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Long-Term Outcomes After the Percutaneous Treatment of Drug-Eluting Stent Restenosis

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Objectives This study sought to evaluate the long-term angiographic and clinical outcomes after the treatment of drug-eluting stent in-stent restenosis (DES-ISR) based on the angiographic pattern of restenosis.

Background Long-term outcomes after percutaneous treatment of DES-ISR are unclear.

Methods This study performed a retrospective analysis of 481 consecutive de novo DES-ISR lesions (n = 392) treated percutaneously between August 2002 and July 2007. The lesions were divided based on the pattern of restenosis: focal (305; 63.4%), diffuse (120; 24.9%), and occlusive (56; 11.6%).

Results The majority (65%) of patients had angina or ischemia on presentation and 13% had an acute coronary syndrome. Angiographic follow-up after treatment of DES-ISR was available in 65.5% of lesions. A second angiographic restenosis occurred in 29.1% of the focal group, 45.8% ($p = 0.007$) of the diffuse, and 65.6% ($p < 0.0001$) of the occlusive. The pattern of DES-ISR predicted the pattern of recurrence: occlusive reoccluded in 66.7%; diffuse recurred as diffuse or occlusive in 57.9%; focal as focal in 67.2%. During a median follow-up of 2.97 years (interquartile range: 2.37 to 3.89), major adverse cardiac events occurred in 32.8% of patients with no significant differences among the focal, diffuse, and occlusive groups (30.9%, 38.7%, 31.1%; $p = 0.38$). Diffuse restenosis was associated with a significantly higher target lesion revascularization rate compared with focal (27.1% vs. 15.8%; $p = 0.008$). A disparity between restenosis (65.6%) and target lesion revascularization (18.5%) rates for occlusive DES-ISR suggests that as many recurrent restenoses were occlusive, they were not retreated.

Conclusions DES-ISR identifies a high-risk cohort that is at an increased risk of events, in particular repeat revascularization, during long-term follow-up. The initial pattern of restenosis is the most important predictor of recurrent restenosis or the need for subsequent reintervention. (J Am Coll Cardiol Intv 2011;4:155–64) © 2011 by the American College of Cardiology Foundation

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Drug-eluting stents (DES) have dramatically diminished but not eradicated restenosis and even though they have resulted in single-digit rates in simple lesions, it is not unusual to see double-figure rates of restenosis in more complex lesions and real-world studies (1,2). The widespread use of DES and incorporation into daily practice has led to significant absolute numbers of patients presenting with DES failure (3). Although the optimal management strategy of DES in-stent restenosis (DES-ISR) remains unclear, repeat percutaneous intervention remains the most frequently used treatment (1,3–5). However, the long-term angiographic and clinical outcomes after the percutaneous treatment of DES-ISR are unknown.

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Methods

All consecutive patients successfully treated percutaneously for their first episode of DES-ISR at our centers between August 2002 and July 2007 were included in this retrospective analysis. The study period was chosen from the first episode of DES-ISR treated at our institutions and to allow a minimum of 2 years of clinical follow-up on all patients in the study. Patients were included in the study at the time of treatment for their first episode of DES-ISR after treatment of a de novo lesion, that is, a de novo DES-ISR occurring in a de novo lesion. Exclusion criteria included: restenotic DES implanted at the index lesion to treat bare-metal stent or plain old balloon angioplasty (POBA) restenosis; previous treatment of a DES-ISR; and previous brachytherapy to the treated vessel. A previous episode of bare-metal stent restenosis in another vessel was not an exclusion criterion but the DES-ISR had to be the first episode in that patient. In addition, 8 patients with occlusive restenosis in whom successful recanalization was not possible were excluded from the current analysis. In Figure 1, we provide a flow chart describing how patients were selected for this study.

Abbreviations and Acronyms

DES = drug-eluting stent(s)
ISR = in-stent restenosis
MACE = major adverse cardiac event(s)
MI = myocardial infarction
POBA = plain old balloon angioplasty
ST = stent thrombosis
TLR = target lesion revascularization

All patients provided informed consent for the procedure and subsequent data collection and analysis for research purposes. Procedural anticoagulation and antiplatelet therapy followed standard protocols. The choice of treatment strategy was at the operator's discretion. Aspirin was continued indefinitely and thienopyridine prescribed for at least 1 month after POBA and at least 6 to 12 months after repeat DES implantation. Angiographic follow-up was clinically driven or scheduled at the operator's discretion.

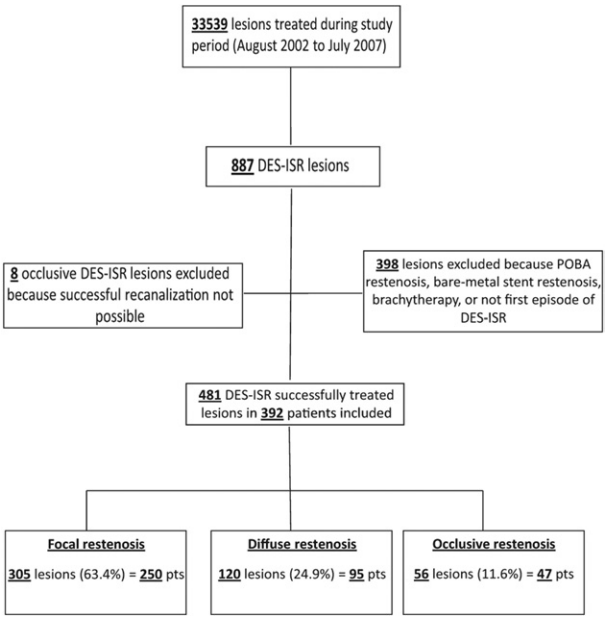

Figure 1. Consort-Type Flow Chart Showing Patient Selection for This Study

During the study period, 887 drug-eluting stent in-stent restenosis (DES-ISR) lesions were treated at our institutions, of which 406 were excluded because of prior treatment with a stent, balloon, or brachytherapy. Another 8 occlusive restenotic lesions were also excluded from this analysis because successful recanalization was not possible. POBA = plain old balloon angioplasty.

Data collection, end points, and study definitions. Clinical follow-up was performed by telephone contact or office visit at 1, 6, and 12 months after the index procedure. Angiographic follow-up was clinically driven or scheduled at the operator's discretion. Angiographic success was defined as a final residual stenosis <20% with TIMI (Thrombolysis In Myocardial Infarction) flow grade 3 (6). DES-ISR was defined as a luminal diameter stenosis of >50% within a DES or within 5 mm of the stent edges. The lesions were divided according to pattern of restenosis into 3 groups: focal, diffuse, and occlusive (7). Focal ISR lesions were defined as ≤10 mm in length and positioned at the body of the stent, the proximal or distal margin, or a combination of these sites, whereas diffuse ISR was defined as >10 mm in length. Proliferative restenosis was included in the latter group because of the low prevalence (only 4 cases) in our population. Occlusive DES-ISR were defined as completely occluded stents that were not associated with acute clinical presentations, such as an acute coronary syndrome or occluded DES, in which no intracoronary thrombus was visible after recanalization.

The clinical end points analyzed were periprocedural myocardial infarction (MI), death, after-discharge MI, stent thrombosis (ST), target vessel revascularization, target le-

sion revascularization (TLR), and major adverse cardiac events (MACE). MACE was defined as a composite of death, MI, and target vessel revascularization during the follow-up period and was evaluated on a per-patient basis. We also analyzed TLR separately on a per-lesion basis. All deaths were considered cardiac unless otherwise documented. We defined post-procedural non–Q-wave MI as a creatinine kinase-myocardial band elevation of >3 times the upper limit of normal (8). Creatinine kinase was routinely measured after percutaneous coronary intervention in all patients at both centers. Nonprocedural or after-discharge MI was defined as an elevation of troponin above the upper range limit in combination with at least 1 of the following: symptoms of ischemia; electrocardiographic changes indicative of new ischemia; or the development of pathological Q waves on electrocardiogram. We defined TLR as repeat revascularization within the stent or within the 5-mm borders proximal or distal to the stent edge at the follow-up angiogram. Target lesion revascularization was considered ischemic-driven if associated with a positive functional study result and/or ischemic symptoms and a target lesion diameter stenosis of ≥50% by visual estimation, or a target lesion diameter stenosis of ≥70% with or without documented ischemia. Multiple TLR was defined as more than 1 TLR of the same restenotic lesion. As many restenotic lesions, especially reocclusive lesions, may have not been treated at follow-up because of concerns by the operator of the futility of this treatment, we were concerned that TLR would not correctly reflect the outcomes of the different patterns of DES-ISR. Thus, we defined a new end point for this study to measure this potential disparity, called theoretical TLR. Theoretical TLR was defined as the estimated TLR if every restenosis was treated, that is, the sum of TLR plus untreated angiographic restenosis. To clarify this disparity, we also calculated the percentage of restenotic lesions that were treated by dividing the number of TLR by the total number of lesions with angiographic restenosis. We defined target vessel revascularization as any repeat revascularization of the target vessel. The definition of ST was in accordance with the Academic Research Consortium definitions of definite, probable, possible ST (9).

Statistical methods. Continuous variables are presented as mean ± SD or medians (interquartile range [IQR]) and categorical variables as frequencies (%). The normality of the distribution of the continuous variables was tested by means of the Kolmogorov-Smirnov goodness-of-fit test. Continuous variables were compared among groups using analysis of variance with Fisher least-significant difference post-hoc tests for correction for multiple comparisons. Categorical variables were compared with chi-square statistic or Fisher exact test where appropriate. Patients lost to follow-up in whom no event had occurred before the follow-up windows were not included in the denominator for calculations of binary end points.

Exploratory survival analysis was performed to assess the impact of restenosis type on the risk of TLR and angiographic restenosis by means of Cox regression analysis using purposeful selection of covariates (10). Candidate variables included covariates associated at univariate analysis with TLR and angiographic restenosis (all with a p value <0.2) as well as variables judged to be of clinical importance from previous published literature. Restenosis type was forced into the multivariable model as an entry criteria because it is the variable of interest. As observations recorded in the same patient cannot be considered independent (11), the sandwich estimator of variance-covariance matrix was employed to take into account clustered data (more lesions within the same subject).

The results are reported as adjusted hazard ratios with associated confidence intervals (CIs). The proportional hazards assumption of the final model was assessed and verified (10). Goodness-of-fit of the Cox regression model was assessed with the Grønnesby-Borgan-May test (12,13). A p value <0.05 was considered statistically significant, and all reported p values are 2-sided. Statistical analysis was performed using Stata software (version 7.0, Stata Corporation, College Station, Texas).

Results

During the study period, 887 DES-ISR lesions were treated at our institutions, of which 406 were excluded because of prior treatment with a stent, balloon, or brachytherapy (Fig. 1). Thus, a total of 481 lesions in 392 patients that were successfully treated percutaneously for their first episode of DES-ISR were analyzed for this study. The pattern of restenosis was focal in 305 lesions (63.4%), diffuse in 120 (24.9%), and occlusive in 56 (11.6%).

Baseline clinical characteristics of the patients and lesions treated are presented in Table 1. Clinical characteristics in patients presenting with different patterns of DES-ISR were similar except for a higher incidence of insulin-treated diabetes in diffuse restenosis. The median time from implantation of DES at the index lesion to treatment for DES-ISR was 224 days (IQR: 175 to 330 days) and was similar for all 3 patterns of restenosis (p = 0.97). The majority (65%) of patients treated for DES-ISR in this study had angina or ischemia on presentation. DES-ISR resulted in an acute coronary syndrome in 13% of patients, and this acute presentation was more frequent with diffuse rather than focal or occlusive restenosis (21.1% vs. 9.2% vs. 14.9%; p = 0.012). In patients with occlusive restenosis, the index lesion treated with a DES was more likely to be a chronic total occlusion (p < 0.0001) and possibly as a result longer stent lengths were implanted (p = 0.006). Sirolimus-eluting and paclitaxel-eluting stents were the most frequently implanted stents during the study period and thus represented the most frequent stent type in each restenosis

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Table 1. Baseline Clinical Characteristics of the Patients and the Lesions Treated in the 3 Groups

	Overall	Focal	Diffuse	Occlusive	p Value
Patients	392	250	95	47	—
Age, yrs	63.9 ± 9.7	63.6 ± 9.3	65.4 ± 10.6	62.1 ± 9.7	0.12
Male	327 (83.4)	215 (86)	74 (77.9)	38 (80.9)	0.17
Ejection fraction, %	53.5 ± 10.2	53.5 ± 9.8	52.7 ± 11.6	55.2 ± 9.3	0.42
Previous MI	163 (41.6)	105 (42)	42 (44.3)	16 (34)	0.50
Previous CABG	103 (26.3)	69 (27.6)	20 (21.1)	14 (29.8)	0.39
Family history	176 (44.9)	108 (43.3)	40 (42.1)	28 (59.6)	0.10
Hypertension	283 (72.2)	183 (73.2)	67 (70.5)	33 (72.2)	0.84
Hypercholesterolemia	294 (75)	188 (75.2)	73 (76.8)	33 (70.2)	0.69
Current smoker	51 (13)	34 (13.6)	11 (11.6)	6 (12.8)	0.88
Diabetes mellitus	146 (37.2)	84 (33.6)	41 (43.2)	21 (44.7)	0.14
Diet-controlled	13 (3.3)	8 (3.2)	2 (2.1)	3 (6.4)	0.40
Oral therapy	87 (22.2)	54 (21.6)	20 (21.1)	13 (27.7)	0.63
Insulin therapy	46 (11.7)	22 (8.8)	19 (20)	5 (10.6)	**FvD 0.004** FvO 0.68 DvO 0.16
Clinical presentation					
ACS	50 (12.8)	23 (9.2)	20 (21.1)	7 (14.9)	**FvD 0.003** FvO 0.25 DvO 0.3
Stable angina	120 (30.6)	73 (29.2)	35 (36.8)	12 (25.5)	FvD 0.17 FvO 0.6 DvO 0.17
Silent ischemia	85 (21.7)	57 (22.8)	14 (14.7)	14 (29.8)	FvD 0.09 FvO 0.3 **DvO 0.03**
Planned angiographic follow-up	137 (34.9)	97 (38.8)	26 (27.4)	14 (29.8)	FvD 0.05 FvO 0.24 DvO 0.76
Lesions	481	305	120	56	—
Lesion characteristics at initial DES implantation	—	—	—	—	—
Bifurcation	123 (25.6)	88 (28.9)	28 (23.3)	7 (12.7)	FvD 0.25 **FvO 0.01** DvO 0.1
Chronic total occlusion	75 (15.6)	33 (10.8)	22 (18.3)	20 (36.4)	**FvD 0.04** **FvO <0.0001** **DvO 0.001**
Details of DES that restenosed					
SES, n (%) [% of SES]	271 (56.3)	194 (63.6) [71.6]	54 (45) [19.9]	23 (41.1) [8.5]	**FvD <0.0001** **FvO 0.002** DvO 0.62
PES, n (%) [% of PES]	189 (39.3)	103 (33.8) [54.5]	56 (46.7) [29.6]	30 (53.6) [15.9]	**FvD 0.01** **FvO 0.005** DvO 0.39
ZES, n (%) [% of ZES]	14 (2.9)	5 (1.6) [35.7]	7 (5.8) [50]	2 (3.6) [14.3]	**FvD 0.02** FvO 0.33 DvO 0.52
TES, n (%) [% of TES]	7 (1.5)	3 (1) [42.9]	3 (2.5) [42.9]	1 (1.8) [14.3]	0.49
Stent diameter, mm	2.84 ± 0.36	2.85 ± 0.34	2.85 ± 0.37	2.74 ± 0.41	0.20
Stent length, mm	28.66 ± 13.34	27.46 ± 12.64	29.53 ± 12.66	33.74 ± 17.15	FvD 0.17 **FvO 0.002** DvO 0.06

Data are presented as absolute numbers and percentages or mean ± SD, unless otherwise specified. **Bold** p values are statistically significant.

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; DES = drug-eluting stent(s); DvO = diffuse versus occlusive; FvD = focal versus diffuse; FvO = focal versus occlusive; MI = myocardial infarction; PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s); TES = tacrolimus-eluting stent(s); ZES = zotarolimus-eluting stent(s).

pattern. In comparison with sirolimus-eluting stents, paclitaxel-eluting stents were more frequently associated with diffuse (29.6% vs. 19.9%; p = 0.02) and occlusive restenosis (15.9% vs. 8.5%; p = 0.02) but less frequently with focal restenosis (54.5% vs. 71.6%; p < 0.0001).

Procedural characteristics are displayed in Table 2. DES-ISR was treated more often with repeat DES implantation rather than balloon angioplasty in all types of restenosis (p < 0.05 for all comparisons). In diffuse and occlusive restenosis, the operator was more likely to implant a DES that eluted a different drug to the one that restenosed. Intravascular ultrasound usage was similar in the 3 groups.

Angiographic follow-up was available in 315 lesions (65.5%): 200 lesions (65.6%) in the focal group; 83 lesions (69.2%) in the diffuse group; and 32 lesions (57.1%) in the occlusive group (p = 0.30). Angiographic outcomes and patterns of recurrent restenosis are shown in Figure 2 and Table 3. There was a highly significant difference in restenosis rates after treatment between the groups, with a much higher recurrent restenosis in the occlusive (65.6%) and diffuse (45.8%) groups. In general, in all 3 groups, the same or a worse pattern of restenosis recurred in two-thirds of the restenotic lesions, that is, two-thirds of focal lesions recurred as focal ISR, two-thirds of occlusive ISR reoccluded, and about two-thirds of diffuse lesions recurred as diffuse or occlusive restenosis. The rate of recurrent restenosis was similar in diabetics versus nondiabetics (35.2% vs. 38.4%; p = 0.65). For the focal restenosis group, which represents the largest subgroup in this study, the rate of recurrent restenosis was again similar in diabetics versus nondiabetics (30.6% vs. 28.1%; p = 0.84). Furthermore, the rate of recurrent restenosis after treatment of focal DES-ISR was similar after POBA (42.4% vs. 36%; p = 0.72) and repeat DES implantation (20.5% vs. 23.4%; p = 0.91) in diabetics versus nondiabetics, respectively.

Clinical follow-up was available in 387 (99%) patients with a median follow-up time of 2.97 years (IQR: 2.37 to 3.89 years) and ≥2 years of follow-up available in 95% of eligible patients. The duration of clinical follow-up was not statistically different between the 3 groups (p = 0.41). There were no in-hospital deaths or periprocedural revascularizations and the rate of periprocedural MI was similar in the 3 groups (Table 4). About one-third of patients with DES-ISR experienced a MACE during long-term follow-up, irrespective of the pattern of restenosis treated at initial presentation. There were no significant differences between the groups in the rates of death or MI. The rates of TLR were significantly higher for diffuse compared with focal DES-ISR, both when calculated per-patient (28% vs. 16.5%; relative risk [RR]: 1.7, 95% CI: 1.11 to 2.61; p = 0.02) and per-lesion (27.1% vs. 15.8%; RR: 1.7, 95% CI: 1.16 to 2.55; p = 0.008). Although restenosis rates were highest for the occlusive group, TLR rates were not concordantly high, suggesting that many recurrent restenoses were not retreated. Indeed only 47.6% of occlusive DES-ISR were retreated in comparison with 82.6% focal and 84.2% of diffuse restenoses. We also calculated what the theoretical TLR rate would have been if every restenosis had been treated. The difference between actual and theoretical

Table 2. Procedural Characteristics of the Lesions Treated

	Overall	Focal	Diffuse	Occlusive	p Value
Lesions, n	481	305	120	56	—
Repeat DES implantation	318 (66.1)	180 (59)	89 (74.2)	49 (87.5)	**FvD 0.004** **FvO <0.0001** **DvO 0.045**
Homo-DES	111 (34.9)	73 (40.6)	26 (29.2)	12 (24.5)	FvD 0.07
Hetero-DES	207 (65.1)	107 (59.4)	63 (70.8)	37 (75.5)	**FvO 0.04** DvO 0.55
BMS implantation	4 (8)	2 (0.7)	2 (1.7)	0	**<0.0001**
POBA	159 (33.1)	123 (40.3)	29 (24.2)	7 (12.5)	**FvD 0.002** **FvO <0.0001** DvO 0.13
Max balloon diameter, mm	2.62 ± 1.01	2.61 ± 1.05	2.68 ± 0.92	2.49 ± 0.93	0.50
Max inflation pressure, atm	17.64 ± 5.51	17.67 ± 5.68	17.46 ± 4.95	17.87 ± 5.80	0.89
Stent diameter, mm	3.02 ± 0.46	3.07 ± 0.47	3.05 ± 0.41	2.77 ± 0.43	FvD 0.81 **FvO <0.0001** **DvO 0.001**
Stent length, mm	24.76 ± 13.99	19.13 ± 7.57	28.48 ± 11.79	39.08 ± 22.06	**FvD <0.0001** **FvO <0.0001** **DvO <0.0001**
IVUS	105 (21.8)	68 (22.3)	27 (22.5)	10 (17.9)	0.74

Values are presented as n (%) or mean ± SD. **Bold** p values are statistically significant.

BMS = bare-metal stent(s); hetero-DES = implantation of stent eluting a different drug; homo-DES = implantation of stent eluting the same drug; IVUS = intravascular ultrasound; max = maximum; POBA = plain old balloon angioplasty; other abbreviations as in Table 1.

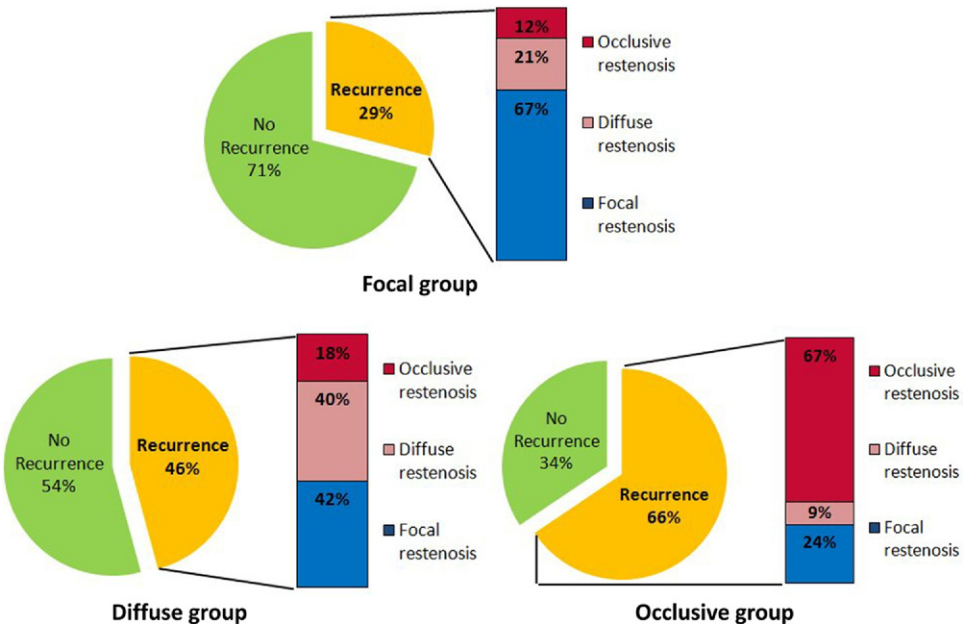

Figure 2. Patterns of Recurrent Angiographic Restenosis According to the Initial Pattern of Restenosis

For each of the initial patterns of restenosis, the rate of recurrent restenosis after treatment of DES-ISR is shown as a pie chart with the pattern of recurrence in the bar graph. Abbreviations as in Figure 1.

TLR rates was approximately 5% for the focal and diffuse groups, but was about 20% for the occlusive restenosis group, again confirming that many occlusive restenoses were not retreated (Fig. 3).

In relation to antiplatelet therapy, 56% of patients were still receiving dual antiplatelet therapy at 1 year after treatment of the restenosis. The median time to dual antiplatelet therapy discontinuation was 356 days (IQR: 180 to 413 days). According to the Academic Research Consortium definition of ST, the overall rate of definite/probable ST was 1.3% after the treatment of DES-ISR. There were 2 (0.5%) cases of very late definite ST, which both occurred in the focal DES-ISR group, at 757 days (on dual antiplatelet therapy) and at 1,185 days (only on aspirin), both after repeat DES implantation. The 3 cases of probable ST (2 in the focal and 1 in diffuse DES-ISR

Table 3. Angiographic Outcomes Based on the Pattern of Restenosis

	Overall	Focal	Diffuse	Occlusive	p Value
Lesions with angiographic follow-up, n	315	200	83	32	—
Time-to-angiographic documentation of restenosis, median [IQR]	299 [180–539]	349 [188–678]	267 [179–480]	181 [93–309]	**0.007**
Angiographic restenosis	117 (37.1)	58 (29.0)	38 (45.8)	21 (65.6)	**FvD 0.007** **FvO <0.0001** DvO 0.056
Recurrent restenosis pattern					
Focal	60 (51.3)	39 (67.2)	16 (42.1)	5 (23.8)	**FvD 0.02** **FvO 0.001** DvO 0.16
Diffuse	29 (24.8)	12 (20.7)	15 (39.5)	2 (9.5)	**FvD 0.045** FvO 0.25 **DvO 0.02**
Occlusive	28 (23.9)	7 (12.1)	7 (18.4)	14 (66.7)	FvD 0.38 **FvO <0.0001** **DvO <0.0001**

Values are presented as n (%) or median (interquartile range). **Bold** p values are statistically significant.
Abbreviations as in Tables 1 and 2.

Table 4. In-Hospital and Follow-Up Clinical Events in the Overall Cohort and by Restenosis Pattern

	Overall	Focal	Diffuse	Occlusive	p Value
Patients, n	392	250	95	47	
In-hospital events					
Periprocedural myocardial infarction	9 (2.3)	5 (2)	3 (3.2)	1 (2.1)	0.81
Death	0	0	0	0	—
Acute thrombosis	0	0	0	0	—
Cumulative events*	387	249	93	45	
MACE	127 (32.8)	77 (30.9)	36 (38.7)	14 (31.1)	0.381
Death	25 (6.5)	15 (6)	6 (6.5)	4 (8.9)	0.77
Cardiac death	17 (4.4)	12 (4.8)	2 (2.2)	3 (6.7)	0.41
MI	18 (4.7)	13 (5.2)	2 (2.2)	3 (6.7)	0.39
TVR	105 (27.1)	62 (24.9)	32 (34.4)	11 (24.4)	0.19
TLR (per patient)	77 (19.9)	41 (16.5)	26 (28)	10 (22.2)	**FvD 0.02** FvO 0.34 DvO 0.47
TLR (per lesion)	90/476 (18.9)	48/304 (15.8)	32/118 (27.1)	10/54 (18.5)	**FvD 0.008** FvO 0.61 DvO 0.22
t-TLR (per lesion)	119/476 (25.0)	60/304 (19.7)	38/118 (32.2)	21/54 (38.9)	**FvD 0.006 FvO 0.002** DvO 0.39
Ratio of TLR/restenosis (per lesion)	90/117 (76.9)	48/58 (82.6)	32/38 (84.2)	10/21 (47.6)	FvD 0.85 **FvO 0.005 DvO 0.008**
Multiple TLR (per patient)	18 (4.7)	10 (4)	7 (7.5)	1 (2.2)	0.278
Multiple TLR (per lesion)	21/476 (4.4)	10/304 (3.3)	10/118 (8.5)	1/54 (1.9)	**0.04**
ARC stent thrombosis					
Definite ST	2 (0.5)	2 (0.8)	0	0	0.57
Probable ST	3 (0.8)	2 (0.8)	1 (1.1)	0	0.79
Definite/probable ST	5 (1.3)	4 (1.6)	1 (1.1)	0	0.67

Values are presented as n (%). **Bold** p values are statistically significant. *Except periprocedural MI.

ARC = Academic Research Consortium; MACE = major adverse cardiac event(s); ST = stent thrombosis; TLR = target lesion revascularization; t-TLR = theoretical TLR; TVR = target vessel revascularization; other abbreviations as in Tables 1, 2, and 3.

group) were adjudicated due to the occurrence of an acute MI in the territory of the treated restenotic lesion.

Multivariable Cox regression analysis was used to identify independent predictors of TLR and recurrent restenosis. The candidate variables assessed, the results of the final multivariable that included only significant independent predictors or important confounders, and the p value for the goodness-of-fit test of the proportional hazards model are shown in Table 5. Diffuse restenosis (hazard ratio [HR]: 2.05, 95% CI: 1.30 to 3.22; $p = 0.02$) and previous bypass surgery were the only independent predictors of TLR. However, for recurrent restenosis, both diffuse (HR: 2.19, 95% CI: 1.42 to 3.38; $p < 0.0001$) and occlusive (HR: 4.86, 95% CI: 2.82 to 8.34; $p < 0.0001$) patterns of restenosis as well as previous bypass surgery were predictive, whereas repeat DES implantation was associated with a 50% (95% CI: 25% to 66%; $p = 0.001$) reduction in restenosis.

Discussion

The main findings of this study of the long-term outcomes of the treatment of DES-ISR are: 1) DES failure identifies a group of patients who are at high risk of future events after treatment, in particular repeat revascularization; 2) the pattern of DES-ISR is an important predictor of the occurrence and pattern of recurrent restenosis, as well as the need for subsequent reintervention; and 3) treatment of DES-ISR with repeat DES implantation appears to be associated with a reduction in recurrent restenosis and does not seem to influence the risk of late stent thrombosis.

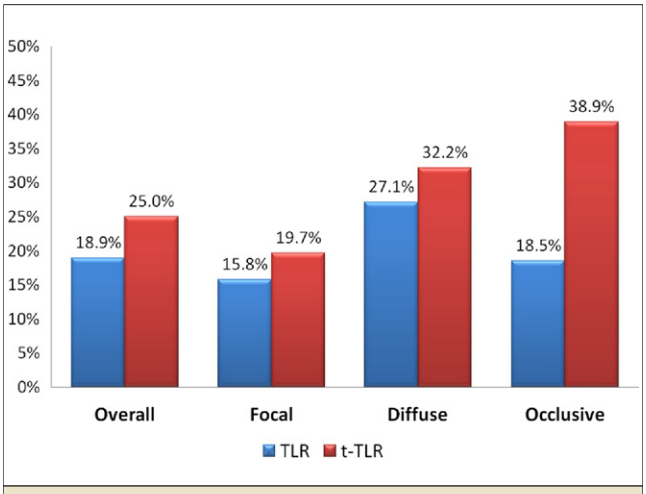

Figure 3. Rates of Actual TLR and t-TLR for the 3 Groups of Restenosis Patterns

The bar graph demonstrates the rates of actual target lesion revascularization (TLR) and theoretical TLR (t-TLR) calculated per lesion for the overall cohort and for each pattern of restenosis. Theoretical-TLR was defined as the estimated TLR if every restenosis was treated, that is, the sum of TLR plus untreated angiographic restenosis.

In a previous study from our center (14) of 250 DES-ISR lesions, we demonstrated that nonfocal DES-ISR is predictive of TLR at medium-term follow-up. A number of studies have examined the outcomes after the treatment of DES-ISR but many have been limited by the lack of adequate angiographic follow-up (15–18), small sample sizes (5,19,20), or short follow-up periods (16,18). In this study, we report the angiographic and clinical long-term outcomes of 481 de novo DES-ISR lesions after their first percutaneous treatment, analyzed based on the pattern of restenosis. Similar to bare-metal stent restenosis (21), DES-ISR is not a benign entity as it presents as an acute coronary syndrome in 13% of patients overall and in up to 20% of patients with diffuse restenosis. Furthermore, this study confirms that DES-ISR identifies a high-risk cohort that have failed our best available antirestenotic therapy and that will have a significant recurrence and MACE rate with repeat percutaneous intervention. Indeed, in this study, 1 of 3 patients treated for DES-ISR had an event during a median follow-up period of 3 years, irrespective of the initial pattern of restenosis. As a result, coronary artery bypass surgery may be considered as a viable treatment alternative for complex DES restenosis, particularly when it occurs in the left main or left anterior descending coronary arteries (1).

This study confirms the prognostic importance of the pattern of DES-ISR, which not only predicted the recurrence of restenosis but also the pattern. In comparison with focal DES-ISR, recurrent restenosis after percutaneous treatment occurs 2.2 times more often with diffuse restenosis and 4.9 times more frequently with occlusive restenosis. Also, an aggressive pattern of restenosis begets aggressive restenosis after treatment, that is, occlusive ISR will reocclude in two-thirds and diffuse restenosis will recur as diffuse or occlusive restenosis in about two-thirds of recurrent restenoses cases. It is noteworthy that both on univariate and multivariable analysis, the presence of diabetes mellitus did not influence the rate of recurrent restenosis after the treatment of DES-ISR. We believe that this may be because the occurrence of DES-ISR identifies a high-risk lesion-patient cohort with a higher rate of recurrent events, where the presence of diabetes may no longer confer an additive risk.

These data also provide valuable insights into the most aggressive pattern of restenosis. In comparison with the other patterns of restenosis, in lesions with occlusive DES-ISR, the index lesion was more often a chronic total occlusion (36.4%), with longer stents implanted at the index procedure, and the DES-ISR was treated with longer stents

Table 5. Multivariable Analysis for Predictors of TLR (Per-Lesion) and Angiographic Restenosis

		Final Multivariable Model				
End Point	Univariate Predictors Assessed	Variable	Hazard Ratio	95% Confidence Interval	p Value	Grønnesby-Borgan-May Goodness-of-Fit p Value
Target lesion revascularization	Restenosis type, restenotic DES length, previous MI, previous CABG, hypertension, hypercholesterolemia, diabetes, presenting symptoms, ejection fraction, repeat DES implantation, restenotic DES type, stent length, intravascular ultrasound	Diffuse vs. focal ISR	2.05	1.30–3.22	0.002	0.64
		Occlusive vs. focal ISR	1.45	0.70–3.00	0.32	
		Previous CABG	1.58	1.01–2.48	0.04	
		Restenotic DES length (per 10 mm of stent)	0.98	0.86–1.11	0.74	
Recurrent angiographic restenosis	Restenosis type, occlusive index lesion, bifurcation index lesion, restenotic DES length, restenotic DES diameter, age, previous CABG, diabetes, ejection fraction, repeat DES implantation, restenotic DES type, stent length, minimum lumen diameter	Diffuse vs. focal ISR	2.19	1.42–3.38	<0.0001	0.63
		Occlusive vs. focal ISR	4.86	2.82–8.34	<0.0001	
		Previous CABG	1.52	1.03–2.25	0.04	
		Repeat DES implantation	0.50	0.34–0.75	0.001	

ISR = in-stent restenosis; other abbreviations as in Tables 1 and 4.

(39.08 ± 22.06 mm). Although occlusive DES-ISR was highly predictive of recurrent restenosis, it was not associated with the need for repeat revascularization on univariate or multivariable analysis. Indeed, there was a marked disparity between restenosis (66.7%) and TLR (18.5%) rates for the occlusive group, which led us to define a new end point for this study, that is, the theoretical TLR if every restenosis was treated. The theoretical TLR was 38.9% and as can be seen in Figure 3, there was again a marked discordance between actual and theoretical TLR for the occlusive group. In fact, less than one-half of occlusive restenoses were retreated, whereas over 80% of focal and diffuse restenoses underwent repeat revascularization. We believe that these data confirm that as occlusive DES-ISR most often recurs as a reocclusion, operators often decide not to repeat percutaneous intervention because of the perceived futility of this procedure. It is interesting to note that in the occlusive group, only focal recurrent restenoses were retreated whereas recurrent occlusive restenoses were left untreated.

The optimal percutaneous treatment of DES-ISR still remains unclear, that is, conventional angioplasty versus repeat DES for focal DES-ISR; or implanting a DES with a different drug (hetero-DES) versus the same drug (homo-DES). The only randomized trial performed (ISAR-DESIRE 2 [Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 2] study) (3) demonstrated that in sirolimus-eluting stent restenosis, treatment with either repeat sirolimus-eluting stent or switching to a paclitaxel-eluting stent was associated with a comparable degree of efficacy or safety. Our study does not clarify the appropriate strategy for treating DES-ISR, but it does reinforce the concept that when treating DES restenosis we should make every attempt to optimize the final result and not fail the second time (1). Multivariable analysis did confirm that repeat DES implantation was effective in reducing recurrent restenosis. This finding seems to hold even in the focal restenosis group in which repeat DES implantation was more effective than POBA. Finally, the effectiveness of new technologies such as drug-eluting balloons in treating DES-ISR is not clear.

Study limitations. This study suffers the obvious limitations inherent to observational nonrandomized registries. Our rate of angiographic follow-up may also be considered a limitation particularly when considering the analysis of recurrent patterns of restenoses after treatment. However, the rates of angiographic follow-up were similar in the 3 groups and are quite high for a registry study. The results of this study are applicable only to the first generation of DES. Because the treatment strategy and choice of stent was at the operator's discretion, we did not perform any analysis of outcomes based on treatment strategy.

Conclusions

DES-ISR identifies a high-risk cohort of patients who are at an increased risk of events after treatment, in particular repeat revascularization, during long-term follow-up. The initial pattern of restenosis is the most important predictor of recurrent restenosis or the need for subsequent reintervention. Repeat DES implantation appears to be a viable alternative while awaiting the promising results of new technologies such as drug-eluting balloons.

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Key Words: angioplasty ■ antiplatelet therapy ■ drug-eluting stent(s) ■ restenosis ■ stent thrombosis.