

## Clinical Research

## Drug-Eluting Stents: Immediate and Long-Term Results

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**Introduction:** In this study we present our findings from a series of patients who underwent coronary angioplasty and implantation of drug-eluting stents with rapamycin or paclitaxel.

**Methods:** Two hundred and twenty-three consecutive patients with 343 coronary lesions underwent angioplasty with implantation of 220 rapamycin-eluting stents (Cypher) and 297 paclitaxel-eluting stents (Taxus).

**Results:** During the follow up period, 32 patients with 49 lesions had a new coronary angiographic examination because of ischaemia recurrence. The mean follow up time for these patients was  $7.2 \pm 3.0$  months (2.9-17.1 months). Seven patients showed angiographic restenosis (>50% diameter stenosis) in 9 lesions where stents had been implanted. The type of restenosis was focal in 7 of those lesions (in one it was multifocal), usually at the proximal edge of the stent. In 2 lesions the restenosis was diffuse (1 in-stent, 1 extending beyond the stent margins). The incidence of major adverse coronary events was 4.4% (10 patients: 1 death, 1 non-Q myocardial infarction, 1 Q myocardial infarction and 7 target vessel revascularisation procedures).

**Conclusions:** Our findings demonstrate that drug-eluting stents can be used in routine clinical practice, regardless of the type of stenosis and the patients' clinical characteristics. The type of restenosis is mainly focal, though diffuse restenosis may also occur when complex lesions are treated with multiple stents.

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**R**andomised studies comparing drug-eluting stents (rapamycin or paclitaxel) with conventional stents have shown beyond doubt that the former have lower rates of restenosis and need for revascularisation over a follow up period of 6-12 months.<sup>1-9</sup> Although drug-eluting stents can be used successfully in patients with restenosis within a previous stent,<sup>2,10-12</sup> or in bifurcations and complex lesions,<sup>13,14</sup> most randomised studies have only included patients with one-vessel disease and lesions in native vessels. There have been very few reports of the use of these stents in everyday clinical practice.<sup>15</sup> Restenosis has been described at the stent margins or within the stent itself.<sup>16,17</sup>

Here we present our experience from a consecutive series of patients who underwent implantation of a drug-eluting stent

(Cypher or Taxus), regardless of their clinical characteristics or the anatomical features of their lesions. All the cases of restenosis that became apparent because of symptoms or laboratory findings of myocardial ischaemia are described and analysed.

### Methods

Between September 2002 and March 2004, all patients who had indications for coronary stenting in the haemodynamics laboratory of Athens Euroclinic were treated using drug-eluting stents with either rapamycin or paclitaxel, according to availability and to the judgement of cardiologist performing the procedure. Patients with "unprotected" left main disease, lesions in vessels >4 mm in diameter, or with contraindi-

cations for aspirin or clopidogrel were excluded. Age, acute myocardial infarction, the presence of angiographically visible thrombus within the stenosis, restenosis of a previous stent, renal dysfunction defined by a serum creatinine level >1.7 mg/ml, a high-risk angiographic picture of the stenosis, were not considered as contraindications for stenting. Written informed consent was obtained from all patients and the study was approved by the hospital's Scientific Committee.

### Methodology of stent implantation

All patients were under treatment with aspirin (100 mg), clopidogrel (300 mg) and all received enoxaparin prior to stenting. In addition, platelet glycoprotein IIb/IIIa receptor inhibitors were given to patients with acute coronary syndrome, diabetes mellitus, or a need for multiple stent implantation. The stents were deployed with or without balloon predilatation. High pressure balloon inflation after stent deployment was carried out at the discretion of the cardiologist performing the procedure. In certain patients this was necessary in order to achieve <20% residual stenosis with TIMI 3 flow. In cases with disaggregation or incomplete coverage of the lesion a further, similar stent was deployed. After stenting, aspirin (100-325 mg daily) was prescribed for life and clopidogrel (75 mg daily) for at least 12 months.

### Angiography and classification of restenosis

Coronary artery imaging was performed in multiple projections after the administration of intracoronary nitrates. A quantitative analysis of all angiographic data from before and after stent deployment, as well as from coronary angiograms recorded during follow up, was carried out using an edge-detection technique. Restenosis was defined as >50% luminal stenosis and was classified as either in-stent, if it was confined within the stent's boundaries, or in-segment, if it was within 5 mm of the proximal or distal end of the stent.

Lesions were categorised according to the classification of Mehran et al<sup>18</sup> as follows:

- focal, if the lesion was <10 mm in length and was located at the articulation or gap (type IA), at the proximal or distal end of the stent (type IB), within the body of the stent (type IC), or a combination of those locations (type ID);
- diffuse in-stent (type II), if the lesion was >10 mm in length and was confined within the stent without extending beyond its margins;

- diffuse hyperplastic (type III), if the lesion was >10 mm in length and extended beyond the stent margins;
- complete occlusion (type IV), if there was TIMI 0 flow.

### Follow up

All patients had a clinical follow up and myocardial scintigraphy or stress echocardiography 3 and 6 months after angioplasty. All patients who reported symptoms of angina or ischaemia during one of the above tests were referred for repeat coronary angiography.

### Definitions

Major adverse cardiac events were defined as death from any cause, myocardial infarction, need for target vessel revascularisation, and in-stent thrombosis. Q infarction was defined as the occurrence of Q waves on more than two consecutive leads, with elevated CK-MB levels. Target vessel revascularisation was defined as repeat angioplasty or surgical revascularisation on an emergency or programmed basis.

### Results

Qualitative variables are given as absolute values and percentages. Continuous variables are expressed as mean  $\pm$  standard deviation.

A total of 223 consecutive patients, with 343 lesions, were treated with 220 Cypher and 297 Taxus stents. The patients' clinical characteristics are given in table 1. Forty-six patients (20.6%) were diabetic. Details of the angioplasty procedures are shown in table 2 and the results of the quantitative angiographic analysis before and after stent deployment are given in table 3.

**Table 1.** Clinical characteristics of 223 consecutive patients.

Age (years)	56.7 $\pm$ 11.1
Sex (men)	203 (91%)
Diabetes mellitus	46 (20.6%)
Hypertension	132 (59.2%)
Dyslipidaemia	184 (82.5%)
Unstable angina	81 (36.3%)
Acute myocardial infarction	29 (13.0%)
Ejection fraction (%)	50.46 $\pm$ 9.49
Multivessel disease	180 (80.7%)
Platelet glycoprotein IIb/IIIa inhibitors (%)	173 (77.5%)

**Table 2.** Procedure details for 343 lesions.

<b>Vessel</b>	
• LAD	168 (49%)
• LCX	86 (25.1%)
• RCA	83 (24.2%)
• Intermediate branch	3 (0.9%)
• Grafts	3 (0.9%)
<b>Lesions</b>	
• Ostial	2 (0.6%)
• Bifurcation	46 (13.4%)
• In-stent restenosis	27 (7.8%)
• Chronic occlusion	11 (3.2%)
<b>Type of lesion</b>	
• A/B1	136 (39.6%)
• B2/C	207 (60.4%)
Lesions/patient	1.34 ± 0.58
Stents/lesion	1.50 ± 0.75
<b>Type of stent</b>	
• Cypher	220 (42.6%)
• Taxus	297 (57.4%)
Stenting without predilatation	145 (42.3%)

LAD – left anterior descending branch; LCX – left circumflex; RCA – right coronary artery.

One patient underwent successful primary angioplasty for a massive anterior septal infarction, with deployment of two Taxus stents (3.5 × 16 mm and 3.0 × 9 mm) in the anterior descending coronary artery branch and stenting of two lesions in the right coronary artery (both Taxus 3.5 × 8 mm) under administration of enoxaparin and eptifibatide. Two days later he developed an acute coronary syndrome with ST-segment elevation on the precordial leads, followed by cardiac arrest and unsuccessful cardiopulmonary resuscitation.

Another patient showed subacute thrombosis 4 days after the implantation of a Taxus stent in a lesion in the proximal section of the right coronary artery and needed a new revascularisation procedure as a result. During follow up, 32 patients with 49 lesions had a new coronary angiographic examination because of ischaemia (symptoms or reversible ischaemia). The mean follow up time before repeat angiography was 7.2 ± 3.0 months (range 2.9 to 17.1). Seven patients had angiographic restenosis (>50% diameter stenosis) in 9 lesions, in which 14 stents had been deployed. In the remaining 25 patients no target lesion restenosis was observed and the presence of symptoms or reversible ischaemia was attributed to deterioration of a pre-existing lesion in another part of the coronary net (11 patients) or to microvascular disease (14 patients). Five of the 9 lesions with restenosis had been treated with Cypher stents and 4 with Taxus stents.

**Table 3.** Quantitative coronary angiography before and after stenting.

	Before	After
Vessel diameter	2.87 ± 0.53	3.0 ± 0.52
Minimum lumen diameter	0.80 ± 0.47	2.88 ± 1.61
% diameter stenosis	73.35 ± 15.80	11.37 ± 11.01
Lesion length	11.78 ± 3.99	–

Details of the cases in which restenosis occurred are given in table 4. The type of restenosis was focal at 7 sites (multifocal in 2), mainly at the proximal edge of the stent. Diffuse restenosis was seen at 2 sites (1 in-stent, 1 proliferative). Taxus stents had been used in both patients. None of these patients had diabetes.

No patient died during the long-term follow up. One patient had acute thrombosis 17 months after deployment of a Cypher stent in the mid segment of the left anterior descending artery. This patient, however, had stopped taking clopidogrel 8 months previously. The total incidence of major adverse cardiac events overall was 4.4% (10 patients: 1 death, 1 non-Q myocardial infarction, 1 Q infarction, 7 patients who needed target lesion revascularisation). The percentage of patients needing target lesion revascularisation was 3.1%. These patients were treated by a new angioplasty with implantation of a Cypher or Taxus stent.

## Discussion

In this study we present our experience from a consecutive series of patients who underwent angioplasty with implantation of Cypher or Taxus stents. The percentage of patients who needed a new procedure because of restenosis in the target lesion was significantly lower than that reported for conventional metallic stents.<sup>19</sup>

In the FIM<sup>20</sup> and RAVEL<sup>21</sup> trials, which studied non-complex coronary lesions with low risk of restenosis, no restenosis was seen during the follow up period. In the SIRIUS trial,<sup>3</sup> which included more complex lesions treated with rapamycin-eluting stents, the restenosis rate reported was low (4.1%), with most cases of restenosis occurring solely in the proximal part of the stent, and less often in the distal part or in both those regions. This observation resulted in a recommendation for predilatation with smaller balloons, so as to avoid injury to the endothelium during stent deployment, complete coverage of the lesion with long or overlapping stents and inflation of a small, high pressure balloon

**Table 4.** Patients with restenosis after implantation of drug-eluting stents: clinical, procedural and morphological characteristics.

Patient No.	1	2	3	4	5	6	7
Age	50	53	46	38	71	66	61
Sex	Male	Male	Male	Male	Male	Male	Male
Diabetes mellitus	No	No	No	No	No	No	No
Clinical picture	Ischaemia	Unstable angina	Recent MI	Acute MI	Unstable angina	Unstable angina	Ischaemia
No. of lesions	1	2	1	1	1	3	4
Target vessel	LAD	RCA	RCA	LAD	LAD	LAD	LAD/Diag/OM
Vessel region	Distal	Mid/Distal	Proximal	Mid-Distal	Mid	Proximal/Mid/Distal	Mid-Distal/Proximal/Proximal
Lesion characteristics							
AHA type	B2	B2/C	B2	C	C	B2/B2/C	B2-B2/B2/B2
Bifurcation	No	No/Yes	No	No	Yes	No/Yes/Yes	No-No/Yes/No
Long	No	Yes/Yes	No	Yes	Yes	No/No/Yes	Yes-Yes/Yes/Yes
ISR	No	Yes/No	No	No	No	No /No /No	No-No /No /No
Stents/lesion	1	1/3	1	4	1	1/1/1	1-3/1/3
Overlapping stent	NA	NA/Yes	NA	No	NA	NA/NA/NA	NA-Yes/NA/Yes
Type of stent	C	C/C	C	T-T-T-T	C	T/T/T	T-T-T-T/C/T-T-T
Stent diameter (mm)	2.5	3.0/2.75	2.75	2.75-2.5-2.25-2.25	3.0	3.5/3.0/2.5	2.75-2.5-2.5-2.5-2.5/2.5/2.75-2.75-2.75
Length of stent (mm)	8	18/39	8	8-20-12-16	18	16/12/20	16-16-20-8/28/8-12-12
Final pressure (mmHg)	11	13/11	14	9-9-9-9	12	12/12/12	10-10-10-10/12/10-16-10
Balloon predilatation	Yes	No/No	Yes	No-Yes-Yes-Yes	Yes	Yes/Yes/No	Yes-Yes/Yes/Yes
Max BD (mm)	2.5	NA/NA	2.5	NA-2.5-2.0-2.0	3.0	2.5/3.0/NA	2.5-2.5/2.5/2.5
Max BL (mm)	15	NA/NA	15	NA-15-20-20	15	15/10/NA	15-15/15/15
Max BP (mmHg)	8	NA/NA	10	NA-8-8-8	8	8/8/NA	8-8/8/8
Balloon dilatation after stenting	No	No/No	No	No	Yes	No	No-No /No /No
Max BD (mm)	NA	NA/NA	NA	NA	3.0	NA/NA/NA	NA-NA/NA/NA
Max BL (mm)	NA	NA/NA	NA	NA	15	NA/NA/NA	NA-NA/NA/NA
Max BP (mmHg)	NA	NA/NA	NA	NA	20	NA/NA/NA	NA-NA/NA/NA
Restenosis characteristics							
Type	IB	IB/NA	ID	III	ID	IB/NA/II	NA-NA/IB/IB
Location	Proximal end	Proximal end /NA	Proximal and distal end	In-segment	Distal end, in-stent	Proximal end/NA/in-stent	NA-NA/Proximal end /Proximal end
Comments	Injury caused by balloon outside stent margins	NA	Injury caused by balloon outside stent margins	No stent overlapping/diffuse disease	NA	Diffuse disease	Diffuse disease

AHA – American Heart Association; BD – balloon diameter; BL – balloon length; BP – balloon pressure; C – Cypher; Diag – diagonal branch; ISR – in-stent restenosis; LAD – left anterior descending branch; MI – myocardial infarction; NA – not applicable; OM – marginal branch; RCA – right coronary artery; T – Taxus.

following deployment in order to minimise the chances of restenosis at the ends of the stent.

An analysis of the findings of the Taxus II trial showed that restenosis at the distal end of the stent was reduced by the use of Taxus stents, while there was also a tendency towards reduction in the restenosis rate at the proximal end.<sup>22</sup>

Analysis of the diabetic patients in the SIRIUS trial showed a trend towards a greater need for revascularisation in that subgroup (especially those taking insulin) when compared with non-diabetic patients.<sup>23</sup> Even in high risk populations of diabetic patients no case of diffuse in-stent restenosis was seen in rapamycin-eluting stents. It is interesting that diffuse restenosis was observed in both diabetic and non-diabetic patients. In another study, diabetes mellitus was the only factor correlated with restenosis.<sup>24</sup> In our study, the patients with diffuse restenosis were not diabetic. However, in those patients diffuse disease and long lesions were treated by the implantation of multiple stents. In a subgroup of the SECURE trial, where intravascular ultrasound was used, 13 of the 30 lesions with in-stent restenosis following implantation of a Cypher stent showed diffuse restenosis (2 diffuse in-stent, 11 diffuse hyperplastic).

Incomplete coverage of the lesion, spaces between deployed stents, damage to the endothelium from the use of intraluminal balloons other than those used for stenting, and stent underexpansion, have all been correlated with restenosis of drug-eluting stents.<sup>17,18,25,26</sup> All of these procedural and operator-related factors may be responsible for failure of drug-eluting stents. In our series of patients, most cases of restenosis at the stent margins could be attributed to endothelial injury from the use of an intraluminal balloon outside the deployed stent, incomplete coverage of the lesion, and spaces between stents. The fact that both our cases of diffuse restenosis occurred following the treatment of diffuse disease with deployment of multiple stents suggests that the initial disease played a role in the outcome.

### Limitations of the study

The present study is based on our experience from the treatment of patients with drug-eluting stents in everyday clinical practice and so has several limitations. First, coronary angiography was performed during follow up only in patients with symptoms or reversible myocardial ischaemia. No angiographic examinations were carried out on patients who were free of symptoms and had a negative stress test. Second, intracoronary ultrasound was not used in all patients who had restenosis; thus, we

do not have detailed information about the morphology of the regions where restenosis occurred. This, of course, represents normal daily practice in most haemodynamic laboratories.

### Conclusions

Our findings demonstrate that drug-eluting stents can be used routinely in clinical practice, regardless of the nature of the stenoses and the patients' clinical characteristics. The type of restenosis is mainly focal, though diffuse restenosis may also occur following the treatment of complex lesions with multiple stents.

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