Clinical and Angiographic Outcomes After Placement of Multiple Overlapping Drug-Eluting Stents in Diffuse Coronary Lesions

Cheol Whan Lee, MD, Kyoung-Ha Park, MD, Young-Hak Kim, MD, Myeong-Ki Hong, MD, Jae-Joong Kim, MD, PhD, Seong-Wook Park, MD, PhD, and Seung-Jung Park, MD, PhD*

Multiple overlapping drug-eluting stents have increasingly been used to treat diffuse coronary disease, but the safety and efficacy of this approach remains unclear. We assayed the clinical and angiographic outcomes after placement of "full metal jacket" stents (stented length ≥60 mm) in 347 consecutive patients (352 lesions) with very long de novo coronary lesions. Mean age was 61.0 ± 10.1 years, and the mean stented length was 71.9 ± 13.7 mm. The procedural success rate was 97.7%. Major in-hospital complications (1 death, 2 cases of acute stent thrombosis) occurred in 3 patients (0.7%). Angiographic follow-up data, obtained for 230 (234 lesions) of the 328 eligible patients (70.1%), showed that the restenosis rate was 13.7%. Multivariate analysis found that the reference artery diameter (odds ratio 0.05, 95% confidence interval [CI] 0.01 to 0.33, p = 0.002) and the use of Taxus stents (odds ratio 2.88, 95% CI 1.03 to 8.04, p = 0.043) were significant predictors of restenosis. During follow-up (16.6 ± 6.9 months), 9 deaths (6 cardiac and 3 noncardiac), 1 nonfatal myocardial infarction, and 13 target lesion revascularizations occurred. The cumulative probability of survival without major adverse cardiac events (cardiac death, Q-wave myocardial infarction, and target lesion revascularization) was 95.4 ± 1.1% and 91.4 ± 2.1% at 1 and 2 years, respectively. Left ventricular dysfunction (ejection fraction <45%) was the only predictor of stent thrombosis (hazard ratio 18.24, 95% CI 1.65 to 201.19, p = 0.018) and cardiac death/Q-wave myocardial infarction (hazard ratio 5.37, 95% CI 1.28 to 22.49, p = 0.021). In conclusion, full metal jacket drug-eluting stents may be a safe and effective method to treat diffuse coronary disease and may be a useful treatment option for complex long lesions. **(Am J Cardiol 2006;98:918–922)**

The efficacy of drug-eluting stents (DESs) in reducing restenosis has been established in randomized clinical trials,[1–3] and their use in coronary interventions has increased. These trials usually enrolled patients with simple lesions, with most treated patients having relatively short narrowings. In real-world settings, however, multiple overlapping stents are often required to treat diffuse disease or long dissections. Furthermore, in clinical practice, the stented length has increased for full lesion coverage. When bare metal stents were used, these procedures were associated with a high rate of restenosis and were not generally recommended.[4–6] DESs have been found to reduce the need for reintervention and may be an improvement over bare metal stents in treating complex long lesions.[7] Little information is available, however, about the safety and efficacy of very long overlapping DESs in patients with diffuse disease.[8,9] We have determined the clinical and angiographic outcomes after placement of full metal jacket stents to treat diffuse coronary artery disease.

Methods

Study patients: The patient population consisted of a consecutive series of 347 patients (352 lesions) at Asan Medical Center who had been treated with "full metal jacket" stents, defined as a stented length ≥60 mm without gaps, for de novo diffuse coronary lesions from February 2003 to May 2005. Of these patients, 264 (266 lesions) had been treated with sirolimus-eluting stents and 83 (86 lesions) with paclitaxel-eluting stents. Angiographic follow-up at 6 months, or earlier if symptoms occurred, was attempted unless patients experienced any major adverse cardiac event during the first 30 days after the procedure, medical conditions were present contraindicating angiographic follow-up, or the patients were >80 years old.

Stenting procedure: A Cypher (Cordis, Miami Lakes, Florida) or Taxus (Boston Scientific, Natick, Massachusetts) stent was used in all patients. Stent implantation was performed according to standard techniques, and the operators selected stents. Complete lesion coverage was recommended, as well as angiographic optimization with <20% residual stenosis by visual estimate. During the procedure,

Department of Medicine, Asan Medical Center, University of Ulsan, Seoul, Korea. Manuscript received January 27, 2006; revised manuscript received April 25, 2006 and accepted May 1, 2006.

This study was supported by grants from the CardioVascular Research Foundation, Asan Institute for Life Science (Grant 2006-217), and the Korea Health 21 R&D Project, Ministry of Health & Welfare, Korea (Grant 0412-CR02-0704-0001).

*Corresponding author: Tel: 82-2-3010-3150; fax: 82-2-486-5918.

E-mail address: sjpark@amc.seoul.kr (S.-J. Park).

0002-9149/06/$ – see front matter
doi:10.1016/j.amjcard.2006.05.011

Table 1
Clinical characteristics

Characteristic	n = 347
No. of coronary lesions	352
Age (yrs)	61.0 ± 10.1
Men	252 (72.6%)
Current smoker	97 (28.0%)
Diabetes mellitus	126 (36.3%)
Total serum cholesterol ≥200 mg/dl	77 (22.2%)
Hypertension	201 (57.9%)
Clinical presentation	
Stable angina pectoris	184 (53.0%)
Unstable angina pectoris	133 (38.3%)
Acute myocardial infarction	30 (8.6%)
Previous myocardial infarction	21 (6.1%)
Previous percutaneous coronary intervention	75 (21.6%)
Previous coronary bypass surgery	11 (3.2%)
Multivessel coronary disease	257 (74.1%)
Left ventricular ejection fraction (%)	58.0 ± 10.1

Table 2
Angiographic and procedural characteristics

Characteristic	n = 353
Lesion characteristics	
Target coronary vessel	
Left anterior descending	193 (54.8%)
Left circumflex artery	14 (4.0%)
Right coronary artery	124 (35.1%)
Left main to left anterior descending	22 (6.3%)
Chronic total occlusion	60 (17%)
Ostial lesion	40 (11.4%)
Bifurcation	54 (15.3%)
Procedural characteristics	
Balloon/artery ratio	1.32 ± 0.18
Direct stenting	15 (4.3%)
Maximal inflation pressure (atm)	15.5 ± 3.5
Stents per lesion	2.5 ± 0.7
Stent length per lesion (mm)	71.9 ± 13.7
Quantitative coronary angiography	
Lesion length (mm)	55.8 ± 12.9
Reference vessel diameter (mm)	2.82 ± 0.40
Before intervention	
Minimal lumen diameter (mm)	0.66 ± 0.53
Diameter stenosis (%)	68.5 ± 13.5
After intervention	
Minimal lumen diameter (mm)	2.66 ± 0.40
Diameter stenosis (%)	4.5 ± 13.4
Follow-up	
Minimal lumen diameter (mm)	2.14 ± 0.68
Diameter stenosis (%)	22.9 ± 23.8
Acute gain (mm)	1.99 ± 0.58
Loss (mm)	0.52 ± 0.67
Angiographic restenosis	
Cypher stent	20/180 (11.1%)
Taxus stent	12/54 (22.2%)
Use of glycoprotein IIb/IIIa inhibitor	11 (3.1%)
Intravascular ultrasound guidance	256 (72.7%)

patients received a bolus of 8,000 U of heparin, with a repeat bolus of 2,000 U to maintain an activated clotting time of ≥300 seconds. All patients were pretreated with aspirin and clopidogrel. Aspirin (100 to 200 mg/day) was used indefinitely, and clopidogrel (75 mg/day) was used for ≥6 months.

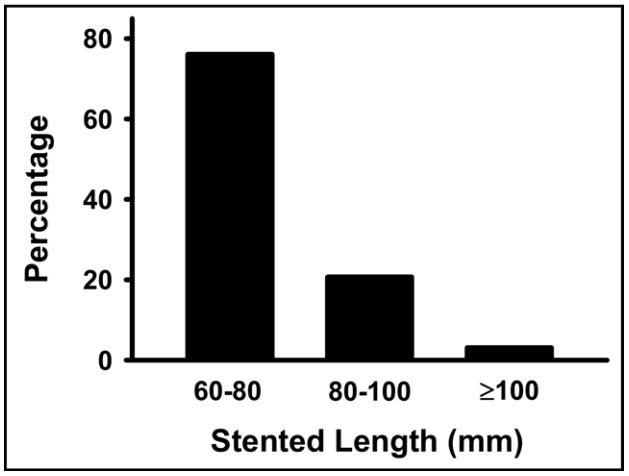

Figure 1. Distribution of stented lengths.

Angiographic analysis: All angiographic analyses were performed by 2 experienced angiographers unaware of the study goal. The percentage of diameter stenosis, minimal lumen diameter, and reference diameter using an on-line quantitative angiographic analysis system (Xcelera Cath 1.1, Philips, The Netherlands) were measured before predilation, after the stenting procedure, and at follow-up. The angiographic measurements were made during diastole after intracoronary nitroglycerin administration using a guiding catheter to calibrate magnification. Single matched views with the worst diameter stenosis were compared.

Definitions and clinical follow-up: All demographic, clinical, angiographic, and procedural characteristics were prospectively entered into the Asan Medical Center database. An echocardiographic examination was performed before angioplasty, and the left ventricular ejection fraction was calculated according to a modified Simpson's rule. Follow-up information was obtained by chart review and telephone interview, and all follow-up investigations were extended ≥6 months. Restenosis and major adverse cardiac events (cardiac death, Q-wave myocardial infarction, and target lesion revascularization) were evaluated. Procedural success was defined as successful stenting at the desired position with <30% residual stenosis and the absence of death, Q-wave myocardial infarction, or the need for either emergency bypass surgery or repeat revascularization during hospitalization. The diagnosis of procedural non–Q-wave myocardial infarction was based on an creatine kinase (CK)-MB elevation >3 times normal in the absence of new pathologic Q waves on postintervention electrocardiograms. Restenosis was defined by a diameter stenosis of ≥50% in the segment inside the stent or 5 mm proximal or distal to the stent at follow-up angiography. Deaths were classified as either cardiac or noncardiac. Deaths that could not be classified were considered cardiac. Myocardial infarction during follow-up was diagnosed when the CK-MB was elevated >3-

Table 3
Predictors of angiographic restenosis by logistic regression analysis

Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p Value	OR	95% CI	p Value
Reference artery diameter	0.05	0.01–0.34	0.002	0.05	0.01–0.33	0.002
Use of Taxus stent	2.29	1.04–5.05	0.041	2.88	1.03–8.04	0.043
Stented length	1.03	1.01–1.05	0.012			
Reference artery diameter >2.5 mm	0.22	0.08–0.59	0.002			
Stented length >80 mm	2.51	1.13–5.56	0.024			
Diabetes	1.39	0.61–3.18	0.427			
Lesion length	1.02	0.99–1.05	0.289			
Postintervention minimal lumen diameter	0.45	0.17–1.21	0.115			

OR = odds ratio.

fold with chest pain for ≥30 minutes or with the appearance of new electrocardiographic changes.

Statistical analysis: Data are expressed as means ± SDs for continuous variables and as frequencies for categorical variables. Continuous variables were compared using the unpaired Student's *t* test and categorical variables by the chi-square test. Regression analysis was performed to identify the determinants of restenosis. The Kaplan-Meier method was used to analyze the occurrence of clinical events during follow-up. Statistical significance was defined as a 2-sided value of $p < 0.05$.

Results

Baseline characteristics: The baseline clinical and angiographic characteristics of the patients are listed in Tables 1 and 2. Mean patient age was 61.0 ± 10.1 years (range 31 to 86); 36.3% had diabetes mellitus and 10.4% had left ventricular dysfunction (ejection fraction <45%). The average number of stent overlaps per lesion was 2.5 ± 0.7 (range 2 to 6), the average overlapped length was 1.9 ± 0.8 mm (range 0.5 to 3.5), and the total stented length was 71.9 ± 13.7 mm (range 60 to 150; Figure 1).

Procedural results: The procedural success rate was 97.7%. Adjunct high-pressure balloon dilation was required to achieve optimal stent expansion in all patients. The incidence of procedural non–Q-wave myocardial infarction was 19.6%. During hospitalization, major complications (cardiac death, Q-wave myocardial infarction, repeat revascularization, or emergency bypass surgery) occurred in 3 patients (0.9%). One patient (0.3%) died of cardiac tamponade immediately after the procedure. Two other patients, treated with Cypher stents, developed acute stent thrombosis with Q-wave myocardial infarction (0.6%) 4 and 12 days after the procedure. The latter patient died suddenly at 1 month after discharge.

Angiographic restenosis: Angiographic follow-up data were obtained for 230 (234 lesions) of the 328 eligible patients (follow-up rate 70.1%). Restenosis was documented in 30 patients with 32 lesions (13.7%) (in-stent 12.4% and in-segment 13.7%). There were 21 incidents of focal restenosis (65.6%), 6 of diffuse (18.8%), 1 of diffuse proliferative (3.1%), and 4 of total (12.5%) restenosis. Patients treated with Taxus stents had a higher restenosis rate than those treated with Cypher stents (22.2% vs 11.1%, $p = 0.044$), as well as a higher rate of late loss (0.78 ± 0.52 vs 0.45 ± 0.68 mm, $p = 0.002$). Univariate predictors of restenosis included the reference artery diameter, use of Taxus stents, and stented length (Table 3). Diabetes, lesion length, and minimal lumen diameter after the procedure were not significantly related to restenosis. On multivariate analysis, the reference artery diameter (odds ratio 0.05, 95% confidence interval [CI] 0.01 to 0.33, $p = 0.002$) and the use of Taxus stents (odds ratio 2.88, 95% CI 1.03 to 8.04, $p = 0.043$) were independent predictors of restenosis.

Table 4
Major clinical events during hospitalization and at follow-up

Characteristic	In-Hospital (n = 347)	Follow-up (n = 346)
Death	1 (0.3%)	9 (2.6%)
Cardiac death	1 (0.3%)	6 (1.7%)
Noncardiac death	0	3 (0.9%)
Myocardial infarction	70 (20.2%)	1 (0.3%)
Q-wave	2 (0.6%)	1 (0.3%)
Non–Q-wave	68 (19.6%)	0
Cardiac death/Q-wave myocardial infarction	2 (0.6%)	7 (2.0%)
Target lesion revascularization	2 (0.6%)	13 (3.8%)
Repeat intervention	2 (0.6%)	12 (3.5%)
Bypass surgery	0	1 (0.3%)

Clinical outcomes: Clinical follow-up data were available for all patients (16.6 ± 6.9 months), and the clinical events are listed in Table 4. During follow-up, 9 deaths (6 cardiac and 3 noncardiac), 1 Q-wave myocardial infarction, and 13 target lesion revascularizations occurred. Late stent thrombosis occurred in 1 patient 2 months after the procedure, and angiography showed thrombotic occlusion of a stented lesion. This patient had been taking clopidogrel and aspirin. The event-free survival rate for cardiac death/Q-wave myocardial infarction was 98.2 ± 0.7% and 96.3 ± 1.3% at 1 and 2 years, respectively (Figure 2). The cumulative probability of survival without major adverse cardiac events was 95.4 ± 1.1% and 91.4 ± 2.1% at 1 and 2 years,

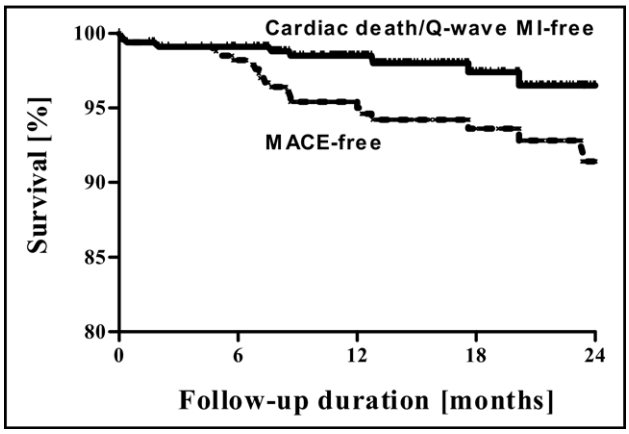

Figure 2. Event-free survival curves for cardiac death/Q-wave myocardial infarction (MI) or major adverse cardiac events (MACEs).

respectively. Left ventricular dysfunction (ejection fraction <45%) was the only significant predictor of stent thrombosis (hazard ratio 18.24, 95% CI 1.65 to 201.19, p = 0.018) and cardiac death/Q-wave myocardial infarction (hazard ratio 5.37, 95% CI 1.28 to 22.49, p = 0.021). No factors were predictive of major adverse cardiac events.

Discussion

The results we present have shown that the full metal jacket approach is a safe procedure in the treatment of diffuse coronary disease, with acceptable immediate and late clinical outcomes, that the reference artery size and type of DES are predictors of restenosis, and that left ventricular dysfunction is related to stent thrombosis or cardiac death/Q-wave myocardial infarction after the procedure. These findings suggest that multiple overlapping DESs may be an effective treatment option for complex long lesions.

Diffuse coronary disease has been a technical challenge for the interventional cardiologist, with disappointing clinical outcomes. Conventional balloon angioplasty is rarely sufficient for angiographic success, and multiple stents are usually needed to treat complex long lesions. Long stents can achieve excellent immediate results, with few immediate complications, but the risk of restenosis increases with stent length.[4–6] Long bare-metal stents have seldom been used because of the high rate of restenosis, and coronary artery bypass surgery has often been performed on this subset of patients. DESs have eliminated much of the restenosis previously observed with bare metal stents, and DESs have been increasingly used in high-risk lesions and in populations excluded from clinical trials. In addition, the trend is increasing toward the use of multiple overlapping DESs without clear trial support. Studies of small series of patients have shown that implantation of multiple overlapping stents to treat very long diffuse disease is safe and associated with good mid-term outcomes.[8,9] Our series included a relatively large number of patients with very long diffuse disease, confirming that this method results in acceptable clinical outcomes. In the present study, however, there appeared to be a high rate of procedural CK-MB elevation, which may have been related to a heavy plaque burden. Although it was not associated with major adverse cardiac events during the follow-up, procedural CK-MB elevation may be a limitation to the full metal jacket approach. This procedure is, therefore, considered experimental, and its use should not be generalized until its safety and efficacy has been demonstrated in large randomized trials.

Restenosis affects a significant number of patients with complex long lesions. We found that the reference artery size was an important predictor of angiographic restenosis, suggesting that full metal jackets may be effective in relatively large vessels. However, this approach resulted in an increased risk of restenosis in small vessels, requiring further improvement. In addition, we found that Cypher and Taxus stents resulted in restenosis rates of 11.1% and 22.2%, respectively, suggesting that the risk of restenosis is influenced by the type of DES used. In several head-to-head comparison trials, the results favored Cypher stents, which had lower rates of late loss and restenosis.[10,11] It is unclear, however, whether differences exist in the effectiveness of currently approved DESs in patients with very long diffuse disease. Additional randomized studies are required to determine whether the 2 types of DESs differ in safety and efficacy.

Although DESs constitute a major achievement in preventing restenosis, concerns have been raised regarding polymer-associated thrombogenicity and delayed vascular healing. Stent thrombosis is a rare event and may not be increased by DESs[12]; however, the probability of stent thrombosis increases with stent length. We found that 2 patients experienced acute (0.6%) and 1 experienced late (0.3%) stent thrombosis after the index procedure. All patients developed Q-wave myocardial infarctions, and 1 patient died 1 month after the event. We also found that patients with left ventricular dysfunction were at high risk of stent thrombosis and cardiac death after full metal jacket stenting. Furthermore, a previous study has demonstrated that a low left ventricular ejection fraction increased the risk of late stent thrombosis.[13] Taken together, these results suggest that the full metal jacket approach may be associated with an acceptable risk of stent thrombosis, but that it should be used carefully in patients with poor left ventricular function.

Our study had several potential limitations. First, the lack of a control group treated with bypass surgery or medical therapy precluded a determination of the role of treatment differences on clinical outcomes. Second, the choice of DES was left to the physician, leading to possible selection bias. Third, the angiographic follow-up was incomplete, possibly leading to an error in the restenosis rate.

1. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnàr F, Falotico R, for the RAVEL Study Group. A randomized comparison of a sirolimus-

eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002:346:1773–1780.
2. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE, for the SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349:1315–1323.
3. Colombo A, Drzewiecki J, Banning A, Grube E, Hauptmann K, Silber S, Dudek D, Fort S, Schiele F, Zmudka K, Guagliumi G, Russell ME, for the TAXUS II Study Group. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. *Circulation* 2003;108:788–794.
4. Kobayashi Y, De Gregorio J, Kobayashi N, Akiyama T, Reimers B, Finci L, Di Mario C, Colombo A. Stented segment length as an independent predictor of restenosis. *J Am Coll Cardiol* 1999;34:651–659.
5. Kereiakes D, Linnemeier TJ, Baim DS, Kuntz R, O'Shaughnessy C, Hermiller J, Fink S, Lansky A, Nishimura N, Broderick TM, Popma J. Usefulness of stent length in predicting in-stent restenosis (the MULTI-LINK stent trials). *Am J Cardiol* 2000;86:336–341.
6. Mauri L, O'Malley AJ, Cutlip DE, Ho KK, Popma JJ, Chauhan MS, Baim DS, Cohen DJ, Kuntz RE. Effects of stent length and lesion length on coronary restenosis. *Am J Cardiol* 2004;93:1340–1346.
7. Dawkins KD, Grube E, Guagliumi G, Banning AP, Zmudka K, Colombo A, Thuesen L, Hauptman K, Marco J, Wijns W, Popma JJ, Koglin J, Russell ME, for the TAXUS VI Investigators. Clinical efficacy of polymer-based paclitaxel-eluting stents in the treatment of complex, long coronary artery lesions from a multicenter, randomized trial: support for the use of drug-eluting stents in contemporary clinical practice. *Circulation* 2005;112:3306–3313.
8. Tsagalou E, Chieffo A, Iakovou I, Ge L, Sangiorgi GM, Corvaja N, Airoldi F, Montorfano M, Michev I, Colombo A. Multiple overlapping drug-eluting stents to treat diffuse disease of the left anterior descending coronary artery. *J Am Coll Cardiol* 2005;45:1570–1573.
9. Aoki J, Ong AT, Rodriguez Granillo GA, McFadden EP, van Mieghem CA, Valgimigli M, Tsuchida K, Sianos G, Regar E, de Jaegere PP, et al. "Full metal jacket" (stented length ≥64 mm) using drug-eluting stents for de novo coronary artery lesions. *Am Heart J* 2005;150:994–999.
10. Kastrati A, Mehilli J, von Beckerath N, Dibra A, Hausleiter J, Pache J, Schühlen H, Schmitt C, Dirschinger J, Schömig A, for the ISAR-DESIRE Study Investigators. Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. *JAMA* 2005;293:165–171.
11. Windecker S, Remondino A, Eberli FR, Jüni P, Räber L, Wenaweser P, Togni M, Billinger M, Tüller D, Seiler C, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. *N Engl J Med* 2005;353:653–662.
12. Moreno R, Fernandez C, Hernandez R, Alfonso F, Angiolillo DJ, Sabate M, Escaned J, Banuelos C, Fernandez-Ortiz A, Macaya C. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. *J Am Coll Cardiol* 2005;45:954–959.
13. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;293:2126–2130.