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Clinical and Angiographic Outcome of Sirolimus-Eluting Stent for the Treatment of Very Long Lesions

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ABSTRACT

Background and Objectives : Compared to bare metal stent, drug-eluting stent has improved the clinical and angiographic outcomes for *de novo*, simple lesions. In real world clinical practice, we often encounter more complex, long lesions, which increase the rate of restenosis and cardiovascular events. The aim of this study was to evaluate the clinical and angiographic outcome of sirolimus-eluting stent (SES) for the treatment of very long lesions in real world clinical practice. **Subjects and Methods :** We implanted multiple SESs (>40 mm in total length) in 113 de novo lesions in 113 patients. The average length of the implanted stents was 58±14 mm (range: 41-112 mm) and a mean of 2.2 stents were implanted in each lesion and the average stent diameter was 3.0 ±0.3 mm. **Results :** Procedural and angiographic success were achieved in all the patients without death or coronary artery bypass surgery. Non-Q wave MI (CK-MB≥ 3 times the normal value) developed in 13 patients (11.5%). Two patients experienced late stent thrombosis after discharge (1.8%). The major adverse cardiac events (MACE)-free survival was 94% at 12 months. There were two sudden cardiac deaths. Six months follow up angiography was performed on 76 patients (67%) and angiographic binary restenosis developed in 7 patients (9.2%). All of them were the focal type in-stent restenosis and these were found to be located at the distal stents. **Conclusions :** In conclusion, long lesion coverage with SESs is feasible with a favorable mid-term outcome in real world clinical practice. **(Korean Circulation J 2006;36:490-494)**

KEY WORDS : Percutaneous coronary angioplasty ; Stents ; Outcome.

Introduction

Drug-eluting stent (DES) lowers the amount of intimal hyperplasia and it significantly improves the clinical outcome of percutaneous coronary intervention (PCI) for treating short lesions.[1-3] In clinical practice, we encounter more restenosis-prone lesions such as left main lesions, restenotic lesions, small vessels, bifurcation lesions and long lesions than are present in the patients included in clinical trials. The target lesion length has been shown to be an independent predictor of in-stent restenosis and long lesion stenting had a high risk for revascularization in era of bare metal stenting.[4)5)] Yet there is a lack of solid evidence pertaining to the safety and effectiveness of DES stents for treating long lesions and there's a great need to demonstrate this. Therefore, we evaluated the clinical and angiographic outcomes of long lesion coverage with using serolimus-eluting stents (SES) in the real world clinical practice.

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Subjects and Methods

Study subjects

Between March 2003 and May 2004 at three cardiovascular centers where more than 800 PCIs were performed in a year, 113 long lesions in 113 patients

were treated with implanting multiple SESs (Cypher, Johnson & Johnson, USA). All the patients had both the clinical indications for PCI and an angiographic diameter stenosis ≥50%. The inclusion criterion was the presence of de novo coronary lesions that were planned to be implanted with multiple SESs (a total stent length ≥40 mm per lesion). Patients with restenotic lesions, lesions in saphenous vein grafts and lesions involving the left main coronary artery were excluded from this study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and all the patients gave us an informed consent.

Stent implantation and medication after stenting

All 113 lesions in 113 patients were treated with multiple SESs. The stents were implanted according to the standard interventional techniques. For the scheduled procedures, all the patients received aspirin 200 mg/day and clopidogrel 75 mg or ticlopidine 500 mg for 3 days before the procedure. The emergency patients received loading dosage of aspirin and clopidogrel. All lesions were predilated with using an optimal sized balloon according to the decision of the operating doctor. All the segments with stenosis ≥20% at the target lesions were completely covered with stents. The length and number of the required stents were decided upon by the operating doctor according to visual estimation. All the procedures were performed without intravascular ultrasound guidance. After the procedures, the patients received ticlopidine 500 mg/day or clopidogrel 75 mg/day for 6 months and aspirin 200 mg/day indefinitely. Cilostazol 100 mg/twice a day was given to the patients who had very long stents ≥65 mm implanted or if they were were unable to take ticlopidine or clopidogrel. We did not use abciximab.

Peri-procedural and 12-months clinical follow-up

Procedural success was defined as a diameter stenosis <30% in the treated segment after stent implantation and no major cardiovascular events such as death, Q-wave myocardial infarction or emergency coronary bypass surgery. Myocardial infarction was documented by an increase in the serum creatinine kinase-MB level of more than three times the upper limit, which measured 24 hours after the procedure. Patients were clinically followed in the outpatient clinic for 12 months and data was also obtained by serial telephone interviews. Stent thrombosis was classified as acute (≤1 day), sub-acute (2-30 days) and late (>30 days) thrombosis based on the angiographic and clinical findings. All the patients were monitored for any major cardiovascular events (MACEs); these were defined as cardiac death, myocardial infarction, stent thrombosis or a need for revascularization.

Follow-up angiography

Angiographic follow-up study at 6 months was recommended for all the patients. If any clinical evidence of myocardial ischemia developed at during the follow-up time, then hospital admission and coronary angiography were recommended. Angiographic binary restenosis was defined as a narrowing of ≥50% of the vessel diameter at the site of the previous dilatation. The indication for a new revascularization at a site of previous PCI was the occurrence of restenosis with the correlating symptoms. The restenosis patterns were qualitatively assessed using the Mehran classification system.[6]

Angiographic analysis

Quantitative coronary angiographic analysis was performed using the computer-assisted automated edge detection method (CASS System II, Pie Medical Imaging, Netherlands) according to 2 observers. At least 2 orthogonal projections were selected for analysis; these were obtained after intracoronary injection of 200 μg nitrogrycerin. The mean reference vessel diameter, the minimal luminal diameter, the lesion length and the percentage diameter stenosis were analyzed for all the patients. The total length of the implanted stents was measured on the final angiogram with using the length measurement program included in the QCA software.

Statistical analysis

Statistical analysis was performed using SPSS 12 (SPSS Inc., Chicago, Illiois). Qualitative data are presented as frequencies and continuous data are presented as means±SDs.

Results

The baseline clinical data are shown in Table 1. The mean age was 59 years and diabetes mellitus was present in 34% of the patients. Glycoprotein IIb/IIIa inhibitors were not given to any patients and all the patients were prescribed more than two antiplatelet agents. The coronary angiographic findings are shown in Table 2. The most commonly treated artery was the left anterior descending coronary artery (55%). The mean reference vessel diameter and mean lesion length were 3.0±0.3 mm and 46.8±12.3 mm, respectively. More than two stents were used in all lesions and a mean of 2.2 stents was used in each lesion. The average stent length was 57.6±13.9 mm long (range: 41-112 mm) and the stent-to-lesion length ratio was 1.2 ±0.3. There were 13 peri-procedural non-Q myocardial infarctions (11.5%), but any Q-wave myocardial infarction, emergency bypass surgery or death did not occur (Table 3).

Table 1. Baseline clinical characteristics of the patients

	n=113 patients
Age (years)	59±11
Male sex	86 (76.1%)
Diabetes mellitus	34 (30.1%)
Smoking	44 (38.9%)
Hypertension	48 (42.5%)
Previous MI history	16 (14.2%)
Prior PCI	2 (1.7%)
Prior CABG	2 (1.7%)
Hypercholesterolemia	52 (46.0%)
Clinical diagnosis	
Stable angina	29 (25.7%)
Unstable angina	33 (29.2%)
Acute myocardial infarction	48 (42.5%)
Silent ischemia	3 (2.7%)
Anti-platelet agent medications	
Aspirin	113 (100%)
Ticlopidine	11 (9.7%)
Clopidogrel	96 (85.0%)
Cilostazol	41 (36.3%)
LVEF (%)	54.6±12.4%

MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, LVEF: left ventricular ejection fraction. Data are expressed as mean±standard deviation

Table 2. Coronary angiographic findings of the patients

	n=113
Treated artery	
LAD	55 (48.7%)
LCX	17 (15.0%)
RCA	41 (36.3%)
No. of disease vessels	
One	39 (34.5%)
Two	55 (48.7%)
Three	19 (16.8%)
Reference vessel diameter (mm)	3.0±0.4
Lesion length (mm)	46.7±12.3

LAD: left anterior descending artery, LCX: left circumflex artery, RCA: right coronary artery

Table 3. Peri-procedure and in-hospital results

	n=113
Used stents	
Number	2.2±0.4
Diameter (mm)	3.0±0.3
Total length (mm)	57.6±13.9
Primary success	113 (100%)
Complications	
QMI	0
Non-QMI (CK-MB ≥ x3 normal value)	13 (11.5%)
Acute stent thrombosis	0
Emergency surgery	0
Cardiac death	0

QMI: Q-wave myocardial infarction, MI: myocardial infarction

During follow-up, late stent thrombosis that was confirmed by coronary angiography occurred in a patient who suffered with dilated cardiomyopathy and a low left ventricular ejection fraction (32%). This developed 50 days after successful implantation of a 56 mm long SES, and it was successfully treated with balloon PCI. The patient was kept on aspirin and clopidogrel until the PCI. Eventually, he suddenly died of ventricular fibrillation 273 days after SES implantation. Another sudden death occurred at home for a patient who suffered with stable angina 512 days after PCI. The patient had taken the prescribed aspirin and clopidogrel only intermittently. This event was perhaps related to late stent thrombosis. Repeat revascularization of the target lesion was required in 6 patients (5.3%). Overall, cardiac events related to the SES occurred in 7 patients (7.1%) including non-fatal myocardial infarction (n=1), repeat target lesion revascularization (n=6) and cardiac death (n=2) (Fig. 1). The

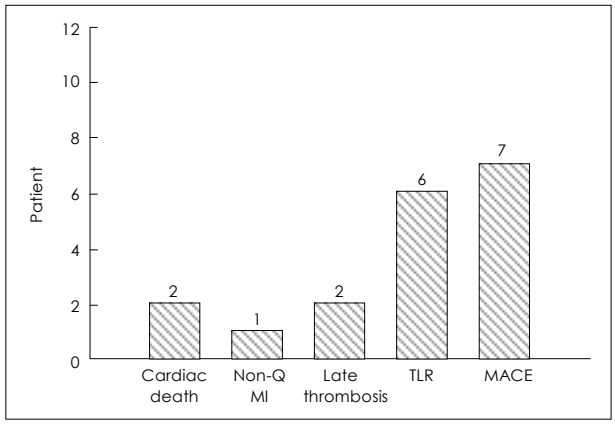

Fig. 1. Major cardiovascular events at 12 months follow-up. MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass surgery, TLR: target lesion revascularization, MACE: major adverse cardiac events.

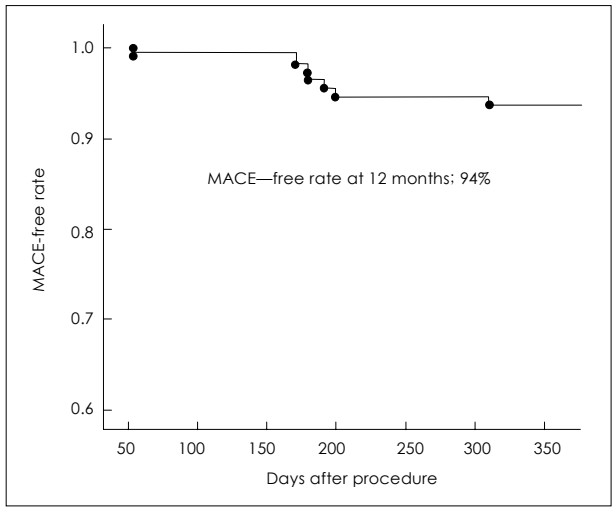

Fig. 2. Freedom from major adverse cardiac events (MACE) defined as cardiac death, myocardial infarction, stent thrombosis, or a need for revascularization was estimated by Kaplan-Meier method.

Table 4. Quantitative coronary angiographic results

	Pre-stent	Post-stent	Follow-up
Reference vessel diameter (mm)	3.04±0.39	3.04±0.34	3.10±0.40
Minimal lumen diameter (mm)	0.38±0.34	2.73±0.32	2.42±0.67
Acute gain (mm)		2.35±0.50	
Late loss (mm)			0.31±0.71
Diameter stenosis (%)	87.32±9.99	8.85±6.76	22.01±18.10

probability of MACE-free survival at 12 months was 94% (Fig. 2).

Angiographic follow-up was available for 76 patients (67%). The results of the post-procedural and follow-up angiographic QCAs are listed in Table 4. Angiographic binary restenosis occurred in 7 patients (9.2%), and all of them were the focal type without any of the diffuse or proliferative types. Four of the 7 patients had in-stent restenosis in the mid-portion of the far distal stents. Another three restenoses developed in the overlapping segments of two stents.

Discussion

The current study demonstrates that the use of SES for the treatment of very long lesions has improved the clinical and angiographic outcomes over that of the bare metal stent era. Diffuse lesion is a morphological characteristic associated with a poorer immediate and long-term clinical outcome after balloon angioplasty with or without stenting.[7)8)] In the Additional Value of NIR Stents for Treatment of Long Coronary Lesions (ADVANCE) Study, the MACE-free rate was 76.6% at 300 days. Several studies that have focused on intermediate length lesions have demonstrated favorable results with using SES. Ruiz-Nodar et al[9)] used 25 mm long SESs in patients who met the exclusion criteria of the RAVEL and SIRIUS studies, and the MACE rate at 6-months was 7%. More recently, obstructed full metal jacket stents that were treated by multiple DESs showed a low 1-year target vessel revascularization rate (7.5%) and MACE rate (18%).[10)] In that study, the 12 month MACE-free rate was 94% although the average stent length was 58±14 mm long.

Stenting in long segments is associated with more vessel trauma, a smaller vessel size and more exposed metal area, and all of this can lead to more neointimal growth and a higher restenosis rate than short stenting. In the bare metal stent era, the stented segment length was an independent predictor of restenosis.[11)] A stent length that exceeded the lesion length increased the risk of restenosis and this was independent of the stented lesion length.[12)] If the stented segment length was >35 mm, then the restenosis rate was 47.2%.[11)] So, we have been trying to reduce the stent length, and performing spot stenting has been suggested as an good strategy.[13)] But in the DES era, operating doctors are willing to completely cover lesions by stents and they are prone to use more long stents. We completely covered the lesions with >20% stenosis. In the present study, we found 7 angiographic restenosis (9.2%) in patients who were asymptomatic and these were found at the scheduled follow-up angiography at 6 months. All of those lesions were the focal type, which were found at the stents' overlapping segments or at the distally implanted stents. Thus, this finding indicates that these overlapping segments and distal small vessels are vulnerable to restenosis and we should try to optimize stent deployment in this type of segments.

Another debatable problem is the subacute and late stent thrombosis. Animal studies have demonstrated that the polymers used in DES are proinflammatory, and this becomes particularly problematic for long stent implantation.[14)] In the SIRIUS tria,[12)] the thrombosis rate at 270 days was 0.4% and in more complex lesions, the subacute stent thrombosis rate was 1.8%.[9)] A pooled meta-analysis of randomized clinical trials and registry studies showed the rate of stent thrombosis after DES to be similar to those of BMS.[15)] The long lesion coverage with long DESs becomes hypercoagulable and more sensitive to inflammation and thrombosis. DES also delays re-endothelialization, and late stent thrombosis (LST) is a progressive phenomenon that can occur at more than one year after implantation.[16)] The rate of stent thrombosis is higher in consecutive "real world" patients than in clinical trials, especially after discontinuation of ticlopidine or clopidogrel.[17)18)] In our study, no subacute stent thrombosis was note although two late stent thrombosis developed at 50 and 512 days after the procedure (1.8%). The rate of LST was much higher in our study, although the cumulative incidence of stent thrombosis was similar to previous reports.[2)] Cilostazol has shown comparable antiplatelet activity to ticlopidine after elective coronary stenting.[19)20)] One out of three patients received triple antiplatelet therapy in this study. That may be the major factor for the lower rate of LST, although future randomized clinical trials are need. However, the high rate of cumulative stent thrombosis underlines the possible need for long term antiplatelet medication for the patients receiving long DES stents.

In conclusion, long lesion coverage with SES is

feasible, and this has a favorable mid-term outcome in "real world" clinical practice. We need to optimize the antiplatelet therapy regimen and its duration for the high risk patients.

There are several limitations in this study because of the small size of the study group and there was no bare metal stent control group. Moreover, follow-up angiography was not done for all the patients. If we conduct intravascular ultrasound sonographic study, then the precise cause and mechanism of restenosis in this study group will be determined and we will be able to further reduce the rate of in-stent restenosis.

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