Clinical Research

Medium-Term Results from the Clinical and Angiographic Follow-up of Patients after Angioplasty and Implantation of Sirolimus-Eluting Stents

Petros S. Dardas, Dimitris D. Tsikaderis, Nikos E. Mezilis, Stavros Hatzimiltiadis

Thessaloniki Heart Institute, "Agios Loukas" Hospital, Thessaloniki, Greece

Key words:
Sirolimus-eluting stents, restenosis.

Introduction: The aim of this study was to evaluate the medium-term clinical and angiographic results, as well as the occurrence and treatment of restenosis, following the implantation of sirolimus-eluting stents (SES) in patients undergoing coronary angioplasty.

Methods: All patients who have an SES implanted in our department are entered into a database, with a view to evaluating the use of such stents in everyday clinical practice. This study included patients who consented to repeat angiography 8 ± 2.4 months after stent implantation. The study population consisted of 91 patients (63 men, mean age 58 ± 8.1 years) with 116 stenoses in all. This represented 17.4% of all patients who had an SES implanted during the study period. All the angiographic examinations were analysed independently using quantitative coronary analysis in order to determine the relationship between clinical and angiographic data and restenosis and late lumen loss.

Results: The mean vessel diameter was 2.5 ± 0.48 mm and the mean lesion length was 12.61 ± 1.54 mm. The late lumen loss was 0.04 ± 0.49 mm. Restenosis was seen in 10 patients (12 vessels), of whom 4 were diabetics. The restenosis was in-stent in 7 vessels, in-segment in 5, and was localised (length of restenosis <10 mm) in all patients. After repeat angioplasty and SES implantation all the patients with restenosis remained free of symptoms 8 ± 1.5 months later. Diabetes mellitus was the only factor to be correlated with restenosis.

Conclusions: Restenosis following implantation of SES is mainly localised and occurs with about the same frequency within and outside the stent. The incidence of major cardiac events and restenosis following SES implantation is low. However, their long term efficacy in everyday clinical practice must be proved in large randomised studies in order to confirm the results presented here.

Manuscript received:
August 16, 2004;
Accepted:
November 24, 2004.

Address:
Petros Dardas

21 Vitsi St., Panorama
Thessaloniki, Greece
e-mail:
pdardas@spark.net.gr

Rapamycin is known to have anti-hyperplastic (anti-inflammatory and anti-proliferative) properties.[1,2] Many studies to date have demonstrated a reduction in restenosis following the implantation of sirolimus-eluting stents (SES) as a result of the inhibition of intimal hyperplasia.[3] However, the implantation of such stents does not completely eliminate restenosis, which is still seen in certain cases.[4] The aim of this study was to evaluate the medium term clinical and angiographic results following angioplasty and SES implantation in everyday clinical practice and to discuss the cases of restenosis occurrence and treatment.

Methods

Since May 2002 SES (Cypher, Cordis, Europa, NV) have been used in our laboratory on a regular basis, with no particular clinical or anatomical exclusion criteria. All patients who have an SES implanted are en-

tered into a database with a view to evaluating the use of these stents in everyday clinical practice. These patients are followed up clinically and paraclinically (scintigraphic assessment of myocardial perfusion) after 6-8 months. Any occurrences of angina are also recorded and where necessary a repeat procedure is carried out (percutaneous or surgical), either in the vessel where angioplasty was performed, or in another vessel, or both, as required.

In the present study we analysed the clinical and angiographic characteristics of a subgroup of patients who had had SES implanted and subsequently underwent repeat angiography 8 ± 2.4 months after the original procedure. This included both patients who had a recurrence of angina and asymptomatic patients with or without a positive thallium stress test.

A total of 91 patients were evaluated (63 men, mean age 58 ± 8.1 years) with 116 stenoses in all. This represented 17.4% of all patients who had an SES implanted during the study period. All patients were given a combination of aspirin (100 mg) and clopidogrel (300 mg bolus 24 hours before the angioplasty procedure and 75 mg after) over a 12-week period. Platelet glycoprotein IIb/IIIa inhibitors were given in certain cases, based on clinical indications (mainly in patients with acute ischaemic syndrome and the presence of intraluminal thrombus). Balloon predilatation and overinflation of the stent after implantation were optional. The number of stents implanted per patient was based on angiographic criteria.

Aims of the study

The aims of the study were to describe the angiographic and clinical results from the follow up of all patients and the management of any cardiac events. Angiographic endpoints were restenosis and late loss of lumen. Restenosis was defined as stenosis >50% and was classified as either in-stent or in-segment (outside the stent but within 5 mm of its ends). Late loss was defined as the difference between the minimum lumen diameter following the angioplasty procedure and that calculated from the repeat angiography. The type of restenosis (in-stent, in-segment, localised, diffuse) was assessed for each patient.

Clinical endpoints included the following:

- Target lesion revascularisation. Percutaneous or surgical reperfusion because of in-stent or in-segment restenosis.
- Target vessel revascularisation. Percutaneous or surgical reperfusion because of restenosis in the target vessel but at a different location from the original lesion.
- In-stent thrombosis (subacute or late).
- Myocardial infarction.
- Death.

A correlation was sought between the above clinical and angiographic endpoints and the following parameters: ejection fraction <40%, diabetes mellitus, vessel diameter, lesion length, lesion calcification, total occlusion, restenosis from a previously treated lesion, degree of overlap between stents, absence of stent predilatation and overinflation.

Statistical analysis

Simple logistic regression analysis was used to assess any correlations and to show any statistically significant differences between the above parameters. The χ^2 test was used for the comparison of variables. Continuous variables are given as mean ± standard deviation and comparisons between mean values in subgroups were made using the Student t-test. Pearson's correlation coefficient was used to examine linear correlations between quantitative parameters and late loss of lumen. A p-value <0.05 was the criterion of statistical significance.

Results

Characteristics of patients and stenoses

The clinical and angiographic characteristics are given in table 1. Of the patients examined, 43% had unstable angina, 26.7% were diabetic, 6% had an ejection fraction <40%, 5.2% had restenosis from a previously treated lesion (Figure 1). Of the lesions, 14.7% were calcified, 6.9% were chronic total occlusions, 16.1% involved a bifurcated vessel and 23.8% contained a significant amount of thrombus. The majority of the lesions (90.5%) were classified as B or C according to the system of the American Heart Association.

Technical characteristics

Of the total of 116 lesions for which SES were implanted, 58 were in the left anterior descending coronary artery branch, 36 in the circumflex, 16 in the right coronary artery and 6 were in grafts. Platelet glycoprotein IIb/IIIa inhibitors were given in 35% of patients. A total of 165 SES were implanted (1.8 stents/patient) and overlapping stents were used in 31% of lesions. The

Table 1. Clinical and angiographic characteristics of the patients (n=91).

Clinical syndrome	Clinical characteristics	Angiographic characteristics
Stable angina (55%)	Diabetes (26.7%)	Restenosis from prior lesion (5.2%)
Unstable angina (43%)	History of infarction (44.8%)	Type B (78.5%)
Acute myocardial infarction (2%)	Ejection fraction <40% (6%)	Type C (12%)
	Renal failure (1.2%)	Calcified lesions (14.7%)
		Complete occlusion (6.9%)
		Bifurcated vessels (16.1%)

mean SES diameter was 3 ± 0.18 mm and the mean length was 20 ± 12.1 mm. SES placement without predilatation was used in 46% of vessels. The maximum inflation pressure was 14 ± 2 Atm and overinflation with a larger balloon was performed in 68% of vessels (Table 2).

Quantitative coronary angiography

The mean vessel diameter was 2.5 ± 0.48 mm and the mean lesion length was 12.61 ± 1.54 mm. Table 3 shows the luminal stenosis as a percentage, the minimum lumen diameter and the late loss of lumen (0.04 ± 0.49 mm) in and around the stent.

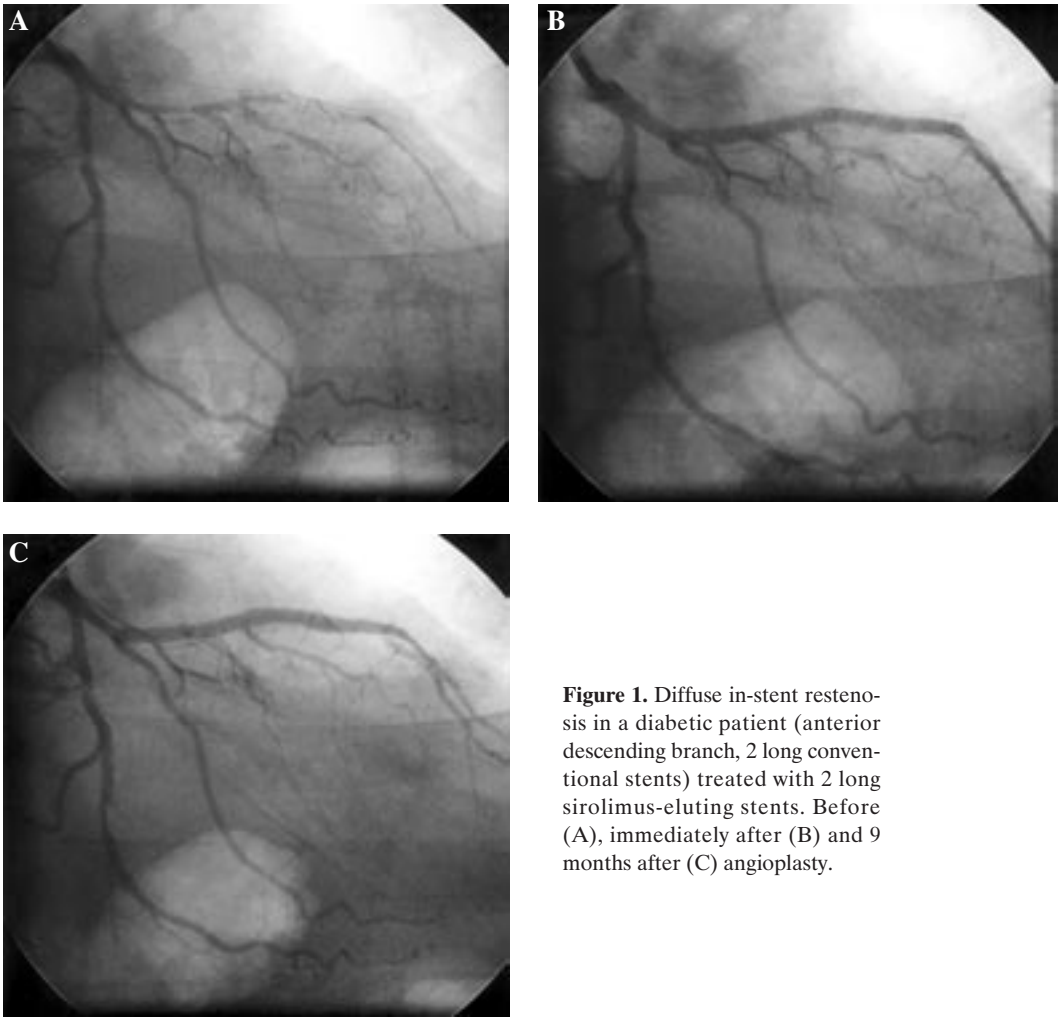

Figure 1. Diffuse in-stent restenosis in a diabetic patient (anterior descending branch, 2 long conventional stents) treated with 2 long sirolimus-eluting stents. Before (A), immediately after (B) and 9 months after (C) angioplasty.

Table 2. Technical characteristics

Vessel	LAD: 58, Cx: 36, RCA:16, grafts: 6
Number of stents	165 (1.8 stents/patient)
Stent length	30 ± 12.1 mm
Stent diameter	3 ± 0.18 mm
Without predilatation	46%
Maximum inflation pressure	14 ± 2 Atm
Overinflation	76%
Overlapping stents	31%

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

Clinical and angiographic results – restenosis characteristics

Table 4 shows the major undesirable cardiac events from all patients. No patient died. One suffered an acute myocardial infarction due to late thrombosis 3 months after angioplasty (clopidogrel was stopped 7 days before the event). Repeat angiography showed total occlusion of the responsible vessel and the patient was treated conservatively. Restenosis was seen in 10 patients (12 vessels), 4 of whom were diabetics. The restenosis was in-stent in 7 vessels, in-segment in 5, and was localised (length of restenosis <10 mm)[5] in all patients. Seven patients (9 vessels) with restenosis (6 vessels in-stent, 3 vessels within 5 mm before the stent) were treated with repeat angioplasty and implantation of a new SES (Figure 2). Two patients with restenosis were treated with coronary bypass surgery. In both cases the restenosis proximal to the stent included the final section of the main branch and the initial stenosis (anterior descending branch and circumflex artery) was at the ostium. One patient underwent aortocoronary bypass because of the development of coronary artery disease in the same vessel, but at a different location from the original lesion (tar-

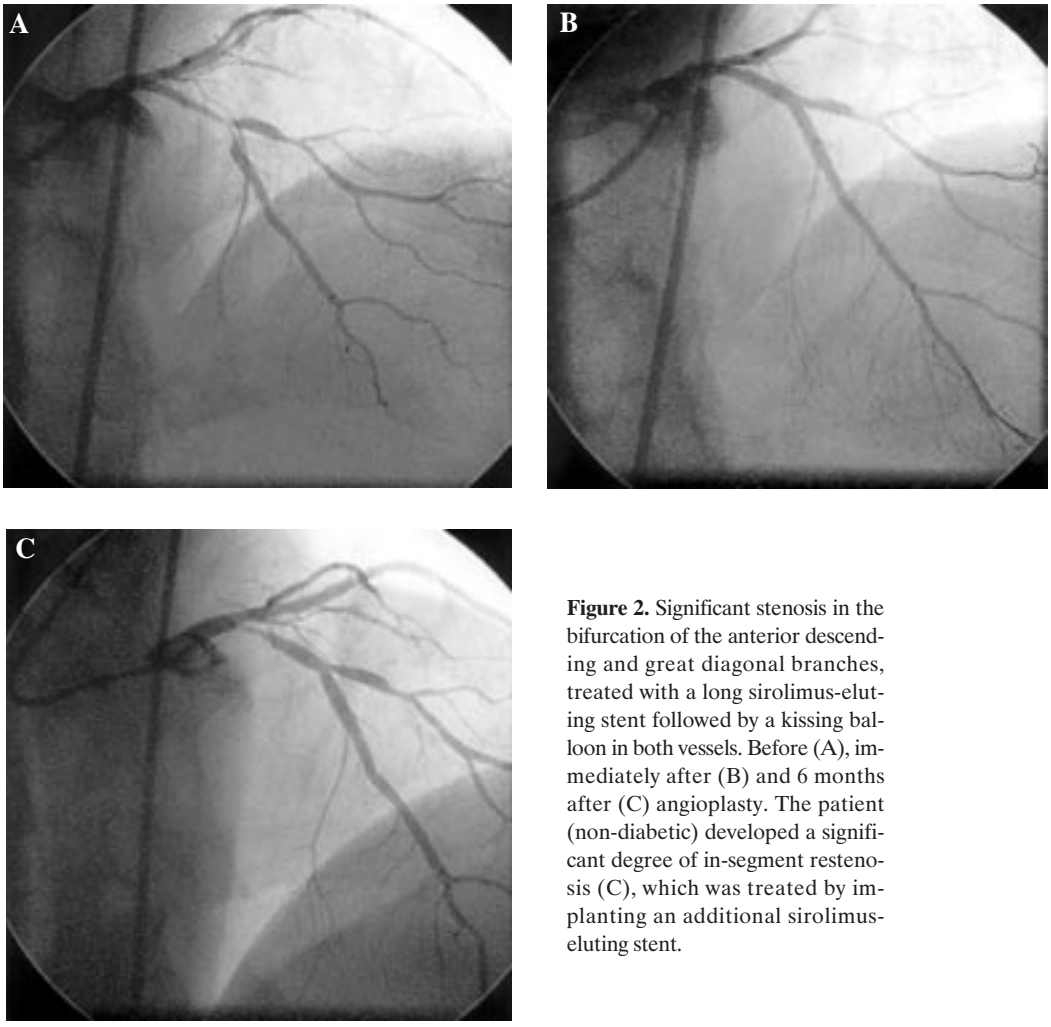

Figure 2. Significant stenosis in the bifurcation of the anterior descending and great diagonal branches, treated with a long sirolimus-eluting stent followed by a kissing balloon in both vessels. Before (A), immediately after (B) and 6 months after (C) angioplasty. The patient (non-diabetic) developed a significant degree of in-segment restenosis (C), which was treated by implanting an additional sirolimus-eluting stent.

Table 3. Quantitative coronary angiography before and immediately after angioplasty and stenting and on repeat coronary angiography.

	RD (mm ± SD)	LL (mm ± SD)	DS (% ± SD)	MLD (mm ± SD)	Late Loss (mm ± SD)
Before	2.50 ± 0.48	12.61 ± 11.54	59 ± 14.3	0.86 ± 0.4	
After			16 ± 9.53	2.26 ± 0.3	
Repeat			21 ± 14.1	2.23 ± 0.5	0.04 ± 0.49
			p: NS	p: NS	

RD – vessel reference diameter, LL – lesion length, DS – diameter stenosis, MLD – minimum lumen diameter, Late Loss - late loss of lumen. p refers to the difference between "After" and "Repeat" values.

get vessel revascularisation). One patient with moderate restenosis was free of symptoms and was treated conservatively. All the patients with restenosis who were treated with repeat angioplasty and a new stent remain free of symptoms 8 ± 1.5 months after the repeat procedure.

Of the clinical and angiographic parameters referred to above (Table 5), only diabetes showed a statistically significant correlation with restenosis (Figure 3). In addition, diabetes, chronic occlusion, lesion length and vessel reference diameter were all significantly correlated with late loss of lumen (Table 6).

Discussion

Compared to previous studies concerning SES implantation,[6-8] the present study included patients with more risk factors (diabetes), more complex and longer lesions. These are patients who are encountered in everyday clinical practice. The clinical results, with a low incidence of undesirable events, and the angiographic findings on follow up confirm the low percentages of restenosis and clinical events associated with the use of SES that have been reported in multicentre studies. Thus, the treatment of complex lesions with SES is a fully acceptable method. No aneurysms were seen in

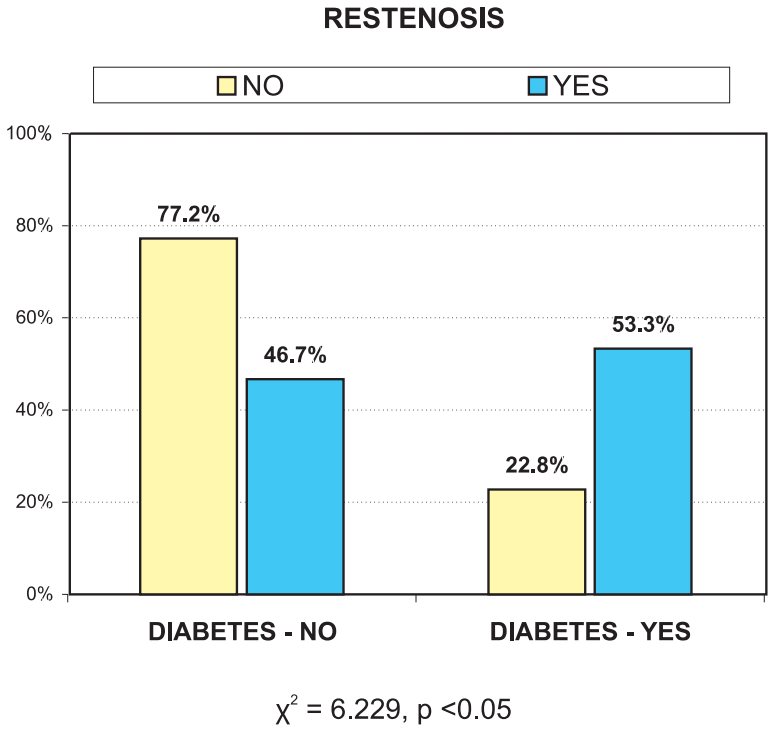

Figure 3. Correlation between diabetes and angiographic restenosis.

Table 4. Major cardiac events.

Death	0
Infarction	1
Subacute thrombosis	0
Late thrombosis	1
Target lesion revascularisation	7 (angioplasty) 2 (bypass)
Target vessel revascularisation	1 (bypass)

any patient who underwent repeat angiography. It is also worth noting that the incidence of thrombosis was low.

The type of restenosis is different when SES are used. Restenoses associated with conventional stents are more often diffuse,[9] while in SES the restenosis is localised in the majority of cases. Our findings are in full agreement with those of a previous study that reported restenosis data after SES implantation.[10] Such localised restenotic lesions can be treated more easily and effectively, either by simple balloon angioplasty[11,12] or with a new SES implantation. In our patients with restenoses we preferred repeat angioplasty with new SES implantation. The most common type of restenosis occurs at the margins of the stent (in-segment), mainly at the proximal margin, and this was the case in 42% of our patients who showed restenosis. According to previous studies,[3,10] restenosis at the ends of the stent is mainly due to incomplete covering of the lesion, which extends beyond the stent boundary. This can sometimes create problems. Two of our patients who had restenosis before the stent needed surgical treatment because the restenosis extended to the peripheral part of the main stem. Thus, our current technique, in accordance with the most recent indications and studies,[3,10,13] includes predilatation (when necessary) with smaller balloons, the use of longer stents aimed at fully covering the lesion, and, again when judged necessary, high pressure inflations using short balloons, within the stent margins. Since this technique has been in force we have not encountered any further cases with restenosis beyond the stent boundaries.

The outcomes in patients who showed restenosis, either in-stent or in-segment, and were treated with repeat angioplasty and new SES have been good so far, with all those patients remaining free of symptoms since the repeat procedure. However, it is still too early to draw firm conclusions or to make general treatment recommendations for this group of patients.

Diabetes, chronic occlusion, lesion length and vessel diameter are clinical and angiographic parameters that are correlated with the late loss of lumen. Only diabetes was found to be positively correlated with angiographic restenosis (>50% luminal stenosis).

Table 5. Correlation of clinical and angiographic parameters with restenosis in 116 treated lesions (χ^2 test of independence).

		Restenosis				
		No		Yes		p
Ejection fraction <40%	No	95	(94.1%)	14	(93.3%)	$\chi^2 = 0.012$
	Yes	6	(5.9%)	1	(6.7%)	p: NS
Diabetes	No	78	(77.2%)	7	(46.7%)	$\chi^2 = 6.229$
	Yes	23	(22.8%)	8	(53.3%)	p <0.05
Restenosis from prior lesion	No	96	(95.0%)	14	(93.3%)	$\chi^2 = 0.078$
	Yes	5	(5.0%)	1	(6.7%)	p: NS
Chronic occlusion	No	93	(92.1%)	15	(100.0%)	$\chi^2 = 1.276$
	Yes	8	(7.9%)	0	(0.0%)	p: NS
Calcification	No	88	(87.1%)	11	(73.3%)	$\chi^2 = 1.987$
	Yes	13	(12.9%)	4	(26.7%)	p: NS
Overlapping stents	No	70	(69.3%)	10	(66.7%)	$\chi^2 = 0.043$
	Yes	31	(30.7%)	5	(33.3%)	p: NS
Without predilatation	No	53	(52.5%)	10	(66.7%)	$\chi^2 = 1.060$
	Yes	48	(47.5%)	5	(33.3%)	p: NS
Overinflation	No	26	(25.7%)	2	(13.3%)	$\chi^2 = 1.098$
	Yes	75	(74.3%)	13	(86.7%)	p: NS

Table 6. Correlation of clinical and angiographic parameters with late loss of lumen (Pearson's correlation).

	Late Loss	
	Coefficient (r)	p
Lesion length	0.197	<0.05
Reference diameter	- 0.249	<0.01
Diabetes	0.106	<0.01
Total occlusion	0.230	<0.05

Limitations of the study

This study was not randomised and angiographic follow up was not possible in all patients who underwent SES implantation. As a result, the overall restenosis rate could not be determined. Also, the lack of the systematic use of intracoronary ultrasound did not permit a more detailed description of the features and mechanisms responsible for the restenosis in some patients.

Conclusions

The incidence of major cardiac events and restenosis associated with the use of SES in everyday clinical practice is low, even in the case of complex lesions, confirming the benefit from the use of these stents that has been reported in large studies.[3,14] Restenosis is mainly localised and occurs in-stent and in-segment with about the same frequency. It is seen more often in diabetic patients.

It appears that, while SES are being used more and more often to treat more and more complex lesions in sicker and sicker patients, their long term efficacy continues to be good. However, the results reported here need to be confirmed by large, randomised studies.

References

1. Marx SO, Marks AR: Bench to bedside: the development of rapamycin and its application to stent restenosis. Circulation 2001; 104: 1188-1193.
2. Suzuki T, Kopia G, Hayashi S, et al: Stent-based delivery of sirolimus reduces neointimal formation in a porcine coronary model. Circulation 2001; 104: 1188-1193.
3. Moses JW, Leon MB, Popma JJ, et al: Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003; 349: 1315-1323.
4. Degertekin M, Regar E, Tanbe K, et al: Sirolimus-eluting stent for treatment of complex in-stent restenosis: the first clinical experience. J Am Coll Cardiol 2003; 41: 184-189.
5. Mehran R, Dangas G, Abizaid AS, et al: Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. Circulation 1999; 100: 1872-1878.
6. Sousa JE, Costa MA, Abizaid A, et al: Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries: a quantitive coronary angiography and three dimensional intravascular ultrasound study. Circulation 2001; 103: 192-195.
7. Rensing BJ, Vos J, Smits PC, et al: Coronary restenosis elimination with a sirolimus-eluting stents: first European human experience with 6-month angiographic and intravascular ultrasonic follow-up. Eur Heart J 2001; 22: 2125-2130.
8. Morice M-C, Serruys PW, Sousa JE, et al: A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002; 346: 1773-1780.
9. Mehran R, Dangas G, Abizaid AS, et al: Angiographic patterns of in-stent restenosis: classification and implications for long term outcome. Circulation 1999; 100: 1872-1878.
10. Lemos PA, Saia F, Jurgen MR, et al: Coronary restenosis after sirolimus-eluting stent implantation: morphological description and mechanistic analysis from a consecutive series of cases. Circulation 2003; 108: 257-260.
11. Baim DS, Levine MJ, Leon MB, Levine S, Ellis SG, Schatz RA: Management of restenosis within the Palmaz-Schatz coronary stent (the US multicenter experience). Am J Cardiol 1993; 71: 364-366.
12. Mehran R, Mintz GS, Popma JJ, et al: Mechanisms and results of balloon angioplasty for the treatment of in-stent restenosis. Am J Cardiol 1996; 78: 618-622.
13. Schofer J, Schluter M, Gershlic AH, et al for the E-SIRIUS Investigators: Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomized control trial (E-SIRIUS). Lancet 2003; 362: 1093-1099.
14. Lemos PA, Lee Chi-hang, Degertekin M, et al: Early outcome after sirolimus-eluting stent implantation in patients with acute coronary syndromes (RESEARCH Registry). J Am Coll Cardiol 2003; 41: 2093-2099.