Characterization and Clinical Outcomes of Drug-Eluting In-Stent Restenosis

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ABSTRACT: **Background:** The best therapeutic alternative for patients suffering from in-stent restenosis after drug-eluting stent implantation remains to be elucidated.

Objective: To characterize the pattern, treatment and outcomes of DES-related in-stent restenosis in patients treated at our institution.

Methods: We determined the incidence and major adverse clinical events in 71 consecutive patients with DES failure among 2473 patients who were treated with 2548 drug-eluting stents between 2004 and 2007. We analyzed the clinical data, procedural parameters and clinical outcomes.

Results: The type and number of stents implanted were as follows: Cypher (n=1808), Endeavor (421) and Taxus (319); of these, 53 (2.9%), 10 (2.4%), and 8 (2.5%) patients respectively presented with restenosis. The mean time to restenosis was 11.3 ± 9.9 months. Patients' mean age was 65 ± 11 years; 75% were male, and 68% had diabetes mellitus. Unstable angina was the clinical presentation in 52 (73%). At 6 months, 3 patients had developed myocardial infarction (4.2%), repeat restenosis at follow-up was diagnosed in 8 patients (11.3%), the overall major adverse clinical events rate was 18.3% (13 patients), and 2 patients died (2.8%).

Conclusions: Drug-eluting stent-related restenosis is relatively infrequent but remains a clinical challenge. It occurs more frequently in complex lesion subsets, but the overall intermediate-term prognosis is tolerable.

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KEY WORDS: in-stent restenosis, drug-eluting stent

Drug-eluting stents were designed to prevent in-stent restenosis. However, the optimal management of DES-related restenosis has yet to be defined. The results of multiple studies suggest that the DES implant is the treatment of choice for patients with ISR after bare-metal stent implantation [1-5]. Although the use of DES has significantly decreased restenosis, there is little information on the long-term results of in-stent restenosis following DES implantation. Thus, the challenge remains to identify the best therapeutic options for patients presenting with ISR after DES implantation.

Our study investigated the clinical characteristics and pattern of restenosis, including its association with different DES types, the outcome at 6 months relative to the pattern of restenosis, and the general outcome for coronary patients.

DES = drug-eluting stent
ISR = in-stent restenosis

PATIENTS AND METHODS

In our institution, the rate of DES is ~40% and is regulated by restricted indications such as proximal to mid-left anterior descending or proximal left circumflex lesions, diffuse coronary stenosis, in-stent restenosis and total coronary artery occlusion. Between January 2004 and February 2007, we identified 2473 consecutive patients who underwent 2548 DES implantations (71% Cypher® eluting sirolimus drug, 17% Endeavor® eluting zotarolimus drug, and 12% Taxus® eluting paclitaxel drug). Of these, we identified 79 consecutive patients with DES failure: 71 who experienced DES restenosis and 8 who had DES-related thrombosis.

In-stent restenosis was defined as a luminal stenosis of at least 50% located within the stent or within 5 mm of the stent edges. The ISR pattern was classified according to the Mehran system [6] as follows:

- Focal ISR lesions were defined as ≤ 10 mm of length, in the body and/or the edges of the stents
- Diffuse ISR lesions were diffuse lesions ≥ 10 mm in length occurring intrastent, and they were proliferative, extending beyond the stent margins
- Occlusive lesions.

The clopidogrel loading dose was 300–600 mg. A clopidogrel loading regimen was administered prior to interventions (e.g., 6–24 hours) in all acute coronary syndrome patients and immediately following the procedure in other cases. The duration of clopidogrel therapy was at least 3–12 months for those with a Cypher stent, 6–12 months for those with Taxus stents, and 3–12 months for patients with an Endeavor stent.

Renal failure was defined as a creatinine level > 1.4 g/dl. Major adverse cardiac events beyond the index DES failure event were defined as death, myocardial infarction (Q or

non-Q according to chest pain, electrographic changes, and positive troponin), target vessel revascularization, and/or need for unplanned bypass surgery.

The registry includes detailed demographic, clinical, angiographic and procedural data on the 71 patients who experienced a DES-related restenosis event. Immediate and in-hospital events were recorded, and each patient was surveyed by telephone or at the outpatient clinic with a standardized questionnaire at 30 days, 6 months, and 1 year of follow-up. Survival status at follow-up was determined by the national registries. Repeat revascularization procedures and episodes of acute myocardial infarction were prospectively collected in the hospital database. For patients admitted in the acute phase to peripheral hospitals, the diagnosis of myocardial infarction was confirmed by source documentation obtained from the referring physician.

ANGIOGRAPHIC ANALYSIS

Angiographic films were reviewed at our angiographic core laboratory using the MDView™ Quantitative Angiographic System (Medcon-McKesson, Telemedicine Technology, Tel Aviv, Israel). Analysis was performed by an experienced cardiologist who was unaware of the clinical outcome. Standard morphologic criteria were used for the identification of lesion location, lumen diameters, length, and existence of thrombus. Percent diameter stenosis was determined using standardized calibrated methods before and after interventions, as was TIMI flow grade (0 to 3) before and at the completion of the intervention. We also performed subanalyses on groups according to the ISR pattern and focal restenosis in the Cypher stent (the sirolimus-eluting stent) compared to the Endeavor (zotarolimus-eluting) stent.

STATISTICAL ANALYSIS

Continuous variables are presented as mean ± standard deviation. Statistical analysis was performed using STATISTICA software (StatSoft, Inc. Tulsa, OK, USA), and $P < 0.05$ was considered significant for all analyses.

RESULTS

We obtained baseline demographic and clinical data of 71 consecutive patients who experienced DES-related restenosis events [Table 1]. Patients who developed ISR were more likely to have diabetes mellitus (68%), and 20% of these were insulin-dependent. A total of 44% of patients had a prior history of myocardial infarction and 41% had previous bypass grafts (41%); 80% of the patients had multivessel coronary artery disease. Unstable angina was more likely to be the presentation in this group of patients (73%). Mean time to restenosis was 11.3 ± 9.9 months.

Angiographic data for quantitative analysis are also given in Table 1. Lesion length and stent diameter were on average 3.0 ± 0.4 and 12.8 ± 9.1 mm, respectively.

Table 1. Clinical and coronary angiography data

Patients	**N=71**
Age (yrs)	65 ± 11
Male	53 (75%)
Hypertension	57 (80%)
Dyslipidemia	60 (85%)
Smoker	12 (17%)
Diabetes	48 (68%)
Insulin-dependent	10/48 (20%)
Renal failure	13 (18%)
Previous infarction	31 (44%)
Previous bypass	29 (41%)
Stroke	7 (10%)
Ejection fraction (%)	47 ± 10
Multivessel disease	57 (80%)
Angiography data	
Pre-procedure	
Reference diameter (mm)	3.0 ± 0.4
Minimal diameter (mm)	0.47 ± 0.58
Diameter stenosis (%)	85 ± 18
Lesion length (mm)	12.8±9
Post-procedure	
Reference diameter (mm)	3.2 ± 0.6
Minimal diameter (mm)	2.6 ± 1.0
Diameter stenosis (%)	22 ± 30
Stent diameter (mm)	3.0 ± 0.4
Stent length (mm)	23.3 ± 7.6

CLINICAL OUTCOME AND RESTENOSIS PATTERN

Data were available for all patients at 6 months. The overall rates of death and of myocardial infarction were 2.8% and 4.2%, respectively. Recurrent restenosis occurred in 8 patients (11.8%) and the overall MACE rate was 18.3% (13 patients).

Focal restenosis, according to the Mehran classification [6], constituted the majority of lesions. Restenosis treatment was at the discretion of the clinician, and the re-stenting rate of the lesion was 60% whether it was focal or diffuse. All patients who received an additional stent were treated using another DES. In other words, no bare metal stents were used to treat DES-related in-stent restenosis. Focal ISR was found in 71%, diffuse ISR in 22%, and 7% presented with stent occlusion. Re-stenting was more often performed for focal and diffuse patterns (68% and 53%, respectively) followed by balloon angioplasty alone (26% and 27%, respectively), as compared to bypass surgery or medical therapy in the occlu-

MACE = major adverse clinical events

Table 2. Six month outcome according to in-stent restenosis type

	Focal (N=50)	Diffuse (N=12)	Occlusion (N=5)	*P value*
Death	0	1 (8.3%)	0	0.2
Myocardial infarction	2 (4.2%)	1 (8.3%)	0	0.4
Repeat revascularization	5 (10.6%)	4 (33%)	0	0.08
Target vessel revascularization	5 (10.6%)	3 (25%)	0	0.2
Major adverse cardiac events	7 (14.6%)	5 (42%)	0	0.05

sive pattern. Six month outcomes according to restenosis type were available in 67 patients. The incidence of recurrent coronary intervention increased in the diffuse restenosis type compared to the focal group, as did MACE, with frequencies of 42% versus 14.6% respectively ($P = 0.05$) [Table 2]. There were no increments in mortality or myocardial infarction among the subgroups.

RESTENOSIS ACCORDING TO STENT TYPE

A comparison of Cypher and Endeavor Sprint stents (the "limus" eluting stents) showed Cypher failure in 53 patients (age 64 ± 11 years, 79% male) with 57 lesions who presented with acute coronary syndrome. Ten patients had Endeavor failure (age 72 ± 8.7 years, 80% male). Restenotic patients were often characterized as high risk in both groups, with diabetes (73.5% vs. 80%), hypertension (83% vs. 100%), and dyslipidemia (89% vs. 90%). Cypher stent lengths were 24 ± 8 vs. 19 ± 6 mm for the Endeavor stents ($P = 0.07$), with stent diameters averaging 3.0 ± 0.4 mm (Cypher) vs. 3.2 ± 0.5 mm (Endeavor) ($P = 0.1$). Mean time to DES failure was 12.5 ± 10.6 months for Cypher and 5.2 ± 2.7 months for Endeavor ($P < 0.05$). The vast majority of restenotic lesions (71%) were focal in the Cypher group and diffuse (80%) in the Endeavor group ($P = 0.004$). Accordingly, the incidence of diffuse restenosis was significantly higher in the Endeavor compared to the Cypher stents (12% vs. 80%, $P < 0.0002$). At the 6 month follow-up, the overall MACE (death, myocardial infarction, target vessel revascularization) was 11.3% in the Cypher group and 50% in the Endeavor group ($P = 0.01$). Only four patients in our series presented with Taxus-related restenosis. All four were alive at 6 months follow-up.

DISCUSSION

DES implants have greatly decreased the incidence of restenosis and the need for target lesion revascularization; however, restenosis remains a significant problem because of the increased number of complex disease interventions. Most studies have identified angiographic restenosis rates of 3% to 12% for in-stent or in-segment restenosis, depending on the patient's characteristics and lesion complexity [7]. However, the clinical restenosis rate following DES implantation is even lower.

The present study identified a 2.9% rate of clinical restenosis after DES implantation in the "all comers" group of patients treated at our hospital. The angiographic morphology of restenosis following DES implantation showed focal restenosis as the predominant pattern, especially with the Cypher stent. This pattern of DES-related restenosis, which is easier to treat, has already been described in several studies [8,9]. Reporting their experience with post-DES restenosis, Lee et al. [10] stated that focal ISR occurred in 62% of lesions, while diffuse or proliferative ISR was present in 29% and total occlusion in 9%. Hong and associates [11] reported late need of repeat revascularization, beyond 6 or even 9 months, which was performed in 1.8% of native lesions that were patent on the 6 month follow-up angiogram. Two-thirds of late restenotic lesions had a focal angiographic restenotic pattern [11]. Our data showed that a focal restenotic pattern was the most representative in the Cypher group (79%), while in the Endeavor stent group the pattern was more diffuse. We also described the treatment type when specifically analyzing the subgroup of focal post DES-related restenosis.

A meta-analysis of six randomized trials has indicated a modest benefit with sirolimus-eluting stents compared to paclitaxel-eluting stents [12]. Taxus stents entered the Israeli market after the Cypher and Endeavor stents, and in the present study we compared Cypher and Endeavor, both of which are "limus"-based stents – to detect a restenotic pattern. Based on our experience and compared to the Cypher stent, the Endeavor DES failure showed a more diffuse restenotic pattern, a shorter time to restenosis, and worse overall intermediate-term clinical outcome. Miyazawa et al. [13] in their IVUS study (ENDEAVOR III), compared the vascular response of Endeavor and Cypher stents at baseline and after 8 months and showed larger IVUS-detectable neointimal coverage over stent surface at 8 months. Kandazari et al. [14] found that compared with Cypher, treatment with Endeavor is associated with significantly higher in-segment late lumen loss and binary restenosis at the 8 month angiographic follow-up. This has not been translated into a major clinical adverse outcome.

The preferred treatment approach for DES restenosis is not yet established, but the options include repeat intervention with another DES, use of the same type of stent or use of a stent with a different antiproliferative agent, revascularization with balloon angioplasty/cutting balloon, or bypass surgery. More recently, the use of drug-eluting balloons (rather than drug-eluting stents) may become a viable treatment option for DES failure due to restenosis events [15]. The TAXUS ARRIVE Registry included more than 2400 patients and more than 3000 lesions treated with the Taxus stent. Among those treated with repeat stenting, 5% received bare metal

stents and 58% were treated with DES [16]. Of those treated with DES, 77% were retreated with Taxus stents and 23% treatments involved another DES, mainly Cypher. In our group, treatment type was at the discretion of the clinician, and we found that 69% of focal ISR were re-stented while 27% were treated with balloon angioplasty alone. Patient outcome according to treatment showed a tendency to a better outcome in the balloon angioplasty group but it did not reach statistical significance. Of 57 lesions with Cypher-related stent restenosis, 27 (53%) were treated with the same stent. Some operators preferred to switch stent types in this setting (e.g., Taxus for Cypher restenosis and vice versa), but there were no data to support this approach.

Solinas and team [17] described their experience with repeated DES treatment for DES restenosis, reporting that treatment with either repeated DES implantation or balloon angioplasty for DES-ISR was safe and associated with low overall rates of target-lesion revascularization and major adverse cardiac events at 1 year. They also found that implantation of a different DES type (the "switch" strategy) may result in more favorable outcomes compared to the same DES (no-switch strategy) that had failed originally. Regarding the overall outcome of patients with DES restenosis, Garg et al. [18] found that the repeat revascularization rate for patients treated with a different DES was 14.5%, and 16.7% for the same DES; this difference was not significant. Other studies showed similar data after DES failure regardless of the treatment modality [19,20].

Our study has several limitations: it involved a small group of patients/lesions and was a retrospective analysis. In addition, the treatment groups were not randomly assigned, and no angiographic or ultrasonic follow-up data were obtained.

In summary, according to our experience, DES-related restenosis is relatively infrequent but remains a clinical challenge. It occurs more frequently in complex cases and lesion subsets, but the overall intermediate-term prognosis following repeat percutaneous treatment is acceptable. Further studies regarding the best treatment strategies for focal or diffuse lesions are needed. Treatment options could include using a balloon or cutting balloon and/or drug-eluting balloon or using another drug-eluting stent. Finally, it should be remembered that referring the patient to a coronary bypass surgery is another option for recurrent DES failure.

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"A friend is one before whom I may think aloud"

Ralph Waldo Emerson (1803-1882), American essayist, philosopher, and poet