Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION



# Long-Term Safety and Effectiveness of Unprotected Left Main Coronary Stenting With Drug-Eluting Stents Compared With Bare-Metal Stents

Young-Hak Kim, Duk-Woo Park, Seung-Whan Lee, Sung-Cheol Yun, Cheol Whan Lee, Myeong-Ki Hong, Seong-Wook Park, Ki Bae Seung, Hyeon-Cheol Gwon, Myung-Ho Jeong, Yangsoo Jang, Hyo-Soo Kim, In-Whan Seong, Hun Sik Park, Taehoon Ahn, In-Ho Chae, Seung-Jea Tahk, Wook-Sung Chung, Seung-Jung Park and for the Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization Investigators

*Circulation* 2009;120;400-407; originally published online Jul 20, 2009;
DOI: 10.1161/CIRCULATIONAHA.108.800805
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

# Long-Term Safety and Effectiveness of Unprotected Left Main Coronary Stenting With Drug-Eluting Stents Compared With Bare-Metal Stents

Young-Hak Kim, MD, PhD; Duk-Woo Park, MD, PhD; Seung-Whan Lee, MD, PhD; Sung-Cheol Yun, PhD; Cheol Whan Lee, MD, PhD; Myeong-Ki Hong, MD, PhD; Seong-Wook Park, MD, PhD; Ki Bae Seung, MD, PhD; Hyeon-Cheol Gwon, MD, PhD; Myung-Ho Jeong, MD, PhD; Yangsoo Jang, MD, PhD; Hyo-Soo Kim, MD, PhD; In-Whan Seong, MD, PhD; Hun Sik Park, MD, PhD; Taehoon Ahn, MD, PhD; In-Ho Chae, MD, PhD; Seung-Jea Tahk, MD, PhD; Wook-Sung Chung, MD, PhD; Seung-Jung Park, MD, PhD; for the Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization Investigators

***Background***—Limited information is available on long-term outcomes for patients with unprotected left main coronary artery disease who received drug-eluting stents (DES).

***Methods and Results***—In the multicenter registry evaluating outcomes among patients with unprotected left main coronary artery stenosis undergoing stenting with either bare metal stents (BMS) or DES, 1217 consecutive patients were divided into 2 groups: 353 who received only BMS and 864 who received at least 1 DES. The 3-year outcomes were compared by use of the adjustment of inverse-probability-of-treatment-weighted method. Patients receiving DES were older and had a higher prevalence of diabetes mellitus, hypertension, hyperlipidemia, and multivessel disease. In the overall population, with the use of DES, the 3-year adjusted risk of death (8.0% versus 9.5%; hazard ratio, 0.71; 95% confidence interval, 0.36 to 1.40; $P=0.976$) or death or myocardial infarction (14.3% versus 14.9%; hazard ratio, 0.83; 95% confidence interval, 0.49 to 1.40; $P=0.479$) was similar compared with BMS. However, the risk of target lesion revascularization was significantly lower with the use of DES than BMS (5.4% versus 12.1%; hazard ratio, 0.40; 95% confidence interval, 0.22 to 0.73; $P=0.003$). When patients were classified according to lesion location, DES was still associated with lower risk of target lesion revascularization in patients with bifurcation (6.9% versus 16.3%; hazard ratio, 0.38; 95% confidence interval, 0.18 to 0.78; $P=0.009$) or nonbifurcation (3.4% versus 10.3%; hazard ratio, 0.39; 95% confidence interval, 0.17 to 0.88; $P=0.024$) lesions with a comparable risk of death or myocardial infarction.

***Conclusions***—Compared with BMS, DES was associated with a reduction in the need for repeat revascularization without increasing the risk of death or myocardial infarction for patients with unprotected left main coronary artery stenosis. **(*Circulation*. 2009;120:400-407.)**

**Key Words:** angina ■ angioplasty ■ coronary disease ■ stents

The percutaneous interventional approach for implantation of coronary stents has been shown to be feasible for patients with unprotected left main coronary artery (LMCA) stenosis.[1] Moreover, drug-eluting stents (DES), together with advances in periprocedural and postprocedural adjunctive pharmacotherapies, have improved the outcomes of percutaneous coronary interventions (PCIs) for these complex coronary lesions.[2–10] However, uncertainty remains about the long-term safety of DES in off-label use. In particular, the incidence of late stent thrombosis has been reported to be higher with DES compared with bare metal stent (BMS) implantation.[11–14] Indeed, the US Food and Drug Administration has warned that the risk of stent thrombosis may outweigh the benefits of DES in off-label use such as for unprotected LMCA stenosis.[15] Although midterm pilot studies have shown that, compared with BMS, DES are safe and effective for unprotected LMCA stenosis, these results were obtained in

Received August 14, 2008; accepted June 1, 2009.

From the Asan Medical Center, Seoul (Y.-H.K., D.-W.P., S-.W.L., S-.C.Y., C-.W.L., M-.K.H., S-.W.P., S.-J.P.); Catholic University of Korea, GangNam (K.B.S.) and Yeoido (W.-S.C.), Seoul; Samsung Medical Center, Seoul (H.-C.G.); Chonnam National University Hospital, Gwangju (M.-H.J.); Yonsei University Severance Hospital, Seoul (Y.J.); Seoul National University Hospital, Seoul (H.-S.K.) and Bundang (I.-H.C.); Chungnam National University Hospital, Daejeon (I.-W.S.); Kyungpook National University Hospital, Daegu (H.S.P.); Gachon University Gil Medical Center, Incheon (T.A.); and Ajou University Medical Center, Suwon (S-.J.T.), Korea.

Correspondence to Seung-Jung Park, MD, 388–1 Pungnap-dong, Songpa-gu, Seoul, 138–736, South Korea. E-mail sjpark@amc.seoul.kr



*Circulation* **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.108.800805**

small study populations, in single centers, and after relatively short-term clinical observation.

Clinical Perspective on p 407

The Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization (MAIN-COMPARE) registry was designed to enhance understanding of the real-world outcomes of revascularization therapy for unprotected LMCA stenosis in multiple centers in Korea.[15] The primary objective of this study was to evaluate the long-term safety and effectiveness of PCI with DES compared with BMS for unprotected LMCA stenosis in a series of patients enrolled in the MAIN-COMPARE study. In addition, this study assessed the differential outcomes of the 2 stent types according to lesion location. Bifurcation lesion was defined as significant LMCA stenosis (>50%) at the distal bifurcation by visual estimate.

## Methods

### Patients

The MAIN-COMPARE study enrolled patients with unprotected LMCA stenosis who underwent either coronary artery bypass graft surgery or PCI as the index procedure at 12 major cardiac centers in Korea between January 2000 and June 2006.[16] The LMCA was considered unprotected if there were no patent grafts to the left anterior descending artery or circumflex artery. Patients who had prior coronary artery bypass surgery or underwent concomitant valvular or aortic surgery were excluded. PCI was considered for patients with significant unprotected LMCA stenosis who had suitable anatomy for stenting with contraindications for or disagreement with surgery. The local ethics committee at each hospital approved the use of clinical data for this study, and all patients provided written informed consent.

Patients in the MAIN-COMPARE registry who underwent any stenting at the LMCA were divided into 2 groups: those who received only BMS and those who received at least 1 DES. Before March 2003, when DES became available in Korea, BMS were the default stents in 270 patients. Beginning in March 2003, however, DES were used in 864 patients (91.2%), whereas BMS were used in 83 (8.2%). Thus, our patient population consisted of 353 patients who received only BMS and 864 patients who received at least one DES at the LMCA lesion.

### Procedures

For DES, sirolimus-eluting (Cypher, Cordis Corp, Johnson & Johnson, Miami Lakes, Fla) or paclitaxel-eluting (Taxus, Boston Scientific, Natick, Mass) stents were selected at the operator's discretion. All procedures were performed with standard interventional techniques. Briefly, an ostial or shaft lesion was attempted with a single stent placement. For bifurcation lesions, a single-stent technique in which a stent was placed across the side branch (usually the left circumflex artery) was preferred in patients with diminutive or normal-looking side branches. Two-stent techniques, consisting of T stenting, kissing stenting, culotte technique, or Crush technique, were considered in patients with diseased side branches. The use of predilation, intraaortic balloon pump, or intravascular ultrasound was at the operator's discretion. Stent overexpansion with high-pressure inflation was performed in selected patients with suboptimal expansion or stent inapposition defined as separation of stent strut from the vessel wall as assessed by intravascular ultrasound. Debulking devices, including cutting balloon angioplasty, rotablator, or debulking coronary atherectomy, were used in selected patients with severe calcified or fibrous plaques at the operator's discretion.

Antiplatelet therapy and periprocedural anticoagulation followed standard regimens. Before or during the procedure, patients were administered loading doses of aspirin (200 mg) and clopidogrel (300 or 600 mg) or ticlopidine (500 mg) unless they had previously received antiplatelet medications. After the procedure, patients were maintained on aspirin (100 to 200 mg once daily) and clopidogrel (75 mg once daily) or ticlopidine (250 mg twice daily) for at least 6 months after DES and for at least 1 month after BMS. Longer treatment with clopidogrel was at the operator's discretion. Patients with high-risk clinical profiles or who underwent complicated procedures were administered cilostazol (100 mg twice daily) for at least 1 month at the operator's discretion.

### Data Collection

Patient baseline demographic, clinical, angiographic, and procedural characteristics were collected through the use of standard Internet-based electronic case report forms. Occurrence of death, myocardial infarction (MI), or target lesion revascularization (TLR) was ascertained during hospitalization, at 6 months and 1 year after the procedure, and annually thereafter. Outcomes of interest were centrally adjudicated by physicians.

### Primary Outcomes and Definitions

The primary end point of this analysis was the composite incidence of death or MI at 3 years. All other comparisons were considered the secondary end points of the study.

All deaths were considered of cardiac origin unless a noncardiac origin was established clinically or at autopsy. MI was defined when the patient had creatine kinase-MB levels >3 times the upper limit of the normal after the procedure or creatine kinase-MB levels above normal with ischemic symptoms or signs during follow-up. TLR was defined as any repeat revascularization with PCI or coronary artery bypass surgery in the treated segment or within the adjacent 5 mm. Target vessel revascularization was defined as any repeat revascularization in any left anterior descending artery or left circumflex artery, as well as in the target segment. Chronic kidney disease was documented if the patient had serum creatinine >2.0 mg/dL or creatinine clearance <60 mL/min by the Cockcroft-Gault formula or laboratory examination, was on dialysis, or received renal transplantation.

### Statistics

Differences between groups of patients receiving DES and BMS in baseline clinical, angiographic, and procedural characteristics were compared by use of the $t$ test or Wilcoxon rank-sum test for continuous variables and the $\chi^2$ test or Fisher exact test for categorical variables as appropriate. To make the clinical follow-up of the DES and BMS cohorts comparable and to reduce follow-up bias, clinical outcomes were censored at 3 years in both groups. Cumulative incidence rates of individual and composite outcomes were estimated by the Kaplan-Meier method and compared by the log-rank test.

To reduce the impact of treatment selection bias and potential confounding in an observational study, we performed rigorous adjustment for significant differences in characteristics of patients by use of the weighted Cox proportional-hazards regression models using the inverse-probability-of-treatment weighting (IPTW).[17–19] With that technique, weights for patients receiving BMS were the inverse of (1−propensity score), and weights for patients receiving DES were the inverse of propensity score. The propensity scores were estimated by multiple logistic-regression analysis.[17] To create the propensity score, multiple imputation with Markov Chain Monte Carlo methods was used to fill out incomplete baseline variables with the assumption that data were missing at random.[20] All prespecified covariates were included in the full nonparsimonious models for treatment with DES versus BMS (Table 1). The discrimination and calibration abilities of each propensity score model were assessed by means of the C statistic and the Hosmer-Lemeshow statistic. New propensity scores were incorporated to assess the outcomes of DES implantation in either nonbifurcation or bifurcation LMCA lesions. In addition, for more rigorous adjustment to avoid selection bias and profiles effects, a second Cox model was created with IPTW as the

**Table 1. Baseline Characteristics of Patients Implanted With BMS and DES**

| | All Patients | | |
|---|---|---|---|
| | DES (n=864) | BMS (n=353) | *P* |
| Age, y | 62.7±11.2 | 59.1±12.7 | <0.001 |
| Male gender, n (%) | 619 (71.6) | 253 (71.7) | 0.992 |
| Diabetes mellitus, n (%) | | | |
| Any type | 279 (32.3) | 83 (23.8) | 0.003 |
| Insulin treated | 71 (8.2) | 11 (3.1) | 0.001 |
| Hypertension, n (%) | 452 (52.3) | 147 (41.6) | 0.001 |
| Hyperlipidemia, n (%) | 252 (29.2) | 80 (22.7) | 0.021 |
| Current smoker, n (%) | 224 (25.9) | 101 (28.6) | 0.337 |
| Previous MI, n (%) | 70 (8.1) | 32 (9.1) | 0.582 |
| Previous coronary angioplasty, n (%) | 167 (19.3) | 43 (12.2) | 0.003 |
| Previous congestive heart failure, n (%) | 25 (2.9) | 7 (2.0) | 0.368 |
| Peripheral vascular disease, n (%) | 17 (2.0) | 3 (0.9) | 0.164 |
| Chronic lung disease, n (%) | 28 (3.2) | 2 (0.6) | 0.006 |
| Chronic kidney disease, n (%) | 36 (4.2) | 8 (2.3) | 0.107 |
| Left ventricular ejection fraction, % | 59.4±11.7 | 60.3±11.0 | 0.260 |
| Clinical presentation, n (%) | | | 0.010 |
| Silent ischemia | 27 (3.1) | 6 (1.7) | |
| Stable angina | 267 (30.9) | 86 (24.4) | |
| Unstable angina | 412 (47.7) | 204 (57.8) | |
| MI | 158 (18.3) | 57 (16.2) | |
| Lesion location, n (%) | | | <0.001 |
| Os and shaft | 373 (43.2) | 241 (68.3) | |
| Bifurcation | 491 (56.8) | 112 (31.7) | |
| Extent of diseased vessel, n (%) | | | <0.001 |
| Left main only | 155 (17.9) | 136 (38.5) | |
| Left main plus single-vessel disease | 202 (23.4) | 93 (26.4) | |
| Left main plus 2-vessel disease | 239 (27.7) | 80 (22.7) | |
| Left main plus 3-vessel disease | 268 (31.0) | 44 (12.5) | |
| Right coronary artery disease, n (%) | 374 (43.3) | 77 (21.8) | <0.001 |
| De novo lesions, n (%) | 836 (96.8) | 346 (98.0) | 0.234 |
| Use of glycoprotein IIb/IIIa inhibitors, n (%) | 804 (93.1) | 329 (93.2) | 0.928 |
| Use of intraaortic balloon pump, n (%) | 50 (5.8) | 28 (7.9) | 0.166 |
| Guidance of intravascular ultrasound, n (%) | 643 (74.4) | 261 (73.9) | 0.861 |
| Stents implanted, n | 1.24±0.50 | 1.09±0.31 | <0.001 |
| Total stent length, mm | 32.90±21.73 | 16.70±10.65 | <0.001 |
| Complex stenting (≥2 stents), n (%) | 195 (22.6) | 27 (7.7) | <0.001 |

Values are ±SD.

weights, treatment effect (DES or BMS), and some important risk covariates, which had significant effects ($P<0.1$) on the clinical outcomes.

All reported *P* values are 2 sided, and values of $P<0.05$ were considered to indicate statistical significance. SAS software version 9.1 (SAS Institute, Inc, Cary, NC) was used for statistical analysis.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

# Results

## Patient Characteristics

### *All Patients*

A total of 1217 patients were included in this analysis: 353 received only BMS and 864 received at least 1 DES. Baseline demographic, clinical, angiographic, and procedural characteristics of the 2 groups are shown in Table 1. Compared with patients receiving BMS, those receiving DES were older and had a higher prevalence of diabetes mellitus, hypertension, hyperlipidemia, chronic lung disease, and prior history of PCI. In addition, patients receiving DES had more extensive coronary artery disease, with a higher prevalence of 3-vessel disease and right coronary artery stenosis. Therefore, patients treated with DES received more and longer stents than those treated with BMS. Because of more frequent involvement at bifurcation LMCA, the 2-stent technique was used more frequently in patients receiving DES. Of the 864 patients receiving DES at the LMCA, 662 (76.6%) received sirolimus-eluting stents, 191 (22.1%) received paclitaxel-eluting stents, and 11 (1.3%) received both sirolimus- and paclitaxel-eluting stents.

When the patients were classified according to lesion location, patients having bifurcation lesions were older, were more often male, and had a higher prevalence of hypertension, history of MI or PCI, and multivessel disease. Consequently, they were treated with more stents and longer stents than patients having nonbifurcation lesions (Table 2).

## Outcomes

### *Unadjusted Incidences of Events*

When follow-up was truncated at 3 years, the median and length of follow-up was 36 months (interquartile range, 36 to 36 months) in the BMS group and 36 months (interquartile range, 36 to 36) in the DES group ($P=0.728$). Figure 1 depicts the unadjusted incidence of 3-year adverse outcomes in all patients. At 3 years, 12.7% of patients in the DES group and 8.8% in the BMS group were lost to follow-up. Although the DES and BMS groups had comparable 3-year cumulative incidences of death and composite of death or MI, the former had a significantly lower incidence of TLR. This pattern was observed consistently in patients with nonbifurcation or bifurcation LMCA lesions. In patients with nonbifurcation LMCA lesions, the unadjusted incidences of death and composite of death or MI were similar between the DES and BMS groups (Figure 2). However, compared with BMS, there was a significantly lower incidence of TLR with the use of DES. Similarly, in patients with bifurcation lesions, the 3-year rate of TLR was significantly lower with DES than BMS, although the 2 groups had comparable incidences of death and composite of death or MI, as shown in Figure 3.

**Table 2. Baseline Characteristics of Patients Implanted With BMS and DES According to Lesion Location**

| | Nonbifurcation Lesions | | | | Bifurcation Lesions | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Overall (n=614) | DES (n=373) | BMS (n=241) | P* | Overall (n=603) | DES (n=491) | BMS (n=112) | P* | P† |
| Age, y | 60.2±12.2 | 61.5±11.7 | 58.3±12.8 | 0.002 | 63.2±11.1 | 63.7±10.7 | 60.9±12.4 | 0.032 | <0.001 |
| Male gender, n (%) | 405 (66.0) | 246 (66.0) | 159 (66.0) | 0.995 | 467 (77.5) | 373 (76.0) | 94 (83.9) | 0.069 | <0.001 |
| Diabetes mellitus, n (%) | | | | | | | | | |
| Any type | 178 (29.0) | 118 (31.6) | 60 (24.9) | 0.072 | 185 (30.7) | 161 (32.8) | 24 (21.4) | 0.019 | 0.519 |
| Insulin treated | 42 (6.8) | 33 (8.9) | 9 (3.7) | 0.014 | 40 (6.6) | 38 (7.7) | 2 (1.8) | 0.022 | 0.886 |
| Hypertension, n (%) | 282 (45.9) | 183 (49.1) | 99 (41.1) | 0.053 | 317 (52.6) | 269 (55.0) | 48 (42.9) | 0.023 | 0.021 |
| Hyperlipidemia, n (%) | 148 (24.1) | 98 (26.3) | 50 (20.8) | 0.118 | 184 (30.5) | 154 (31.4) | 30 (26.8) | 0.342 | 0.012 |
| Current smoker, n (%) | 147 (23.9) | 90 (24.1) | 57 (23.7) | 0.892 | 178 (29.5) | 134 (27.3) | 44 (39.3) | 0.012 | 0.028 |
| Previous MI, n (%) | 38 (6.2) | 20 (5.4) | 18 (7.5) | 0.290 | 64 (10.6) | 50 (10.2) | 14 (12.5) | 0.473 | 0.005 |
| Previous coronary angioplasty, n (%) | 88 (14.3) | 64 (17.2) | 24 (10.0) | 0.013 | 122 (20.2) | 103 (21.0) | 19 (17.0) | 0.340 | 0.007 |
| Previous congestive heart failure, n (%) | 18 (2.9) | 12 (3.2) | 6 (2.5) | 0.602 | 14 (2.3) | 13 (2.7) | 1 (0.9) | 0.266 | 0.065 |
| Peripheral vascular disease, n (%) | 6 (1.0) | 5 (1.3) | 1 (0.4) | 0.255 | 14 (2.3) | 12 (2.4) | 2 (1.8) | 0.676 | 0.506 |
| Chronic lung disease, n (%) | 13 (2.1) | 11 (3.0) | 2 (0.8) | 0.075 | 17 (2.8) | 17 (3.5) | 0 | 0.053 | 0.430 |
| Chronic kidney disease, n (%) | 17 (2.8) | 14 (3.8) | 3 (1.2) | 0.064 | 27 (4.5) | 22 (4.5) | 5 (4.5) | 0.994 | 0.110 |
| Left ventricular ejection fraction, % | 59.6±11.3 | 59.2±11.6 | 60.4±10.8 | 0.232 | 59.6±11.7 | 59.5±11.8 | 60.1±11.3 | 0.702 | 0.991 |
| Clinical presentation, n (%) | | | | 0.008 | | | | 0.287 | 0.857 |
| Silent ischemia | 19 (3.1) | 13 (3.5) | 6 (2.5) | | 14 (2.3) | 14 (2.9) | 0 | | |
| Stable angina | 176 (28.7) | 121 (32.4) | 55 (22.8) | | 177 (29.4) | 146 (29.7) | 31 (27.7) | | |
| Unstable angina | 312 (50.8) | 169 (45.3) | 143 (59.3) | | 304 (50.4) | 243 (49.5) | 61 (54.5) | | |
| MI | 107 (17.4) | 70 (18.8) | 37 (15.4) | | 108 (17.9) | 88 (17.9) | 20 (17.9) | | |
| Lesion location, n (%) | | | | | | | | | |
| Os and shaft | 614 (100) | 373 (100.0) | 241 (100.0) | | | | | | |
| Bifurcation | | | | | 603 (100) | 491 (100.0) | 112 (100.0) | | |
| Extent of diseased vessel, n (%) | | | | <0.001 | | | | <0.001 | <0.001 |
| Left main only | 228 (37.1) | 112 (30.0) | 116 (48.1) | | 63 (10.5) | 43 (8.8) | 20 (17.9) | | |
| Left main plus single-vessel disease | 150 (24.4) | 86 (23.1) | 64 (26.6) | | 145 (24.1) | 116 (23.6) | 29 (25.9) | | |
| Left main plus two-vessel disease | 116 (18.9) | 85 (22.8) | 31 (12.9) | | 203 (33.7) | 154 (31.4) | 49 (43.8) | | |
| Left main plus three-vessel disease | 120 (19.5) | 90 (24.1) | 30 (12.5) | | 192 (31.8) | 178 (36.3) | 14 (12.5) | | |
| Right coronary artery disease, n (%) | 200 (32.6) | 150 (40.2) | 50 (20.8) | <0.001 | 251 (41.6) | 224 (45.6) | 27 (24.1) | <0.001 | |
| De novo lesions, n (%) | 602 (98.1) | 366 (98.1) | 236 (97.9) | 0.863 | 580 (96.2) | 470 (95.7) | 110 (98.2) | 0.214 | 0.052 |
| Use of glycoprotein IIb/IIIa inhibitors, n (%) | 590 (96.1) | 358 (96.0) | 232 (96.3) | 0.858 | 543 (90.1) | 446 (90.8) | 97 (86.6) | 0.177 | <0.001 |
| Use of intraaortic balloon pump, n (%) | 29 (4.7) | 17 (4.6) | 12 (5.0) | 0.810 | 49 (8.1) | 33 (6.7) | 16 (14.3) | 0.008 | 0.015 |
| Guidance of intravascular ultrasound, n (%) | 463 (75.4) | 280 (75.1) | 183 (75.9) | 0.808 | 441 (73.1) | 363 (73.9) | 78 (69.6) | 0.356 | 0.364 |
| Stents implanted, n | 1.10±0.35 | 1.14±0.42 | 1.03±0.17 | <0.001 | 1.29±0.54 | 1.31±0.55 | 1.21±0.47 | 0.070 | <0.001 |
| Total stent length, mm | 19.0±13.8 | 22.78±16.08 | 13.13±5.45 | <0.001 | 37.6±22.0 | 40.59±22.32 | 24.38±14.42 | <0.001 | <0.001 |
| Complex stenting (≥2 stents), n (%) | 11 (1.8) | 10 (2.7) | 1 (0.4) | 0.039 | 211 (35.0) | 185 (37.7) | 26 (23.2) | 0.004 | <0.001 |

*DES versus BMS.
†Nonbifurcation versus bifurcation lesions in overall population.
Values are ±SD.

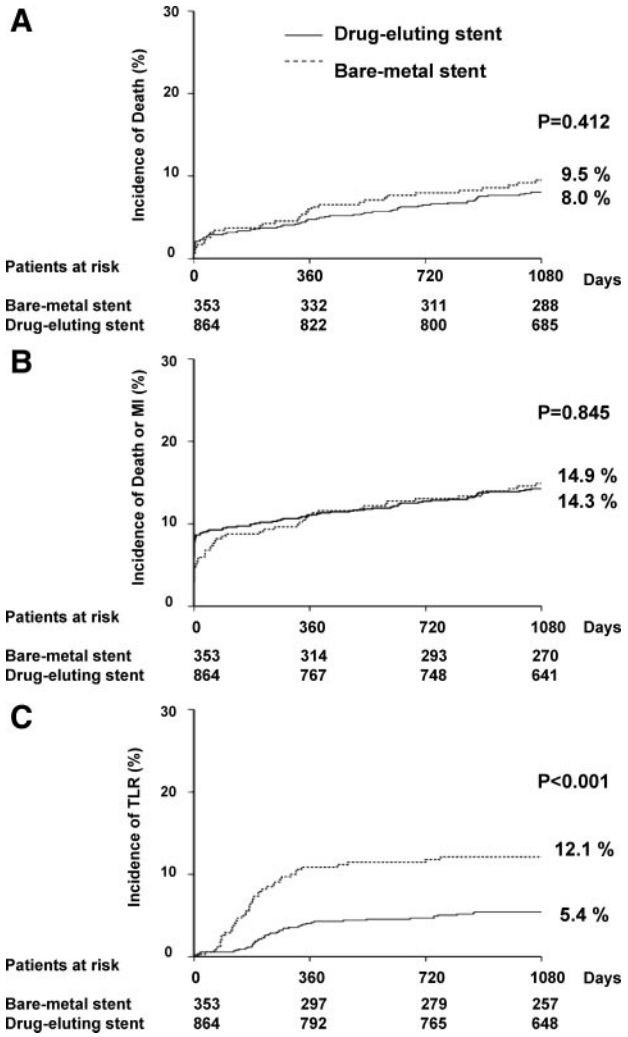


**Figure 1.** Kaplan–Meier incidence curves of outcomes in all patients. A, Three-year incidences of death. B, Three-year incidence of death or MI. C, Three-year incidence of TLR.

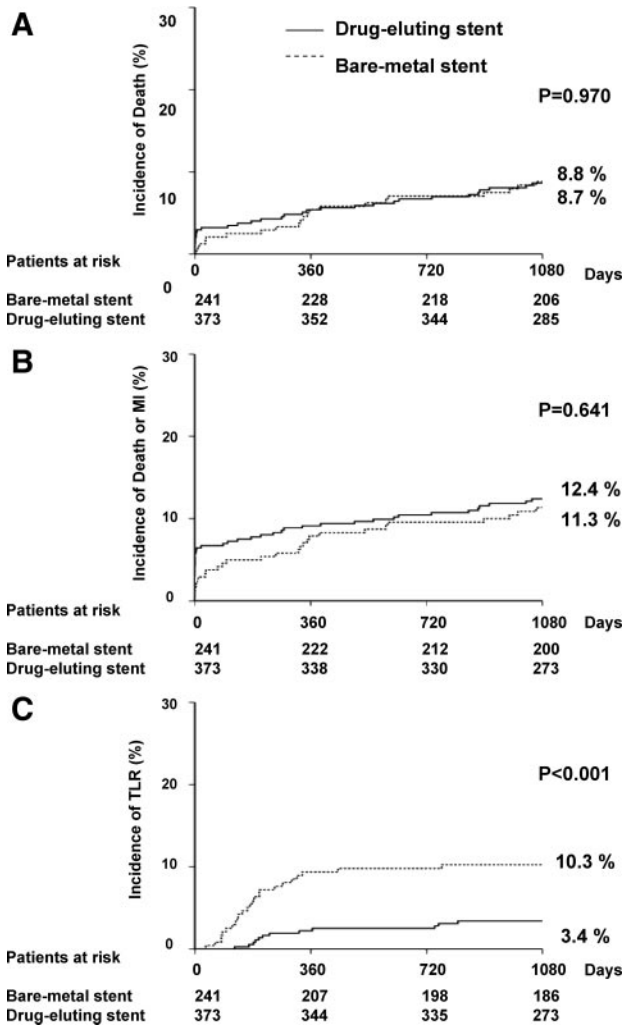


**Figure 2.** Kaplan–Meier incidence curves of outcomes in patients with nonbifurcation LMCA lesions. A, Three-year incidences of death. B, Three-year incidence of death or MI. C, Three-year incidence of TLR.

Moreover, the 3-year rate of target vessel revascularization also was significantly lower with DES (9.8±1.0% versus 15.7±2.0%; $P=0.002$) than BMS. Angiographic stent thrombosis occurred in 6 patients receiving DES and none receiving BMS ($P=0.190$). Among them, late stent thrombosis occurred in 1 patient at 201 days after the procedure.

When patients were classified as those having bifurcation or nonbifurcation lesions, the cumulative incidences of death or MI (17.0±1.5% versus 12.0±1.3%; log-rank $P=0.009$) and target vessel revascularization (14.2±1.5% versus 8.8±1.2%; log-rank $P=0.005$) were significantly higher in those having bifurcation lesions. However, the incidence of death was similar in patients with bifurcation (8.2±1.1%) and nonbifurcation (9.7±1.3%; log-rank $P=0.761$) lesions.

### Adjustments Hazards

Table 3 summarizes the cumulative hazards of adverse outcomes in patients receiving either DES versus BMS using unadjusted and adjusted multivariable analyses. When the outcomes of patients receiving either DES or BMS were adjusted with IPTW, there was a significantly lower risk of TLR and a comparable risk of death and composite of death or MI in the first and second multivariable Cox models. Similarly, in patients classified by lesion location, the risk of TLR remained significantly lower with the use of DES than BMS in both the bifurcation and nonbifurcation groups. The c statistic of the propensity score was 0.848, 0.804, and 0.826 in all patients, those having nonbifurcation lesions, and those with bifurcation lesions, respectively.

## Discussion

The major findings of this study were as follows: (1) the 3-year incidence of mortality or MI was comparably low after PCI with BMS or DES in patients with unprotected LMCA stenosis; (2) compared with BMS, the use of DES was associated with a lower risk of repeat revascularization without an increase in the risk of death or MI; and (3) a significant reduction in repeat revascularization with DES compared with BMS was consistently applied to either bifurcation or nonbifurcation LMCA lesions.

Although DES have been shown to be procedurally feasible for unprotected LMCA stenosis, there is limited informa-

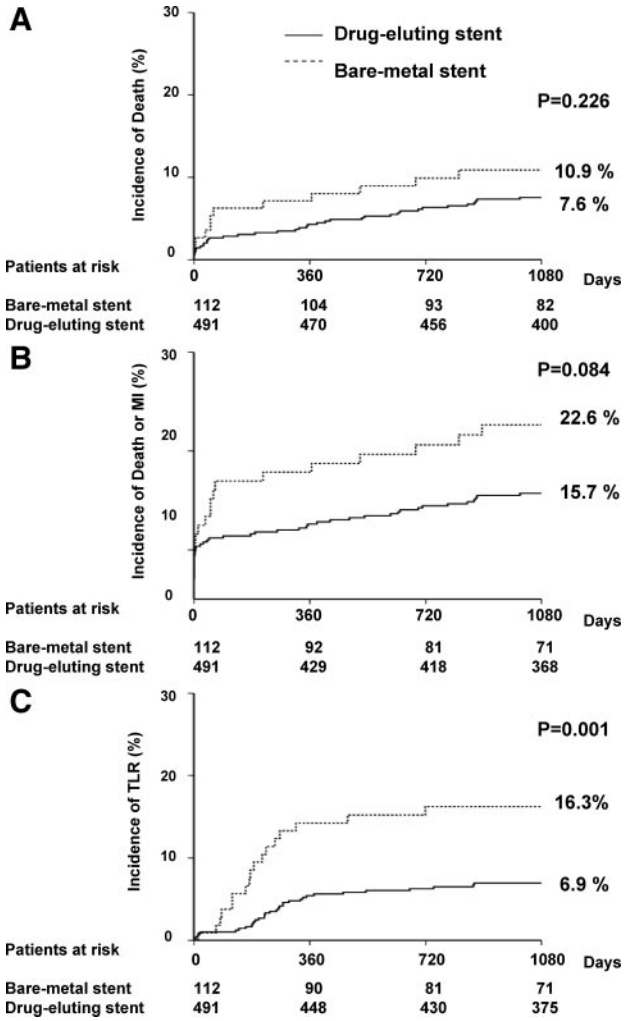


**Figure 3.** Kaplan–Meier incidence curves of outcomes in patients with bifurcation LMCA lesions. A, Three-year incidences of death. B, Three-year incidence of death or MI. C, Three-year incidence of TLR.

tion on long-term outcomes.[2–10] Most published reports have been based on outcomes of small study populations with short follow-up periods and without active control. Longer-term follow-up and a control group of patients receiving BMS are required to fully assess the potential safety of DES because a crossover in event rates between DES and BMS may develop after 1 year.[21] The observation period in our study may be the longest of studies comparing the outcomes of DES and BMS for unprotected LMCA stenosis. Our use of a large nationally based registry of consecutive patients recruited at multiple centers may be a good indicator of real-world outcomes. In addition, in our study, 2-stage adjustments using the multivariable Cox modeling with IPTW were performed to overcome the limitation of observational study.[17,18] The IPTW method may avoid the possibility that the benefit of DES was overestimated as a result of the residual confounding related to the selection of lower-risk population by propensity score matching, which was used in the recent analyses of registry studies.[16–18]

The results of recent pooled analyses and a large registry have suggested that, relative to BMS, DES treatment may increase late mortality as a result of the occurrence of very late thrombosis.[12,13,21] Thus, although recent meta-analysis and large registries have reported the long-term safety of DES compared with BMS,[22–24] the possibility of very late thrombosis has been the major factor limiting global use of DES for unprotected LMCA lesions.

We found, however, that DES were safe for treating this complex lesion in that there were comparable risks of death and MI for the 2 stent types. Indeed, our results were in good agreement with those of large registries enrolling patients for off-label indications of DES that showed that DES, relative to BMS, did not increase the likelihood of long-term mortality or MI in patients with complex coronary lesions.[22–24] For example, the recent large National Heart, Lung, and Blood Institute registry in the United States reported that, compared with BMS, the off-label use of DES for similar indications was associated with a comparable 1-year risk of death and a lower 1-year risk of MI after adjustment.[24] Of interest, a large registry of 13 353 patients in Ontario found that the 3-year mortality rate in a propensity-matched population was significantly higher with BMS than with DES.[23] The comparable incidence of death or MI seen with the 2 stent types may be due, at least in part, to the offsetting risks of restenosis compared with stent thrombosis. Because restenosis or repeat revascularization at LMCA may be associated with death or MI during follow-up,[25] the higher risk of restenosis with BMS may counterbalance the potential risk of mortality resulting from stent thrombosis with DES.[26,27]

Our results indicate that, compared with BMS, DES had significant and durable efficacy in reducing the need for repeat revascularization. In the Kaplan–Meier events curves, a difference in cumulative TLR rate was noted after 6 months and continued for up to 3 years. Accordingly, DES was associated with an ≈60% to 70% reduced risk of 3-year TLR in our analysis. Although a preliminary study observed a gradual luminal narrowing at DES segments in a few patients,[28] our findings may contradict the phenomenon of "late catchup" in DES at the unprotected LMCA. Thus, our results, together with those of randomized and registry studies, indicate that the dramatic efficacy of DES in reducing restenosis may be applicable to a variety of coronary disease subsets, including LMCA lesions.[22–24]

Although all patients in our study had lesions at the unprotected LMCA stenosis, they encompassed a wide spectrum of procedural risks. In particular, previous studies reported that bifurcation involvement was frequent and that PCI for such lesions was associated with a greater risk of repeat revascularization compared with nonbifurcation lesions.[5,29,30] In comparison, 50% of our patients had involvement at the bifurcation LMCA, suggesting a higher frequency of TLR than for nonbifurcation lesions, regardless of whether BMS or DES were used. Of note, however, the relative benefit of DES over BMS in reducing repeat revascularizations was consistently observed for both bifurcation and nonbifurcation lesions without an increase in the risks of death or MI. Indeed, the long-term risk of TLR was similarly reduced by 60% for nonbifurcation and bifurcation stenoses in our multivariate Cox models.

**Table 3. Hazard Ratios for Clinical Outcomes With DES Versus BMS**

| | Unadjusted | | Adjusted by IPTW | | Adjusted by IPTW and Covariates* | |
|---|---|---|---|---|---|---|
| Outcomes | Hazard Ratio (95% CI) | *P* | Hazard Ratio (95% CI) | *P* | Hazard Ratio (95% CI) | *P* |
| Overall patients | | | | | | |
| Death | 0.83 (0.55–1.25) | 0.370 | 0.71 (0.36–1.40) | 0.976 | 0.86 (0.50–1.47) | 0.569 |
| TLR | 0.41 (0.27–0.63) | <0.001 | 0.40 (0.22–0.73) | 0.003 | 0.32 (0.17–0.61) | <0.001 |
| Death/MI | 0.97 (0.70–1.35) | 0.872 | 0.83 (0.49–1.40) | 0.479 | 0.99 (0.62–1.57) | 0.958 |
| Death/MI/TLR | 0.81 (0.62–1.06) | 0.121 | 0.77 (0.50–1.20) | 0.248 | 0.81 (0.54–1.21) | 0.310 |
| Nonbifurcations | | | | | | |
| Death | 0.98 (0.57–1.68) | 0.938 | 1.01 (0.53–1.92) | 0.973 | 1.04 (0.53–2.05) | 0.918 |
| TLR | 0.31 (0.16–0.62) | 0.001 | 0.39 (0.17–0.88) | 0.024 | 0.40 (0.17–0.91) | 0.029 |
| Death/MI | 1.12 (0.70–1.81) | 0.631 | 1.09 (0.62–1.91) | 0.771 | 1.12 (0.62–2.03) | 0.715 |
| Death/MI/TLR | 0.79 (0.54–1.16) | 0.227 | 0.87 (0.54–1.38) | 0.546 | 0.92 (0.57–1.49) | 0.744 |
| Bifurcations | | | | | | |
| Death | 0.67 (0.35–1.29) | 0.229 | 0.54 (0.25–1.18) | 0.124 | 0.82 (0.33–2.03) | 0.661 |
| TLR | 0.38 (0.21–0.67) | <0.001 | 0.38 (0.18–0.78) | 0.009 | 0.34 (0.16–0.71) | 0.004 |
| Death/MI | 0.68 (0.43–1.07) | 0.091 | 0.68 (0.38–1.19) | 0.177 | 0.87 (0.50–1.52) | 0.621 |
| Death/MI/TLR | 0.67 (0.45–0.99) | 0.044 | 0.69 (0.41–1.16) | 0.163 | 0.82 (0.50–1.34) | 0.421 |

CI indicates confidence interval.
*Adjustment was done through the use of the IPTW and significant covariates influencing outcomes.

Our study had several limitations, including its nonrandomized design, which may have significantly affected the results owing to unmeasured confounders, procedure bias, or detection bias. Specifically, patients receiving DES later could have benefited from improvements in PCI procedures and adjunctive medications for coronary artery disease, including long-term treatment of clopidogrel, compared with the patients who received BMS earlier. In fact, no statistical method of adjustment can completely abolish this limitation. Another limitation is that angiographic assessment in a core examination center was not performed; therefore, the relationship of quantitative angiographic parameters with clinical outcomes could not be sufficiently measured. Moreover, some of the earlier DES patients were treated with 3.0-mm sirolimus-eluting stents because bigger DES were not available. A 3.0-mm stent oversized with a bigger balloon after deployment may lead to an unfavorable outcome.[31] Finally, the technical features adopted here may limit the generalization of our results. Our preference for intravascular ultrasound–guided stenting or a selective rather than a systematic 2-stent strategy for bifurcation lesions may be associated with favorable outcomes.[29,32,33]

## Conclusions

Our findings demonstrate the durable safety and efficacy of DES compared with BMS in the treatment of unprotected LMCA stenosis. When combined with previous registry data, our results indicate that PCI with DES is a reliable treatment for unprotected LMCA stenosis. A large randomized comparison study with coronary artery bypass surgery will provide more confidence in the long-term safety, durability, and efficacy of PCI with DES.

## Sources of Funding

All of the authors report receiving grant support from the Korean Society of Interventional Cardiology, Health 21 R&D Project, Ministry of Health and Welfare, Korea (grant 0412-CR02-0704-0001), Asan Institute for Life Science (grant 04.5-361), and the CardioVascular Research Foundation, as part of participation in the MAIN-COMPARE Registry.

## Disclosures

None.

## References

1. Park SJ, Mintz GS. *Left Main Stem Disease*. 1st ed. Seoul, Korea: Informa Healthcare; 2006.
2. Park SJ, Kim YH, Lee BK, Lee SW, Lee CW, Hong MK, Kim JJ, Mintz GS, Park SW. Sirolimus-eluting stent implantation for unprotected left main coronary artery stenosis: comparison with bare metal stent implantation. *J Am Coll Cardiol*. 2005;45:351–356.
3. Chieffo A, Stankovic G, Bonizzoni E, Tsagalou E, Iakovou I, Montorfano M, Airoldi F, Michev I, Sangiorgi MG, Carlino M, Vitrella G, Colombo A. Early and mid-term results of drug-eluting stent implantation in unprotected left main. *Circulation*. 2005;111:791–795.
4. Valgimigli M, van Mieghem CA, Ong AT, Aoki J, Granillo GA, McFadden EP, Kappetein AP, de Feyter PJ, Smits PC, Regar E, Van der Giessen WJ, Sianos G, de Jaegere P, Van Domburg RT, Serruys PW. Short- and long-term clinical outcome after drug-eluting stent implantation for the percutaneous treatment of left main coronary artery disease: insights from the Rapamycin-Eluting and Taxus Stent Evaluated at Rotterdam Cardiology Hospital registries (RESEARCH and T-SEARCH). *Circulation*. 2005;111:1383–1389.
5. Price MJ, Cristea E, Sawhney N, Kao JA, Moses JW, Leon MB, Costa RA, Lansky AJ, Teirstein PS. Serial angiographic follow-up of sirolimus-eluting stents for unprotected left main coronary artery revascularization. *J Am Coll Cardiol*. 2006;47:871–877.
6. Palmerini T, Marzocchi A, Marrozzini C, Ortolani P, Saia F, Savini C, Bacchi-Reggiani L, Gianstefani S, Virzi S, Manara F. Comparison between coronary angioplasty and coronary artery bypass surgery for the treatment of unprotected left main coronary artery stenosis (the Bologna Registry). *Am J Cardiol*. 2006;98:54–59.
7. Lee MS, Kapoor N, Jamal F, Czer L, Aragon J, Forrester J, Kar S, Dohad S, Kass R, Eigler N, Trento A, Shah PK, Makkar RR. Comparison of coronary artery bypass surgery with percutaneous coronary intervention with drug-eluting stents for unprotected left main coronary artery disease. *J Am Coll Cardiol*. 2006;47:864–870.
8. Kim YH, Dangas GD, Solinas E, Aoki J, Praise H, Kimura M, Franklin-Bond T, Dasgupta NK, KIrtan AJ, Moussa I, Lansky AJ, Collins

M, Stone GW, Leon MB, Moses JW, Mehran R. Effectiveness of drug-eluting stent implantation for patients with unprotected left main coronary artery stenosis. *Am J Cardiol*. 2008;101:801–806.
9. Buszman PE, Kiesz SR, Bochenek A, Peszek-Przybyla E, Szkrobka I, Debinski M, Bialkowska B, Dudek D, Gruszka A, Zurakowski A, Milewski K, Wilczynski M, Rzeszutko L, Buszman P, Szymszal J, Martin JL, Tendera M. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. *J Am Coll Cardiol*. 2008; 51:538–545.
10. Meliga E, Garcia-Garcia HM, Valgimigli M, Chieffo A, Biondi-Zoccai G, Maree AO, Cook S, Reardon L, Moretti C, De Servi S, Palacios IF, Windecker S, Colombo A, van Domburg R, Sheiban I, Serruys PW. Longest available clinical outcomes after drug-eluting stent implantation for unprotected left main coronary artery disease: the DELFT (Drug Eluting Stent for Left Main) Registry. *J Am Coll Cardiol*. 2008;51: 2212–2219.
11. Iakovou I, Schmidt T, Bonizzoni E, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA*. 2005;293:2126–2130.
12. Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, Colombo A, Schampaert E, Grube E, Kirtane AJ, Cutlip DE, Fahy M, Pocock SJ, Mehran R, Leon MB. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med*. 2007;356:998–1008.
13. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med*. 2007;356:1020–1029.
14. Kuchulakanti PK, Chu WW, Torguson R, Ohlmann P, Rha SW, Clavijo LC, Kim SW, Bui A, Gevorkian N, Xue Z, Smith K, Fournadjieva J, Suddath WO, Satler LF, Pichard AD, Kent KM, Waksman R. Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. *Circulation*. 2006;113: 1108–1113.
15. Farb A, Boam AB. Stent thrombosis redux: the FDA perspective. *N Engl J Med*. 2007;356:984–987.
16. Seung KB, Park DW, Kim YH, Lee SW, Lee CW, Hong MK, Park SW, Yun SC, Gwon HC, Jeong MH, Jang Y, Kim HS, Kim PJ, Seong IW, Park HS, Ahn T, Chae IH, Tahk SJ, Chung WS, Park SJ. Stents versus coronary-artery bypass grafting for left main coronary artery disease. *N Engl J Med*. 2008;358:1781–1792.
17. Normand SL. Evaluating the optimal timing of angiography: landmark or off the mark? *Circulation*. 2007;116:2656–2657.
18. Robins J, Hernan M, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000;11:550–560.
19. Therneau T, Grambsch, P. *Modeling Survival Data: Extending the Cox Model*. New York, NY: Springer-Verlag; 2000.
20. Rubin D. *Multiple Imputation for Nonresponse in Surveys*. New York, NY: John Wiley & Sons; 1987.
21. Lagerqvist B, James SK, Stenestrand U, Lindback J, Nilsson T, Wallentin L. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. *N Engl J Med*. 2007;356:1009–1019.
22. Kastrati A, Mehilli J, Pache J, Kaiser C, Valgimigli M, Kelbaek H, Menichelli M, Sabate M, Suttorp MJ, Baumgart D, Seyfarth M, Pfisterer ME, Schomig A. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med*. 2007;356:1030–1039.
23. Tu JV, Bowen J, Chiu M, Ko DT, Austin PC, He Y, Hopkins R, Tarride J-E, Blackhouse G, Lazzam C, Cohen EA, Goeree R. Effectiveness and safety of drug-eluting stents in Ontario. *N Engl J Med*. 2007;357: 1393–1402.
24. Marroquin OC, Selzer F, Mulukutla SR, Williams DO, Vlachos HA, Wilensky RL, Tanguay J-F, Holper EM, Abbott JD, Lee JS, Smith C, Anderson WD, Kelsey SF, Kip KE. A comparison of bare-metal and drug-eluting stents for off-label indications. *N Engl J Med*. 2008;358: 342–352.
25. Takagi T, Stankovic G, Finci L, Toutouzas K, Chieffo A, Spanos V, Liistro F, Briguori C, Corvaja N, Albero R, Sivieri G, Paloschi R, Di Mario C, Colombo A. Results and long-term predictors of adverse clinical events after elective percutaneous interventions on unprotected left main coronary artery. *Circulation*. 2002;106:698–702.
26. Stone GW, Ellis SG, Colombo A, Dawkins KD, Grube E, Cutlip DE, Friedman M, Baim DS, Koglin J. Offsetting impact of thrombosis and restenosis on the occurrence of death and myocardial infarction after paclitaxel-eluting and bare metal stent implantation. *Circulation*. 2007; 115:2842–2847.
27. Chen MS, John JM, Chew DP, Lee DS, Ellis SG, Bhatt DL. Bare metal stent restenosis is not a benign clinical entity. *Am Heart J*. 2006;151: 1260–1264.
28. Valgimigli M, Malagutti P, van Mieghem CAG, Vaina S, Ligthart JM, Sianos G, Serruys PW. Persistence of neointimal growth 12 months after intervention and occurrence of delayed restenosis in patients with left main coronary artery disease treated with drug-eluting stents. *J Am Coll Cardiol*. 2006;47:1491–1494.
29. Valgimigli M, Malagutti P, Rodriguez-Granillo GA, Garcia-Garcia HM, Polad J, Tsuchida K, Regar E, Van der Giessen WJ, de Jaegere P, De Feyter P, Serruys PW. Distal left main coronary disease is a major predictor of outcome in patients undergoing percutaneous intervention in the drug-eluting stent era: an integrated clinical and angiographic analysis based on the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) and Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registries. *J Am Coll Cardiol*. 2006; 47:1530–1537.
30. Kim YH, Park SW, Hong MK, Park DW, Park KM, Lee BK, Song JM, Han KH, Lee CW, Kang DH, Song JK, Kim JJ, Park SJ. Comparison of simple and complex stenting techniques in the treatment of unprotected left main coronary artery bifurcation stenosis. *Am J Cardiol*. 2006;97: 1597–1601.
31. Sheiban I, Meliga E, Moretti C, Biondi-Zoccai GGL, Rosano G, Sciuto F, Marra WG, Omede P, Gerasimou A, Trevi GP. Long-term clinical and angiographic outcomes of treatment of unprotected left main coronary artery stenosis with sirolimus-eluting stents. *Am J Cardiol*. 2007;100: 431–435.
32. Mintz GS. Features and parameters of drug-eluting stent deployment discoverable by intravascular ultrasound. *Am J Cardiol*. 2007;100(suppl 2):S26–S35.
33. Leesar MA, Mintz GS. Hemodynamic and intravascular ultrasound assessment of an ambiguous left main coronary artery stenosis. *Catheter Cardiovasc Interv*. 2007;70:721–730.

## CLINICAL PERSPECTIVE

Although the use of drug-eluting stents (DES) has become a common practice for unprotected left main coronary artery stenosis in certain areas, the uncertainty about the long-term safety and durable efficacy of DES remains. In the present substudy of the largest registry of patients receiving revascularization therapy for unprotected left main coronary artery stenosis, DES showed a comparable 3-year risk of death or myocardial infarction compared with bare metal stents. Moreover, the reduction in target lesion revascularization is sustained in late follow-up to 3 years. Of note is that the incidence of stent thrombosis did not differ between the 2 stent types. The superior benefit of DES over bare metal stents was consistently maintained after rigorous adjustment for different baseline characteristics between the 2 stent groups. With regard to the impact of left main coronary artery location, there was no difference in DES benefit between bifurcation and nonbifurcation lesions. In fact, the use of DES decreased the 3-year risk of target lesion revascularization by 60% with comparable risk of death or myocardial infarction for either bifurcation or nonbifurcation left main coronary artery lesions. This study provides important information on the issue of long-term safety and efficacy of DES for the treatment of unprotected left main coronary artery stenosis.