabetes (28%, 32%, 39%, and 48% in classes I to IV, respectively;  $P<0.01$ ). Angioplasty and stenting were used predominantly in classes I and II, whereas classes III and IV were treated with atheroablation. Final diameter stenosis ranged between 21% and 28% ( $P=\text{NS}$  among ISR patterns). TLR increased with increasing ISR class; it was 19%, 35%, 50%, and 83% in classes I to IV, respectively ( $P<0.001$ ). Multivariate analysis showed that diabetes (odds ratio, 2.8), previously recurrent ISR (odds ratio, 2.7), and ISR class (odds ratio, 1.7) were independent predictors of TLR.

**Conclusions**—The introduced angiographic classification is prognostically important, and it may be used for appropriate and early patient triage for clinical and investigational purposes. (*Circulation*. 1999;100:1872-1878.)

**Key Words:** restenosis ■ angioplasty ■ stents ■ angiography

Stents reduce angiographic restenosis in comparison with balloon angioplasty.<sup>1,2</sup> The rate of in-stent restenosis (ISR), although less frequent than postangioplasty restenosis, is becoming increasingly prevalent due to the recent exponential increase in the use of intracoronary stents. Prior studies showed that tubular slotted stents do not recoil and do not allow geometric arterial constriction, which may account for up to 55% of lumen loss in the restenotic process after angioplasty or atherectomy.<sup>3-5</sup> Therefore, ISR is due to neointimal hyperplasia.<sup>6-8</sup> The patterns of in-stent restenosis have been described before as either diffuse (lesion  $> 10$  mm in length) or focal (lesion  $< 10$  mm in length). Previous studies showed a high recurrence rate after treating diffuse ISR with conventional balloon angioplasty.<sup>9-11</sup> Atheroablative devices (ie, excimer laser coronary angioplasty [ELCA] and rotational atherectomy [RA]) have been used in an attempt to improve results.<sup>12,13</sup> However, thus far, no devices have significantly improved outcomes after the treatment of diffuse ISR.

Aside from lesion length, other morphological ISR patterns have not been described or related to prognosis. We developed an angiographic classification for ISR, which was verified by using intravascular ultrasound (IVUS), and assessed long-term clinical follow-up to determine whether this classification schema conveyed important prognostic information.

## Methods

### Patient Population and Treatment of ISR

A total of 325 ISR patients were treated at the Washington Hospital Center from January 1, 1995 through July 31, 1997. We excluded patients if they were treated with nontubular slotted stents ( $n=40$ ), did not undergo IVUS-guided therapy because of operator preference ( $n=26$ ), or were lost to follow-up ( $n=14$ ). The remaining 245 patients were included in this study. Devices to treat ISR were chosen by the operators; they included balloon angioplasty/percutaneous transluminal coronary angioplasty (PTCA), RA, ELCA, and stenting. All devices were applied with standard methods and followed by high-pressure ( $\geq 12$  atm) balloon dilation within the stented area.

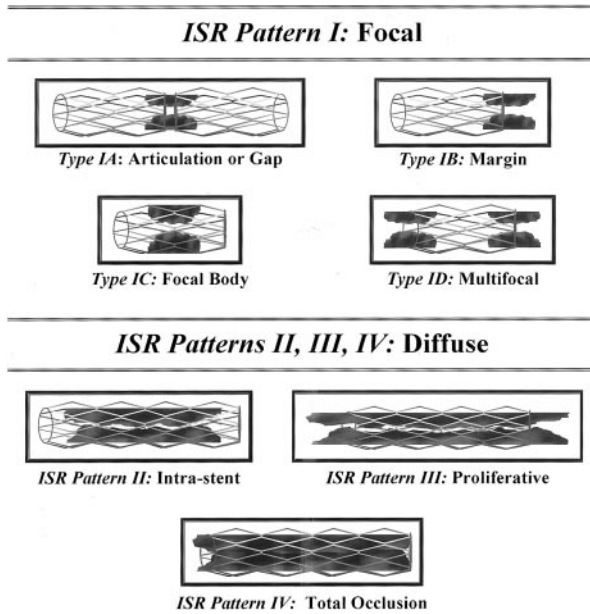
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Schematic image of 4 patterns of introduced classification of ISR in relation to previous dichotomous description of focal vs diffuse ISR. Pattern I contains 4 types (A-D). Patterns II through IV are defined according to geographic position of ISR in relation to previously implanted stent.

**Demographics and Follow-Up**

The hospital charts of all patients were reviewed to obtain clinical demographics and laboratory results. Risk factors for coronary artery disease that were tabulated included diabetes mellitus (only if treated medically), hypertension (only if treated medically), and hyperlipidemia (only if treated medically or if serum cholesterol was >240 mg/dL). Clinical follow-up was performed with telephone contacts or office visits at 1, 3, 6, and 12 months after the procedure. The occurrence of major late clinical events was recorded; these included death, Q-wave myocardial infarction, and target lesion site revascularization (percutaneous or surgical).

**Classification of ISR**

Angiograms were reviewed off-line by 2 independent observers who classified the lesions on separate occasions as follows (Figure).

- Class I: Focal ISR group. Lesions are ≤10 mm in length and are positioned at the unscaffolded segment (ie, articulation or gap), the

body of the stent, the proximal or distal margin (but not both), or a combination of these sites (multifocal ISR)

- Class II: “Diffuse intrastent” ISR. Lesions are >10 mm in length and are confined to the stent(s), without extending outside the margins of the stent(s).
- Class III: “Diffuse proliferative” ISR. Lesions are >10 mm in length and extend beyond the margin(s) of the stent(s).
- Class IV: ISR with “total occlusion.” Lesions have a TIMI flow grade of 0.

**Angiographic Analysis**

An independent core angiographic laboratory performed qualitative and quantitative angiographic analyses. All cineangiograms were analyzed using a computer-assisted, automated, edge-detection algorithm (ARTREK, Quantitative Cardiac Systems). Using the outer diameter of the contrast-filled catheter as the calibration, the minimal lumen diameter (MLD) in diastole before intervention was measured from multiple projections; the results from the single “worst” view were recorded. The reference segment diameter was averaged from user-defined, 5-mm-long, angiographically normal segments proximal and distal to the lesion but between any major side branches. Lesion length was measured as the distance (in millimeters) from the proximal shoulder to the distal shoulder in the projection with the least amount of foreshortening. Ostial lesions were within 3 mm of the coronary ostia or <3 mm distal to a major proximal side branch. These are standard qualitative and quantitative analyses and definitions, and they have been validated and published previously.<sup>14</sup>

**IVUS Imaging**

A total of 293 lesions in 245 patients were considered for inclusion in the present analysis. Five lesions were excluded because they had a poorly visualized stent in the preprocedure angiogram and IVUS assessment was discordant with the angiographic class. Preintervention IVUS imaging was available for all patients, and lesion classification was confirmed qualitatively by IVUS in all 288 lesions included in this study. All IVUS imaging studies were performed before intervention and only after intracoronary administration of 200 μg of nitroglycerin. The IVUS studies were performed using 1 of 2 commercially available systems. The first (InterTherapy/Cardiovascular Imaging Systems Inc) incorporated a single-element, 25-MHz transducer and an angled mirror mounted on the tip of a flexible shaft that was rotated at 1800 RPM within a 3.9F short monorail polyethylene imaging sheath to form planar cross-sectional images in real time. The second (Cardiovascular Imaging Systems Inc.) incorporated a single-element, 30-MHz, beveled transducer within either a 2.9F long monorail imaging catheter having a common distal lumen design (the distal lumen alternatively accommodates the imaging core or the guidewire but not both) or a 3.2F

**TABLE 1. Baseline Patient Characteristics**

	Patterns of ISR			
	Focal (n=91)	Intrastent (n=50)	Proliferative (n=84)	Total Occlusion (n=20)
Age, y	62±11	61±10	63±11	62±10
Male sex	72	73	68	70
Diabetes mellitus*	28	32	39	48
Hypertension	78	79	80	78
Unstable angina	69	72	70	71
Hyperlipidemia	69	70	71	68
History of MI	61	59	60	58
Implanted stents/lesion, n	1.4±0.8	1.7±0.9	1.6±0.8	1.8±1.1
Prior ISR*	9	20	34	50

Values are expressed as percents; continues variables are mean±SD. MI indicates myocardial infarction.

\*P<0.01 by ANOVA.

TABLE 2. Lesion Characteristics

	Patterns of ISR			
	Focal (n=121)	Intrastent (n=61)	Proliferative (n=86)	Total Occlusion (n=20)
Vessel				
Left main	2	4	2	3
Left anterior descending	24	26	27	24
Left circumflex	9	13	14	15
Right coronary artery	29	27	32	12
Saphenous vein graft	37	31	25	34
Aorto-ostial location	26	15	17	12
Types of implanted stents				
Palmaz-Schatz	86	82	84	80
Multilink	12	10	6	20
Microstent	2	8	10	0

Values are expressed as percentages.  $P=NS$  for all comparisons.

short monorail imaging catheter. With both systems, the transducer was withdrawn automatically at 0.5 mm/s to perform the imaging sequence. The IVUS catheter was advanced at least 10 mm distal to the lesion, the video recorder was turned on, the transducer pullback device was activated, and the entire artery was imaged to the aorto-ostial junction. IVUS studies were recorded on 1/2-inch high-resolution s-VHS tapes for off-line analysis. Images were evaluated off-line by an independent, blinded, core IVUS laboratory to verify the accuracy of the angiographic classification, given the limited radiopacity of the stents. The classification schema used was the same used with angiographic criteria.

### Quantitative IVUS Measurements

In-stent restenosis lesion length was measured from number of seconds on videotape. At a pullback speed of 0.5 mm/s, 2 s of videotape playback equals 1 mm of axial stent length. This has been validated in vivo.<sup>15</sup> In-stent restenosis length was defined as the axial length of a stented or nonstented segment (in millimeters) in which  $\geq 75\%$  of intimal hyperplasia (for stented segment) or plaque+media (for nonstented segment) was seen in a cross-sectional area (CSA).

CSA measurements by IVUS have been previously validated.<sup>16-23</sup> Area measurements were performed with a commercially available program for computerized planimetry (TapeMeasure, Indec Systems). The smallest lumen and stent cross sections were identified before and after intervention within the stented segments and traced. The intimal hyperplasia CSA was calculated as stent CSA minus lumen CSA. When the plaque encompassed the catheter, the lumen was assumed to be the physical size of the imaging catheter.

### Statistics

Statistical analysis was performed using StatView 4.02 (Abacus Concepts) or SAS (Statistical Analysis Systems, SAS Institute Inc).

Categorical data are presented as frequencies. Data are presented as mean  $\pm$  1SD. Categorical data were compared using Fisher's exact test. Continuous variables were compared using factorial ANOVA or ANOVA for repeated measures with post hoc analysis.  $P<0.01$  was considered significant. The primary end point was the association of lesion classification with target lesion revascularization (TLR). Univariate variables with  $P<0.2$  were entered into the multivariate model; forward stepping was used to determine the independent predictors of TLR.

### Results

Of the 288 lesions analyzed, 42% (n=121) were focal (class I), 21% (n=61) diffuse intrastent (class II), 30% (n=86) diffuse proliferative (class III), and 7% (n=20) total occlusions. Baseline patient characteristics are presented in Table 1. All groups were well-matched with respect to age and sex. Increasing levels of ISR classification were associated with an increasing prevalence of diabetes mellitus (28%, 32%, 39%, and 48% for classes I to IV, respectively;  $P<0.01$ ) and the number of prior episodes of ISR (9%, 20%, 34%, and 50% for classes I to IV, respectively;  $P<0.01$ ).

Lesion location, including aorto-ostial position, was comparable in all ISR classes, as indicated in Table 2. Device selection was significantly different among the ISR classes. Lesions were treated predominantly with PTCA and stent alone in classes I and II, whereas classes III and IV were exclusively treated with an atheroablative device (RA, ELCA), used either alone or in combination with stenting

TABLE 3. Devices Used for Treatment of ISR

	Patterns of ISR			
	Focal (n=121)	Intrastent (n=61)	Proliferative (n=86)	Total Occlusion (n=20)
PTCA*	53	34	0	0
Stent alone*	22	0	12	0
RA $\pm$ stent*	12	33	48	27
ELCA $\pm$ stent*	22	33	38	73

Values are expressed as percentages.

\* $P<0.01$  by ANOVA.

**TABLE 4. Quantitative Angiographic Results**

	Patterns of ISR			
	Focal (n=121)	Intrastent (n=61)	Proliferative (n=86)	Total Occlusion (n=20)
Preprocedure				
Lesion length, mm*	6.7±3.6	16.4±6.3	35.5±17.6	NA
Stent length, mm	18.3±3.5	24.6±6.2	27.1±5.3	25.7±5.9
RVD, mm*	3.1±0.6	2.7±0.4	2.8±0.8	2.5±0.7
MLD, mm*	1.1±0.6	0.8±0.3	0.5±0.3	0.0±0.0
DS, %*	64±17	70±13	82±10	100±0
Final				
RVD, mm*	3.2±0.6	2.8±0.4	2.8±0.6	2.5±0.6
MLD, mm*	2.5±0.9	2.1±0.6	2.2±0.5	1.8±0.4
DS, %	24±17	21±13	24±15	28±11
Any dissection, %	2.1	2.5	4.2	4.1
Abrupt closure, %	0.0	0.0	0.0	0.0

Continuous variables are mean±SD. DS indicates diameter stenosis, and RVD, reference vessel diameter.

\**P*<0.01 by ANOVA.

(Table 3). Procedural success was achieved in all cases, without evidence of any abrupt vessel closure.

**Angiographic Results**

By classification definition, lesion length increased with increasing levels of ISR classification (Table 4). Class I ISR lesions were associated with larger vessels, and the final MLD achieved was also larger compared with the other classes. Class IV ISR lesions were associated with the smallest vessels, and the MLD achieved was the smallest compared with the other ISR classes. However, all classes achieved similar percent diameter stenosis after transcatheter therapy, despite the different revascularization strategies.

**IVUS Results**

Qualitative IVUS analysis completely verified the accuracy of the angiographic classification of ISR. Quantitative IVUS

measurements (Table 5) verified the angiographic observations that patterns III and IV occurred in vessels with smaller reference dimensions that had a smaller postintervention luminal area. However, the final intimal hyperplasia area was similar among all groups.

**Long-Term Results**

One-year clinical event rates were uniformly high, without significant differences among the groups with respect to death or myocardial infarction (Table 6). However, a significant increase occurred in TLR with increasing levels of ISR classification (class I, 19%; class II, 35%; class III, 50%; and class IV, 83%; *P*<0.0001). This was due to significantly increasing rates in both percutaneous (15%, 26%, 36%, and 67% in classes I through IV, respectively; *P*<0.0001) and surgical (4%, 8%, 14%, and 17% in classes I through IV, respectively; *P*<0.0001) revascularization procedures.

**TABLE 5. Quantitative Results of IVUS**

	Patterns of ISR			
	Focal (n=121)	Intrastent (n=61)	Proliferative (n=86)	Total Occlusion (n=20)
Preprocedure				
Lesion length, mm*	7.3±3.2	18.3±7.5	38.2±16.5	NA
Ref. lumen CSA, mm <sup>2*</sup>	8.6±3.1	7.8±2.2	7.1±2.5	NA
Min. lumen CSA, mm <sup>2</sup>	2.0±1.4	1.8±1.3	1.7±1.2	NA
Min. stent CSA, mm <sup>2</sup>	7.3±2.1	7.1±2.0	6.7±2.0	NA
IH CSA, mm <sup>2</sup>	5.3±1.9	5.3±1.6	5.0±1.6	NA
Final				
Min. lumen CSA, mm <sup>2*</sup>	5.0±1.2	4.5±1.4	4.2±1.4	3.5±1.2
Min. stent CSA, mm <sup>2*</sup>	8.6±2.2	8.3±2.1	8.0±1.9	7.5±2.0
IH CSA, mm <sup>2</sup>	3.5±1.6	3.8±1.7	3.8±1.5	3.9±1.8

Values are mean±SD. IH indicates intimal hyperplasia; Min, minimal; and Ref, reference.

\**P*<0.01 by ANOVA.

TABLE 6. One-Year Events

	Patterns of ISR			
	Focal	Intrastent	Proliferative	Total Occlusion
Death	2.5	2.6	3.3	0.0
Myocardial infarction	1.2	2.6	0.0	0.0
TLR*	19.1	34.5	50.0	83.4
PTCA*	14.8	26.3	36.3	66.7
CABG*	4.3	8.2	13.7	16.7

Values are expressed as percentages. CABG indicates coronary artery bypass surgery.

\* $P < 0.0001$  by ANOVA.

### Multivariate Analysis

We introduced diabetes, reference diameter, final MLD, left anterior descending artery location, number of implanted stents, recurrent ISR, stent type and length, lesion length, and the pattern of ISR according to the introduced angiographic classification in a multivariable model to identify predictors of TLR. The only parameters that independently predicted TLR after treatment of ISR were the pattern of ISR according to the angiographic classification (odds ratio, 1.7;  $P=0.0380$ ), occurrence of previous ISR (odds ratio, 2.7;  $P=0.0006$ ), and presence of diabetes mellitus (odds ratio, 2.8;  $P=0.0003$ ). Final MLD and reference vessel size were eliminated in this model.

### Discussion

ISR presents in various angiographic patterns, which can be classified angiographically. The method of classification we describe relates not only to lesion length but, as introduced in this article for the first time, also to the geographic position of the neointimal proliferative response relative to the initially implanted stent. Angiographic definition of these patterns had an excellent correlation with IVUS assessment, demonstrating that even minimal stent radiopacity was adequate for appropriate recognition of the ISR class angiographically.

The results of the present investigation demonstrate that the classification system we used to characterize the pattern of ISR independently predicted the long-term need for repeat revascularization. The only other 2 predictors were diabetes mellitus and prior episodes of recurrent ISR. In a previous report, we specifically identified diabetes as a powerful determinant of neointimal hyperplasia.<sup>24</sup> Furthermore, this finding has been reported by others.<sup>25</sup>

### Characteristics of ISR

The above 3 factors reflect the intrinsic biological property of the vessel wall to have a tendency to mount an exaggerated neointimal response to injury. The initial proliferative stimulus was initial stent implantation. This resulted in neointimal hyperplasia, and the magnitude of the response was captured by our classification scheme. Accordingly, this response was profound in patients who presented with the highest levels of the classification, ie, proliferative ISR or total occlusion. Indeed, increasing levels of ISR classification were characterized by increased plaque burden at the lesion site and increasing lesion length (Tables 4 and 5). Despite optimal interventional treatment and achievement of similar final

diameter stenosis, the minimal luminal dimensions were less favorable in the highest ISR classes. However, multivariate analysis determined that the independent predictor of future target vessel failure was the preintervention ISR pattern (Figure), whereas the final postprocedure MLD was eliminated. This is a novel paradigm in which a preintervention variable prevails over the conventional results of transcatheter therapy with respect to long-term results.

In addition to the magnitude of intimal hyperplasia, the second characteristic component of this biological phenomenon was the evidence for repeated recurrences after transcatheter therapy. This unique response to vascular injury seen in the highest ISR classes is highly reproducible after repeat vascular injury, with or without a new stent, suggesting a possible genetic basis. We previously reported that intimal hyperplasia thickness is independent of stent size, which implies that ISR disproportionately affects smaller arteries.<sup>26</sup> Other groups have also reported on the importance of previous recurrent ISR as a powerful determinant of future target vessel failure.<sup>27</sup> Moreover, the time to initial ISR has been reported to correlate with future recurrences.<sup>28</sup> These are specific features for ISR that suggest the involvement of a unique response to stent injury in certain individuals that does not conform to the rules identified for post-PTCA restenosis. This response occurs early, is profound, and does not correlate with inadequate device therapy.

The reason for this exaggerated initial neointimal hyperplasia occurring in response to stenting and, subsequently, to any intervention at the target lesion site is unknown. Recent studies have implicated genetic factors in the pathogenesis of ISR (ie, polymorphism of the gene encoding for the angiotensin-converting enzyme correlated with diffuse ISR).<sup>29</sup> Although these results are preliminary, they support the theory of an inherent, intrinsic factor as the main driving force of this process, especially in the higher levels of the classification (ie, proliferative ISR or total occlusion).

### Treatment of ISR

Percutaneous intervention for ISR is safe and yields good angiographic results. Previous studies showed similarly disappointing long-term results after the treatment of diffuse ISR.

An initial hypothesis was that the tissue within the stent may never be completely ablated and, therefore, it acts a stimulus for further tissue proliferation. The luminal result obtained after the treatment of ISR is never as large as at the



time of original stent implantation, and acute tissue recoil may occur.<sup>30</sup> The use of stents to treat ISR abolishes the remaining tissue within the original stent, as shown by IVUS. However, despite the full recovery of the original lumen, stents may also have poor long-term results, thereby contributing to the inadequacy of conventional interventional therapies for the treatment of ISR. However, long-term outcome is heavily influenced by preprocedure patient-related (diabetes) and ISR-related (pattern, previous early recurrence) characteristics.

Our study documents the very high rate of subsequent revascularization after interventional therapy with currently available treatment modalities in patients presenting with the higher ISR classes. Because the assignment of an ISR class can be performed angiographically, early triage of these patients to appropriate therapy is feasible. With respect to current research directions, our study provides the means for proper identification of patients who may benefit most from the use of adjunct therapy (ie, radiation, molecular, or medical). Intracoronary radiation was recently reported as an effective treatment for the high-risk ISR population, and it may complement the deficiency of conventional interventional therapies.<sup>31</sup>

Early and appropriate allocation of healthcare resources for high-risk ISR patients using our angiographic classification may improve cost-effective patient management and help conceptualize newer revascularization strategies.

### Limitations

This is a retrospective analysis and is, therefore, subject to the limitations pertinent to this type of clinical investigation. Data were retrieved from our Quality Assurance Database. The database is updated by an independent coordinating center, which collects and enters the same data for all patients undergoing percutaneous interventions, regardless of clinical indications or disease. We needed to verify the accuracy of the angiographic classification by IVUS and, therefore, excluded patients without IVUS imaging. Because IVUS is routinely available at our institution, only a small number of patients were excluded for this reason. Patients were not excluded because of an inability to cross the lesion with the IVUS catheter. Patients with total occlusions were also included.

### Conclusions

ISR presents with various angiographic patterns that provide important prognostic information. Diffuse intrastent, proliferative, and totally occluded ISRs represent a spectrum of increasing disease severity (exaggerated neointimal response), which determines, along with diabetes and previous episodes of recurrent ISR, long-term outcome. In contrast, luminal dimensions after interventional therapy are less important determinants of late clinical results after treatment of ISR. An intrinsic patient-related process seems to be responsible for the high ISR classes, which suggests that such clinical presentations may be due to a distinct biological process. The angiographic classification of ISR provides the means for appropriate and early patient triage for clinical and investigational purposes.

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