Journal of the American College of Cardiology
© 2011 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 57, No. 12, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.10.041

Incidence, Predictors, Treatment, and Long-Term Prognosis of Patients With Restenosis After Drug-Eluting Stent Implantation for Unprotected Left Main Coronary Artery Disease

Jong-Young Lee, MD,* Duk-Woo Park, MD, PHD,* Young-Hak Kim, MD, PHD,* Sung-Cheol Yun, PHD,† Won-Jang Kim, MD, PHD,* Soo-Jin Kang, MD, PHD,* Seung-Whan Lee, MD, PHD,* Cheol-Whan Lee, MD, PHD,* Seong-Wook Park, MD, PHD,* Seung-Jung Park, MD, PHD*

Seoul, Korea

Objectives The aim of this study was to evaluate the incidence, predictors, and long-term outcomes of patients with in-stent restenosis (ISR) after percutaneous coronary intervention (PCI) with drug-eluting stents (DES) for unprotected left main coronary artery (LMCA) disease.

Background Few data on the clinical course and management of patients experiencing restenosis after DES treatment for unprotected LMCA disease have appeared.

Methods Between February 2003 and November 2007, 509 consecutive patients with unprotected LMCA disease underwent DES implantation, with 402 (80.1%) undergoing routine surveillance or clinically driven angiographic follow-up. A major adverse cardiac event was defined as the composite of death, myocardial infarction (MI), or target-lesion revascularization.

Results The overall incidence of angiographic ISR in LMCA lesions was 17.6% (71 of 402 patients, 57 with focal-type and 14 with diffuse-type ISR. Forty patients (56.3%) underwent repeated PCI, 10 (14.1%) underwent bypass surgery, and 21 (29.6%) were treated medically. During long-term follow-up (a median of 31.7 months), there were no deaths, 1 (2.2%) MI, and 6 (9.5%) repeated target-lesion revascularization cases. The incidence of major adverse cardiac event was 14.4% in the medical group, 13.6% in the repeated PCI group, and 10.0% in the bypass surgery group (p value = 0.91). Multivariate analysis showed that the occurrence of DES-ISR did not affect the risk of death or MI.

Conclusions The incidence of ISR was 17.7% after DES stenting for LMCA. The long-term clinical prognosis of patients with DES-ISR associated with LMCA stenting might be benign, given that these patients were optimally treated with the clinical judgment of the treating physician. (J Am Coll Cardiol 2011;57:1349–58) © 2011 by the American College of Cardiology Foundation

Current practice guidelines recommend coronary artery bypass grafting (CABG) as the standard revascularization procedure for patients with unprotected left main coronary artery (LMCA) disease (1–3). More recently, however, percutaneous coronary intervention (PCI) to treat an unprotected LMCA has increased in frequency, associated with improvements in interventional techniques and adjunctive drug therapy. The use of PCI to treat LMCA disease has also been encouraged by the availability of drug-eluting stents (DES), which significantly reduce the rates of restenosis and repeat revascularization (4–6).

Nevertheless, in-stent restenosis (ISR) after DES implantation for unprotected LMCA lesions continues to occur, with such lesions being more clinically problematic compared with other coronary lesions. In addition, the incidence of ISR after DES implantation for unprotected LMCA disease has not been sufficiently evaluated in large numbers of patients, and the long-term prognosis of such patients has not been explored. Therefore, we investigated

From the *Department of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; and the †Division of Biostatistics, Center for Medical Research and Information, University of Ulsan College of Medicine, Seoul, Korea. All authors have reported that they have no relationships to disclose.

Manuscript received August 9, 2010; revised manuscript received October 4, 2010, accepted October 4, 2010.

Abbreviations and Acronyms

CABG = coronary-artery bypass grafting
CI = confidence interval
DES = drug-eluting stent(s)
HR = hazard ratio
ISR = in-stent restenosis
IVUS = intravascular ultrasound
LMCA = left main coronary artery
MI = myocardial infarction
PCI = percutaneous coronary intervention
TLR = target lesion revascularization

the incidence, predictors, treatment, and long-term clinical outcomes of patients with restenosis after DES treatment for unprotected LMCA disease in real PCI practice.

Methods

Study population and angiographic follow-up. Between February 2003 and November 2007, 509 patients with unprotected LMCA disease (defined as >50% stenosis) received PCI with DES implantation at the Asan Medical Center, Seoul, Korea. During this period, DES was used as the default device for PCI. All patients treated with PCI were recommended for routine angiographic follow-up 6 to 12 months after the procedure. However, patients who were at high risk for procedural complications of angiography and who had no symptoms or signs of ischemia as well as patients who declined the recommendation did not undergo routine follow-up angiography but routinely checked noninvasive stress tests (i.e., an exercise treadmill test or a thallium radionuclide scan) or meticulous clinical follow-up. After the 1-year period of surveillance angiographic follow-up, patients underwent annual noninvasive stress tests, exploring the occurrence of inducible ischemia on stress tests (with or without ischemic chest pain) or the recurrence of ischemic symptoms as indicated by a need for repeat angiographic follow-up.

Written informed consent was obtained from all patients, and the ethics committee of our institution approved the design of this study and allowed the use of clinical data.

Treatment strategy for LMCA-ISR lesions. Stent implantation methods for de novo LMCA lesions have been described (7–9). Angiographic ISR at LMCA lesions, detected during either surveillance or clinically driven angiographic follow-up, was treated by ischemia-driven repeat revascularization if the stenosis was at least 50% of the diameter of the target lesion, as documented by a positive functional test, ischemic changes on an electrocardiogram, or ischemic symptoms. Alternatively, ischemia-driven repeat revascularization was performed in the absence of documented ischemia if stenosis was at least 70%, regardless of the presence or absence of ischemic signs or symptoms. Asymptomatic patients with moderate stenosis (50% to 70%) and no evidence of inducible ischemia received optimal medical treatment with meticulous clinical follow-up. Patients requiring ischemic-driven repeat revascularization were treated with CABG or repeated PCI at the discretion of individual physicians, after consideration of clinical or procedural factors such as a clinical overview, lesion anatomy, the complexity of the repeat procedure, and patient and physician preferences.

Patients who underwent repeated PCI for LMCA-ISR lesions were treated either with balloon angioplasty alone or with additional DES stenting; plain or cutting balloon angioplasty was usually preferred to treat focal restenotic lesions, with implantation of additional DES preferred with diffuse lesions or focal lesions yielding unsatisfactory immediate results. Intravascular ultrasound (IVUS)-guided PCI was routinely used for optimal procedural results. After each procedure, patients were maintained on aspirin indefinitely and clopidogrel (75 mg once daily) for at least 12 months. Surgical revascularization was performed with standard bypass techniques. Whenever possible, the internal thoracic artery was preferred for revascularization of the left anterior descending artery.

End points and definitions. The primary end point was the incidence of major adverse cardiac events, defined as the composite of death, acute myocardial infarction (MI), or target lesion revascularization (TLR), after initial treatment for LMCA-ISR.

All events were based on clinical diagnoses as assessed by individual physicians and were adjudicated by an independent group of clinicians. Death was defined as death from any cause. A diagnosis of acute MI was based on the development of new Q waves in at least 2 contiguous leads with an elevated creatine kinase myocardial band fraction or an increase in the creatine kinase myocardial band concentration to 3-fold the normal value in the absence of pathologic Q waves. Electrocardiography and blood sampling for the measurement of creatinine kinase and its myocardial band isoenzyme were routinely performed before stenting, every 8 h for the first 24 h after the procedure and daily thereafter during hospital stay. A TLR was defined as percutaneous or surgical revascularization for stenosis either within the stent or within 5 mm of the stent. Stent thrombosis was assessed according to the Academic Research Consortium definitions, with pre-specified key end point being definite or probable (10), and by the timing of presentation; stent thrombosis was classified as acute, subacute, late, and very late if it occurred within 24 h, 30 days, 30 days to ≤1 year, or >1 year, respectively. All events were verified carefully and adjudicated by independent clinicians. The patterns of ISR were classified as focal (Mehran ISR pattern I) or diffuse (Mehran ISR pattern II, III, IV) according to geographic position of ISR in relation to previously implanted stent (11).

Follow-up protocol after LMCA-ISR treatment and quantitative coronary angiography. After treatment of LMCA-ISR lesions, clinical follow-up was recommended at 1 month, 6 months, 1 year, and annually thereafter. For validation of complete clinical follow-up data, information on vital status was obtained through May 31, 2009, from the National Population Registry of

Table 1 Baseline Clinical, Angiographic, and Procedural Characteristics of Overall Population and Patients Stratified by Angiographic Follow-Up

Variable	Overall (n = 509)	With Angiographic Follow-Up (n = 402)	Without Angiographic Follow-Up (n = 100)	p Value
Demographic characteristics				
Age (yrs)	60.5 ± 11.0	60.2 ± 10.8	61.4 ± 11.5	0.35
Male	365 (71.17)	289 (71.9)	70 (70.0)	0.71
Cardiac or coexisting conditions				
Diabetes mellitus	173 (34.0)	133 (33.1)	38 (38.0)	0.35
Hypertension	251 (49.3)	203 (50.5)	46 (46.0)	0.42
Hyperlipidemia	212 (41.7)	164 (40.8)	46 (46.0)	0.35
Current smoker	150 (29.5)	118 (29.4)	29 (29.0)	0.95
Previous CVA	34 (6.7)	29 (7.2)	4 (4.0)	0.25
Previous PCI	15 (22.6)	89 (22.1)	25 (25.0)	0.54
Renal failure	12 (2.4)	4 (2.0)	4 (4.0)	0.24
Ejection fraction (%)	61.0 (58.0–65.0)	61.0 (58.0–65.0)	60.5 (56.2–64.7)	0.22
Ejection fraction <40%	16 (3.1)	8 (2.0)	5 (5.0)	0.15
Clinical indication				0.05
Silent/stable angina	240 (47.2)	198 (49.3)	39 (39.0)	
Unstable angina	249 (48.9)	192 (47.8)	54 (54.0)	
Acute MI	20 (3.9)	12 (3.0)	7 (7.0)	
Lesion characteristics				
Location involved				0.005
Ostium, midshaft, or both	198 (38.9)	144 (35.8)	51 (51.0)	
Distal bifurcation	311 (61.1)	258 (64.2)	49 (49.0)	
Extent of diseased vessel				0.49
Left main only	93 (18.3)	68 (16.9)	22 (22.0)	
Plus single-vessel disease	115 (22.6)	91 (22.6)	23 (23.0)	
Plus double-vessel disease	154 (30.3)	128 (31.8)	25 (25.0)	
Plus triple-vessel disease	147 (28.9)	115 (28.6)	30 (30.0)	
Right coronary artery disease	218 (42.8)	168 (41.8)	46 (46.0)	0.45
Restenotic lesion	29 (5.7)	23 (5.7)	6 (6.0)	0.92
Procedural characteristics				
Stent type				0.60
Sirolimus-eluting stents	462 (90.8)	364 (90.5)	92 (92.0)	
Paclitaxel-eluting stents	35 (6.9)	27 (6.7)	7 (7.0)	
Zotarolimus-eluting stents	12 (2.4)	11 (2.7)	1 (1.0)	
Total number of stents in LMCA lesion	1.5 ± 0.7	1.6 ± 0.7	1.4 ± 0.6	0.02
Total length of stents in LMCA lesion	34.4 ± 21.7	35.8 ± 22.5	28.9 ± 17.6	0.005
Average stent diameter in LMCA lesion	3.6 ± 1.5	3.5 ± 1.4	3.4 ± 1.6	0.63
Total number of stents in a patient (including LMCA and other vessels)	2.5 ± 1.4	2.4 ± 1.5	2.5 ± 1.7	0.95
Total length of stents in a patient (including LMCA and other vessels)	56.6 ± 23.3	56.2 ± 25.4	56.9 ± 22.8	0.72
Maximal balloon size	3.9 ± 0.4	3.9 ± 0.4	3.9 ± 0.4	0.43
Maximal pressure	17.3 ± 3.3	17.5 ± 3.2	16.6 ± 3.7	0.02
Use of intra-aortic balloon pump	39 (7.7)	25 (6.2)	12 (12.0)	0.048
Guidance with IVUS	468 (91.9)	373 (93.0)	88 (88.0)	0.05
Glycoprotein IIb/IIIa inhibitor treatment	53 (10.4)	43 (10.7)	10 (10.0)	0.84
Distal bifurcation treatment				0.007
Single stenting	153 (49.2)	118 (45.7)	32 (65.3)	
Complex stenting with ≥2 stents	158 (50.8)	140 (54.3)	17 (34.7)	

Data are shown as mean ± SD or n (%). Ejection fraction (%) is shown as the median and interquartile range.

CVA = cerebrovascular accident; IABP = intra-aortic balloon pulsation; IVUS = intravascular ultrasound; LMCA = left main coronary artery; MI = myocardial infarction; PCI = percutaneous coronary intervention.

the Korea National Statistical Office, with a unique personal identification number for each patient. To ensure accurate assessment of clinical end points, additional information was obtained from visits or telephone contacts with living patients or family members and from medical records obtained from other hospitals, as necessary. Patients undergoing repeated PCI for treatment of LMCA-ISR lesions were recommended for repeated angiographic follow-up 6 to 12 months later to evaluate the incidence of recurrent ISR.

JACC Vol. 57, No. 12, 2011
March 22, 2011:1349–58

Table 2 Clinical, Lesional, and Procedural Characteristics in Patients With or Without ISR Among Those Receiving Angiographic Follow-Up

Variables	With Angiographic Follow-Up (n = 402)	ISR (n = 71)	No ISR (n = 331)	p Value
Demographic characteristics				
Age (yrs)	60.2 ± 10.8	61.1 ± 9.4	60.0 ± 11.1	0.47
Male	289 (71.9)	44 (62.0)	245 (74.0)	0.04
Cardiac or coexisting conditions				
Diabetes mellitus	133 (33.1)	33 (46.5)	100 (30.2)	0.008
Hypertension	203 (50.5)	40 (56.3)	163 (49.2)	0.28
Hyperlipidemia	164 (40.8)	33 (46.5)	131 (39.6)	0.28
Current smoker	118 (29.4)	19 (26.8)	99 (29.9)	0.60
Previous CVA	29 (7.2)	3 (4.2)	26 (7.9)	0.28
Previous PCI	89 (22.1)	17 (23.9)	72 (21.8)	0.69
Renal failure	4 (2.0)	4 (5.6)	4 (1.2)	0.02
Ejection fraction (%)	61.0 (58.0–65.0)	61.0 (58.0–65.0)	60.0 (57.0–64.0)	0.79
Ejection fraction <40%	8 (2.0)	2 (2.8)	6 (1.8)	0.63
Clinical indication				0.86
Silent/stable angina	198 (49.3)	33 (46.5)	165 (49.8)	
Unstable angina	192 (47.8)	36 (50.7)	156 (47.1)	
Acute MI	12 (3.0)	2 (2.8)	10 (3.0)	
Lesion characteristics				
Location involved				0.002
Ostium, midshaft, or both	144 (35.8)	14 (19.7)	130 (39.3)	
Distal bifurcation	258 (64.2)	57 (80.3)	201 (60.7)	
Extent of diseased vessel				0.02
Left main only	68 (16.9)	5 (7.0)	63 (19.0)	
Plus single-vessel disease	91 (22.6)	14 (19.7)	77 (23.3)	
Plus double-vessel disease	128 (31.8)	32 (45.1)	96 (29.0)	
Plus triple-vessel disease	115 (28.6)	20 (28.2)	95 (28.7)	
Right coronary artery disease	168 (41.8)	27 (38.0)	141 (42.6)	0.48
Restenotic lesion	23 (5.7)	12 (16.9)	11 (3.3)	<0.001
Procedural characteristics				
Stent type				0.25
Sirolimus-eluting stents	364 (90.5)	62 (87.3)	302 (91.2)	
Paclitaxel-eluting stents	27 (6.7)	5 (7.0)	22 (6.6)	
Zotarolimus-eluting stents	11 (2.7)	4 (5.6)	7 (2.1)	
Total number of stents in LMCA lesion	1.6 ± 0.7	2.1 ± 0.8	1.5 ± 0.6	<0.001
Total length of stents in LMCA lesion	35.8 ± 22.5	43.2 ± 19.6	34.2 ± 22.8	0.002
Average stent diameter in LMCA lesion	3.5 ± 1.4	3.4 ± 0.3	3.5 ± 1.6	0.63
Total number of stents in a patient (including LMCA and other vessels)	2.5 ± 1.7	2.5 ± 1.6	2.4 ± 1.9	0.37
Total length of stents in a patient (including LMCA and other vessels)	56.9 ± 22.8	56.8 ± 23.2	56.9 ± 22.4	0.25
Maximal balloon size	3.9 ± 0.4	3.8 ± 0.5	3.9 ± 0.4	0.09
Maximal pressure	17.5 ± 3.2	16.3 ± 3.1	17.7 ± 3.2	0.002
Use of intra-aortic balloon pump	25 (6.2)	4 (5.6)	21 (6.3)	0.82
Guidance with IVUS	373 (93.0)	69 (97.2)	304 (92.1)	0.13
Glycoprotein IIb/IIIa inhibitor treatment	43 (10.7)	8 (11.3)	35 (10.6)	0.86
Distal bifurcation treatment				0.002
Single stenting	118 (45.7)	14 (24.6)	104 (51.7)	
Complex stenting with ≥2 stents	140 (54.3)	43 (75.6)	97 (48.3)	

Data are shown as mean ± SD, n (%), or median (interquartile range).
CABG = coronary-artery bypass grafting; ISR = in-stent restenosis; other abbreviations as in Table 1.

Coronary angiograms were digitally recorded and assessed offline in a quantitative angiographic core laboratory (Asan Medical Center, Seoul, Korea), with an automated edge-detection system (CASS II, Pie Medical, Maastricht, the Netherlands) operated by experienced personnel unaware of the study aims. The Medina classification was used to describe the location and distribution of restenosis (12). By convention, the parent vessel of the main bifurcation was defined as the left main into the left anterior descending artery.

Statistical analysis. Continuous variables were compared with the *t* test or the Mann-Whitney *U* test, and categorical

variables were compared with the chi-square or Fisher exact tests, as appropriate.

Cumulative probability and survival curves were constructed from Kaplan-Meier estimates and compared with the log-rank test. Univariate and multivariate Cox regression analyses were used to identify predictors of ISR. Baseline, lesion, and procedural variables with a p value ≤0.1 in univariate analyses were included in multivariable Cox regression model. The final models were determined by backward elimination.

To investigate the relationship between the development of ISR and the subsequent occurrence of hard end points, such as death, MI, and the composite of death or MI, the presence or absence of ISR was entered into a time-updated Cox model (13) adjusted for the covariates, which were identified by the multivariable Cox model with backward elimination with the variables listed in Table 2; a p value ≤0.1 in univariate analysis was the criterion used for inclusion in the final model. Adjusted covariates included age, left ventricular ejection fraction, and stent diameter for death; age, left ventricular ejection fraction, right coronary artery disease, and IVUS guidance for MI; and age, left ventricular ejection fraction, stent diameter, right coronary artery disease, and IVUS guidance for the composite of death or MI.

All p values were 2-sided, and a p value <0.05 was considered statistically significant. All statistical analyses were performed with SPSS (version 12.0 for Windows, SPSS, Inc., Chicago, Illinois) and SAS software (version 9.1, SAS Institute, Inc., Cary, North Carolina).

Results

Incidence, pattern, and clinical presentation of LMCA-ISR. Between February 2003 and November 2007, a total of 509 consecutive patients with unprotected LMCA disease underwent PCI with DES implantation. Figure 1 shows the overall study design. Before the scheduled 6-month angiographic follow-up, 7 patients died (5 due to STEMI presentation with cardiogenic shock, 1 due to lung cancer, and 1 due to prostate cancer). Of the 502 eligible patients who survived for at least 6 months after DES implantation, 402 (80.1%) underwent angiographic follow-up. Table 1 show the clinical, lesional, and procedural characteristics of the overall population and of the patients who did and did not undergo angiographic follow-up. Approximately 82% of the patients, overall, had additional vessel involvement beyond LMCA lesions, and 61% showed distal LMCA involvement. Sirolimus-eluting stents were predominantly used. Most baseline characteristics were similar among patients who did or did not undergo angiographic follow-up, except that distal bifurcation disease and complex stenting (with ≥2 stents) for distal bifurcation treatment were more common in patients who underwent angiographic follow-up.

During a median follow-up time of 3.4 years (interquartile range: 2.5 to 4.7 years), 28 patients (5.6%) died, of whom 12 (2.3% of the overall cohort) died of a cardiovascular disease; 51 (10.0%) including Q-wave 16 (3.2%) and non–Q-wave 35 (7.8%) had an acute MI; and

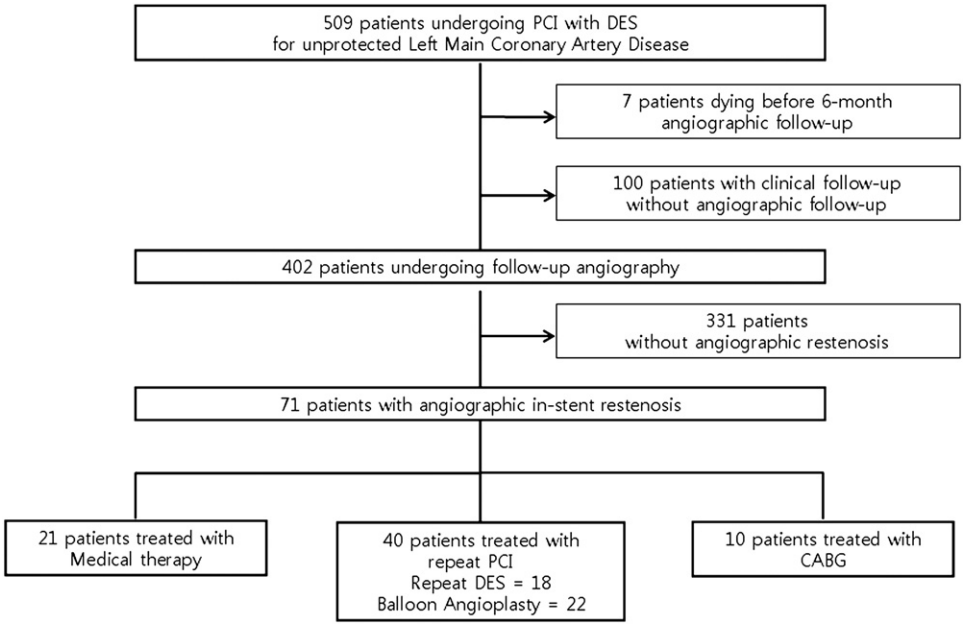

Figure 1 Overall Study Profile

CABG = coronary artery bypass grafting; DES = drug-eluting stent(s); PCI = percutaneous coronary intervention.

50 (10.0%) had a repeat TLR. Compared with patients with follow-up angiography, those without follow-up angiography showed higher incidence of all-cause mortality (3.6% vs. 8.0%, log-rank p = 0.004) but no difference in cardiac mortality (2.0% vs. 2.8%, log-rank p = 0.12) (Fig. 2).

Angiographic ISR at LMCA lesions was detected in 71 (17.7%; in-stent: 15.2%, in-segment: 17.7%) of the 402 patients who underwent angiographic follow-up. Of the 71 patients with ISR, 49 (69.0%) were diagnosed within 1 year, 12 (16.9%) were diagnosed at 1 to 2 years, 8 (11.3%) were diagnosed at 2 to 3 years, and 2 (2.8%) were diagnosed after 3 or more years. The restenosis pattern was focal in 57 patients (80.3%) and diffuse in 14 (19.7%). The overall restenosis rate in nonbifurcation lesion was 9.7% (14 of 144 patients; aorto-ostial 8.3% and mid-shaft 11.1%), and the rate in bifurcation lesions was 22.1% (57 of 258 patients). The Medina classification and location of ISR involvement are illustrated in Figure 3. Eleven patients (15.5%) presented with silent ischemia, 42 (59.2%) presented with stable angina, 17 (23.9%) presented with unstable angina, and 1 (1.4%) presented with a nonfatal MI.

During 3-year follow-up, the cumulative incidence of definite or probable stent thrombosis was 1.8% (9 patients; 6 definite and 3 probable; 3 acute, 1 subacute, 2 late, and 3 very late) in the overall LMCA-DES patients, but there was no occurrence in patients with LMCA-ISR.

Predictors of LMCA-ISR. Table 2 shows a comparison of clinical, lesional, and procedural characteristics between patients with and without ISR, among those receiving angiographic follow-up. Patients with ISR were more likely to be female and had higher rates of diabetes, renal failure, more severe disease, distal bifurcation disease, and procedural complexities, compared with patients without ISR. Univariate and multivariate predictors of overall LMCA-ISR are shown in Table 3. Major determinants of angiographic LMCA-ISR were female sex, existence of a previous restenotic lesion, total number of stents employed, existence of distal bifurcation lesions, and use of complex bifurcation stenting.

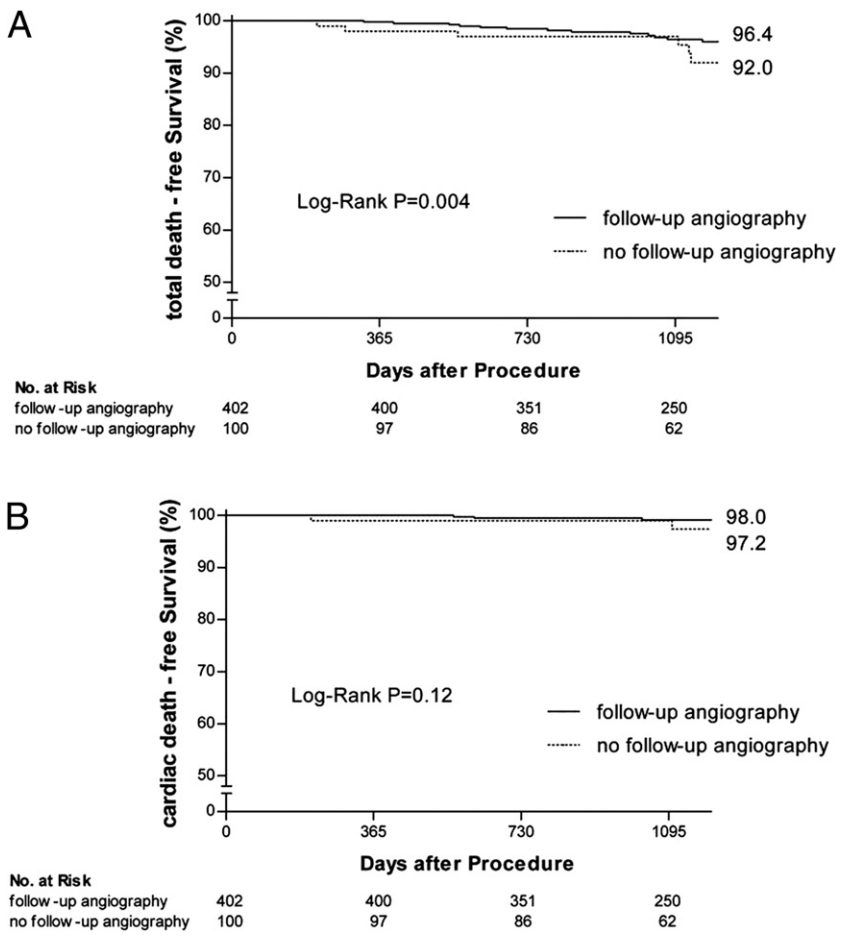

Figure 2 Long-Term Clinical Outcomes According to Follow-Up Angiographic Surveillance

(A) Kaplan-Meier analysis of all-cause mortality-free survival according to follow-up angiography.
(B) Kaplan-Meier analysis of cardiac mortality-free survival according to follow-up angiography.

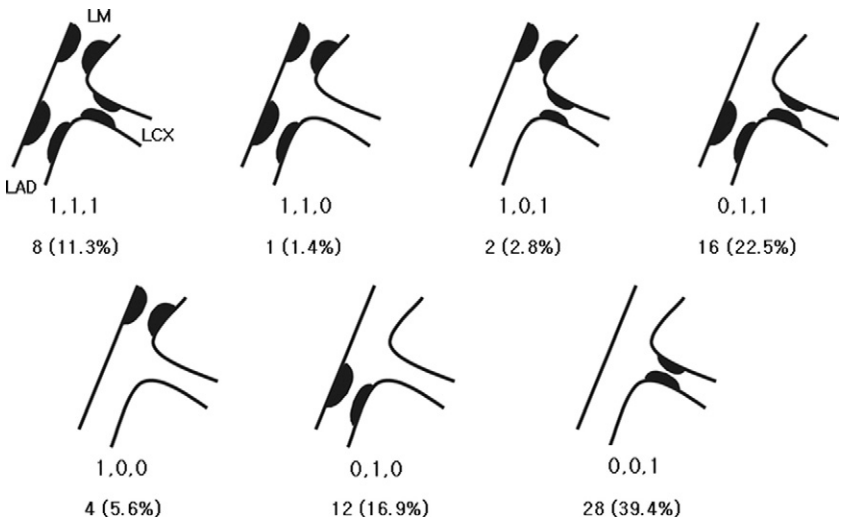

Figure 3 The Medina Classification and Lesion Location of In-Stent Restenosis

We use the 3 components of a bifurcation: left main artery (LM) as the main branch proximal, left anterior descending artery (LAD) as the main branch distal, and left circumflex artery (LCX) as the side branch. It consists in giving a binary value (1, 0) according to whether each of the segments previously defined is compromised or not.

Treatment and long-term prognosis of LMCA-ISR. Among 71 patients with LMCA-ISR, 21 (29.6%) received medical treatment only, 40 (56.3%) were treated with repeated PCI (22 by balloon angioplasty and 18 with additional DES implantation), and 10 (14.1%) underwent CABG. Table 4 shows the differences in the clinical and angiographic features of LMCA-ISR among these 3 groups of patients.

The median follow-up time after initial LMCA-ISR treatment was 31.7 months (interquartile range: 22.4 to 46.6 months). Complete follow-up data for major clinical events were obtained for all patients. During follow-up, no patient died, 1 (2.2%) suffered MI, and 6 (11.1%) required repeat TLR. The overall incidence of major adverse cardiac event-free survival was 86.6% and did not significantly differ among patients treated medically, by PCI, or by CABG (85.6% vs. 86.4% vs. 90.0%; p = 0.91) (Fig. 4).

To evaluate the clinical impact of LMCA-ISR on serious clinical outcomes (death or MI), we performed a time-updated Cox regression analysis. In a multivariate analysis adjusted for covariates, the development of LMCA-ISR did not significantly influence the occurrence of death (adjusted hazard ratio [HR]: 1.37, 95% confidence interval [CI]: 0.38 to 5.00, p = 0.63), MI (adjusted HR: 0.88, 95% CI: 0.19 to 4.08, p = 0.87), or the composite of death or MI (adjusted HR: 1.04, 95% CI: 0.35 to 3.15, p = 0.94).

Table 3 Univariate and Multivariate Predictors of ISR

Variable	Univariate	p Value	Multivariate	p Value
Male	0.61 (0.38–0.99)	0.045	0.41 (0.24–0.69)	0.007
Diabetes mellitus	1.82 (1.14–2.90)	0.012		
Renal failure	3.74 (1.36–10.25)	0.011		
Extent of diseased vessel		0.022		
Left main only	1.00			
Plus single-vessel disease	2.11 (0.76–5.86)	0.15		
Plus double-vessel disease	3.82 (1.49–9.80)	0.005		
Plus triple-vessel disease	2.58 (0.97–6.87)	0.06		
Restenotic lesion	4.20 (2.26–7.84)	<0.001	4.59 (2.40–8.77)	<0.001
Bifurcation involvement	2.40 (1.34–4.31)	0.003	2.56 (1.27–5.19)	0.009
Complex stenting with ≥2 stents in bifurcation lesion*	3.03 (1.64–5.55)	<0.001	2.50 (1.28–4.76)	0.007
Total number of stents	2.60 (1.97–3.43)	<0.001	4.76 (2.94–7.67)	<0.001
Total length of stents	1.01 (1.00–1.02)	0.003		
Maximal balloon pressure	0.89 (0.83–0.95)	0.001		
Maximal balloon size	0.51 (0.27–0.98)	0.043		

Values are hazard ratio (95% confidence interval). *Compared with simple cross-over stenting of distal bifurcation lesions.
ISR = in-stent restenosis.

Table 4 Clinical and Angiographic Characteristics of Patients With ISR, According to Treatment Strategy

Variable	Medical Therapy (n = 21)	Repeated PCI (n = 40)	CABG (n = 10)	p Value
Clinical presentation at ISR detection				0.036
Silent ischemia	6 (28.6)	3 (7.5)	2 (20.0)	
Stable angina	13 (61.9)	25 (62.5)	4 (40.0)	
Unstable angina	2 (9.5)	12 (30.0)	3 (30.0)	
Acute MI	0 (0)	0 (0)	1 (10.0)	
Location of ISR				0.87
LMCA only	1 (4.8)	3 (7.5)	0 (0)	
LAD ostium only	3 (14.3)	7 (17.5)	3 (30.0)	
LCX ostium only	10 (47.6)	15 (37.5)	3 (30.0)	
Multiple	7 (33.3)	15 (37.5)	4 (40.0)	
Type of ISR				0.14
Focal pattern	19 (90.5)	32 (80.0)	6 (60.0)	
Diffuse pattern	2 (9.5)	8 (20.0)	4 (40.0)	
Quantitative coronary angiography				
Reference vessel diameter, mm	4.2 ± 0.6	4.1 ± 0.8	3.9 ± 0.9	0.73
Lesion length, mm	10.5 ± 3.6	7.6 ± 4.4	8.1 ± 4.9	0.025
Diameter stenosis, %	60.8 ± 16.9	68.6 ± 13.1	66.4 ± 11.5	0.035
Minimal luminal diameter, mm	1.2 ± 0.5	0.8 ± 0.4	0.8 ± 0.5	0.043

Data are shown as n (%) or mean ± SD.
LAD = left anterior descending artery; LCX = left circumflex artery; other abbreviations as in Tables 1 and 2.

Discussion

In a large cohort of consecutive patients undergoing DES implantation for unprotected LMCA disease, we noted a cumulative ISR incidence of 17.7%, which might be higher than rates reported in non-LMCA DES implantation (14–17). Long-term prognosis after LMCA-ISR seemed to be benign, given that these patients were optimally treated with the clinical judgment of the treating physician.

The rates of angiographic restenosis after LMCA stenting with DES have been found to vary widely, from 8% to 42% (4,18–26). We found that the overall incidence of LMCA-ISR over 3 years was approximately 18%. This disparity in the incidence of LMCA-ISR among studies might be due to differences in patient selection, the relative frequency of distal bifurcation lesions, interventional techniques, and the completeness and timing of surveillance angiography.

We found that distal bifurcation involvement and a complex stenting strategy were important predictors of ISR after DES implantation, findings similar to those of previous reports on LMCA stenting (27–30). Currently available evidence suggests that outcomes are less favorable when distal LMCA lesions are treated with a 2-stent compared with a single-stent approach. In addition, all measures required to achieve an optimal final result should be considered, with IVUS assessment advocated in most patients for optimization of stent placement.

The choice of treatment strategy (medical treatment, repeated PCI, or CABG) for LMCA-ISR lesions depends primarily on several clinical and angiographic factors, making optimal patient selection crucial in the appropriate treatment of LMCA-ISR lesions and achievement of favorable long-term outcomes. We found that LMCA-ISR treatment strategies were dependent on lesion characteristics, procedural complexities, the extent of extra-LMCA disease, patient clinical characteristics (i.e., age, diabetes, ejection fraction, and other comorbidities), and patient/physician preference. The 3-year outcomes after treatment of LMCA-ISR were similar in the medical, PCI, and CABG groups, indicating that treating physicians exercised excellent clinical judgment, choosing appropriate treatment methods on the basis of knowledge of the coexisting conditions of their patients.

It remains unclear whether routine surveillance angiography should be mandatory after LMCA stenting. Because patients with LMCA restenosis are thought to be at high risk for adverse events, repeat angiography has been suggested, because detection of even a silent LMCA-ISR might be important. However, angiography is unable to predict when a patient might be prone to acute, sudden stent thrombosis, and angiography might be associated with a non-negligible risk in patients who have undergone placement of a left main stent (22,23). Therefore, recent PCI guidelines do not recommend routine angiographic follow-up after LMCA stenting. Exploration of this issue warrants large-scale studies comparing routine and repeat follow-up angiography with noninvasive, functional follow-up after LMCA stenting (31).

Study limitations. First, our work was a retrospective, single-center, observational study. In addition, because we did not systematically perform angiographic follow-up on all LMCA patients receiving PCI, we might have underestimated the "true" incidence of LMCA-ISR. Second, the treatment strategy for LMCA-ISR lesions was at the discretion of the

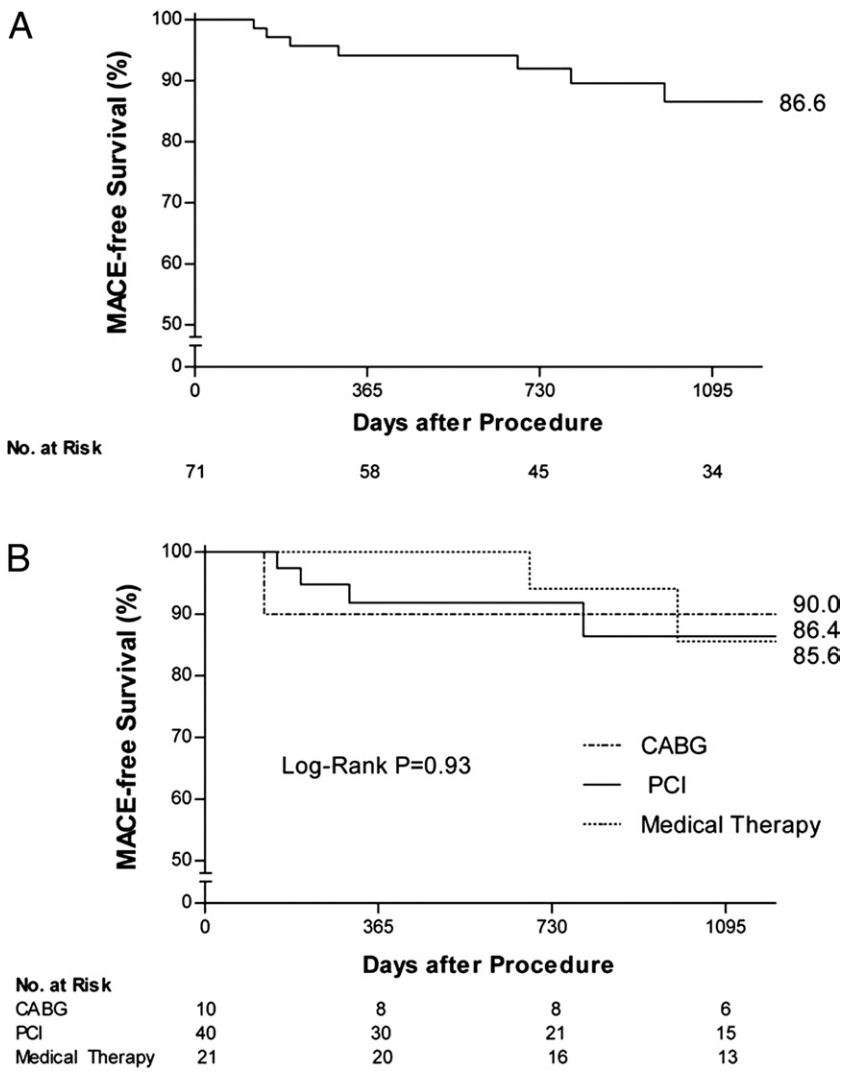

Figure 4 **Long-Term Clinical Outcomes of In-Stent Restenosis**

(A) Kaplan-Meier analysis of event-free survival after major adverse cardiac events (MACE) in patients with overall left main in-stent restenosis. **(B)** Kaplan-Meier analysis of event-free survival after MACE in patients with left main in-stent restenosis according to treatment strategy (medical vs. repeated percutaneous coronary intervention [PCI] vs. coronary artery bypass grafting [CABG]).

treating physician and/or patient, and there were too few patients in each group and they were too dissimilar to compare, so fair comparisons between treatment modalities for treatment of LMCA-ISR lesions are substantially limited due to selection bias. Third, some of the multivariable models might be over-fitted on the basis of small numbers of end point events. Finally, because we evaluated the first generation of DES, the applicability of our findings to the next generation of DES—which seem to be associated with somewhat different efficacy and safety—might be limited.

Conclusions

The incidence of ISR in the 3 years after successful DES implantation in consecutive real-world patients with unprotected LMCA disease was approximately 18%. Female sex, initial restenotic lesions, distal bifurcation lesions, and the use of complex procedures were identified as major predictors of LMCA-ISR. The clinical consequences of LMCA-ISR after DES treatment seemed to be benign, with the incidence of major adverse cardiac event not differing significantly among treatment modalities, given that these patients were optimally treated with the clinical judgment of the treating physician.

Reprint requests and correspondence: Dr. Seung-Jung Park, Department of Cardiology, University of Ulsan College of Medicine, Asan Medical Center, 388-1 Poongnap-dong, Songpa-gu, Seoul 138-736, Korea. E-mail: sjpark@amc.seoul.kr.

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Key Words: left main coronary artery ■ restenosis ■ stent.