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CORRESPONDENCE

Research Correspondence

Angiographic Patterns of Restenosis After Paclitaxel-Eluting Stent Implantation

To the Editor: Polymer-based paclitaxel-eluting stents (PES) (Taxus, Boston Scientific, Natick, Massachusetts) have been shown to reduce neointimal hyperplasia and risk of restenosis (1,2). Operators are now using drug-eluting stents for a wide variety of clinical and anatomical situations, many of which have not been investigated in randomized studies.

The clinical and morphologic features of restenosis after PES implantation have not been adequately evaluated (1,2). The purpose of this study was to describe the angiographic patterns of restenosis after PES implantation in "real-world" patients. This knowledge may help in finding the solution to this important problem.

We identified 977 consecutive patients who underwent PES implantation (977 procedures, 1,688 lesions, 2,023 stents) in three institutions between April 2002 and March 2004. Patients that had in-stent restenosis (ISR) lesions treated, prior brachytherapy at the target vessel, or acute myocardial infarction <48 h before the index procedure were excluded. All patients were pretreated with ticlopidine or clopidogrel and aspirin; a loading dose of 300 mg clopidogrel was given to patients not previously taking the agent. Aspirin was continued indefinitely and clopidogrel or ticlopidine for at least six months after PES implantation. Glycoprotein IIb/IIIa inhibitors were administered at the operators' discretion.

During follow-up, coronary angiograms were obtained as clinically driven (>30 days after procedure, indicated by symptoms or positive ischemic tests). In addition, follow-up angiograms were obtained at 6 ± 1 month in patients treated with PES implantation for bifurcations, left main, chronic total occlusions, small vessels, and long stented length (>36 mm). Cineangiograms were analyzed using a validated edge detection system (CMS, version 5.2, MEDIS, Leiden, the Netherlands). Standard qualitative and quantitative analyses and definitions were used (3). Angiographic success was defined as a minimum stenosis diameter <20% after stenting. For the current study, ISR cases were categorized according to Mehran classification (4).

Baseline demographics, lesion, and procedural characteristics are shown in Table 1. Twenty-six percent of the patient population had diabetes and 78% of the lesions were complex (B2 or C type). In addition, 19% of the lesions were bifurcational and 7.9% were total occlusions. All patients had successful PES implantation, and there was no angiographic evidence of any residual dissection after PES implantation. The mean stent per lesion ratio was 1.23, and glycoprotein IIb/IIIa inhibitors were used in 40% of the patients.

To date, all 977 patients have completed >6 months from the index procedure. At a mean follow-up of 10.5 ± 3.6 months, the rates of target lesion revascularization, target vessel revascularization (TVR) and major adverse cardiac events (death, myocardial infarction, or TVR) were 7.2%, 10.3%, and 11.4%, respectively. A follow-up coronary angiogram was obtained in 576 patients (59%) (747 lesions), and in 201 patients (35%) the angiogram was clinically driven.Among these, ISR was identified in 81 patients and 98 lesions. The mean baseline reference vessel diameter was 2.60 mm. Mean baseline lesion length was 14.10 ± 10.12 mm, and restenotic lesion length was 9.96 ± 6.07 mm (range 2.18 to 26.18 mm), which corresponds to 29% reduction.

Restenosis was found in the body and the edges in 71 lesions (72%), in the edges only in 16 lesions (16%), and in the body of the stent only in 11 lesions (11%). A schematic representation of the patterns of ISR is shown in Figure 1. The pattern of ISR in 49 lesions (50%) was focal (≤10 mm in length) or multifocal (12% of the focal lesions). In the remaining 49 lesions (50%), the pattern of ISR was non-focal: diffuse ISR (>10 mm in length) in 28 lesions

Table 1. Baseline Demographics, Lesion and Procedural Characteristics, and Pre- and Post-Intervention Angiographic Analysis

	PES
Patient characteristics	
Patients (n)	977
Unstable angina (%)	27
Diabetes (%)	26
Previous myocardial infarction (%)	44
Previous percutaneous coronary intervention (%)	41
Previous bypass surgery (%)	23
Multivessel disease (%)	82
Left ventricular ejection fraction (%)	53 ± 10
Lesion characteristics	
Lesions (n)	1,688
Vessels treated	
Left main unprotected (%)	2.6
Left anterior descending artery (%)	43
Saphenous vein graft (%)	2.3
Ostial location (%)	12
Bifurcation (%)	19
Calcium (%)	16
Preintervention TIMI flow grade 3 (%)	84
Thrombus (%)	2.4
Total occlusion (%)	7.9
Procedural characteristics	
Procedures (n)	977
Maximum balloon diameter (mm)	3.04 ± 0.51
Maximum balloon inflation (atm)	15.9 ± 3.5
Stent length per lesion (mm)	27.45 ± 12.56
Stents per lesion	1.23 ± 0.55
Glycoprotein IIb/IIIa inhibitors (%)	40
Quantitative coronary angiography	
Lesions (n)	1,688
Preintervention	
RVD (mm)	2.60 ± 0.70
MLD (mm)	0.96 ± 0.25
DS (%)	66 ± 18
Lesion length (mm)	14.10 ± 10.12
Post-intervention	
MLD (mm)	2.73 ± 0.62
DS (%)	13 ± 11

Values are presented as numbers (relative percentages) or mean ± SD.

DS = diameter stenosis; MLD = minimal lumen diameter; PES = paclitaxel-eluting stent; RVD = reference vessel diameter; TIMI = Thrombolysis In Myocardial Infarction.

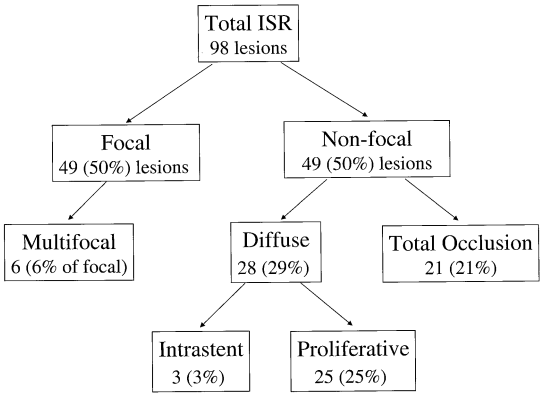

Figure 1. Schematic representation of the patterns of in-stent restenosis (ISR) after paclitaxel-eluting stent implantation.

(29%) (25 diffuse proliferative and 3 diffuse intrastent) and total occlusions in 21 lesions (21%).

Traditionally, the presence of a focal ISR represents a rather benign type of ISR (5). Mehran et al. (4) showed that diffuse intrastent, proliferative, and totally occluded ISR make up a spectrum of increasing disease severity (exaggerated neointimal response). In our study, in contrast to data regarding sirolimus-eluting stents in unselected lesions (6,7), the pattern of ISR after PES implantation was non-focal in 50% of the cases. Whether this finding represents a more exaggerated neointimal response to PES remains to be seen in the ongoing and the upcoming randomized trials between the two types of drug-eluting stents currently available in the market. It is worth noting that in TAXUS IV the pattern of restenosis in 16 lesions with ISR was predominantly focal (62%), but still a considerable percentage (38%) of ISR lesions were non-focal (1). Our study population, compared with TAXUS IV patients, consisted of patients with similar rates of diabetes (26% vs. 24%). However, the mean reference vessel diameter was smaller (2.60 mm vs. 2.75 mm) and the mean lesion length was longer (14.10 mm vs. 13.10 mm). In addition, a greater number of stents per lesion were used in our study (1.23 vs. 1.08). Similar to previous reports with sirolimus-eluting stents, ISR occurred more frequently in the proximal than in the distal stent border (6,7). This finding, which has been attributed to more effective drug effect in the outflow stent border and a possible "wash-out" of the drug, remains to be clarified (7).

The current study presents several limitations. First, this was a retrospective analysis with the inherent caveat of the abscence of a control group. Offsetting this limitation, the data were collected prospectively by independent monitors and entered into a dedicated database, and an independent core laboratory interpreted all angiographic studies. Angiographic follow-up was available in 59% of the patients and in 35% of patients was clinically driven, thereby precluding a homogeneous evaluation of the total restenosis rate for the global treated population. However, the patterns of restenosis were similar between patients that had clinically driven angiography and patients that had systematic elective control angiography. More specifically, out of the 36 ISR lesions in the 28 patients that underwent clinically driven coronary angiogram, 18 (50%) were non-focal; of the 63 lesions in the remaining 53 patients that underwent elective control angiogram, 31 (45%) were non-focal ($p = 0.9$).

In conclusion, restenosis after PES implantation appears in 50% of patients with a non-focal pattern and in the majority of the cases involves the stent edges and more frequently the proximal than the distal border. Diffuse proliferative ISR and ISR with total occlusions are the predominant patterns when non-focal ISR occurs.

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Letters to the Editor

Rescue Angioplasty—The MERLIN Trial

Some of the issues raised by Drs. Grines and O'Neill in their editorial in *JACC* (1) accompanying the Middlesbrough Early Revascularization to Limit Infarction (MERLIN) trial report (2) should be addressed.

Before the trial initiation, we estimated 18% mortality in the conservative group and 6% in the rescue group, as described in the statistical methods section. This may have been optimistic, but was based upon a careful literature search. Power calculations cannot be