ISSN 1936-8798/08/$34.00
PUBLISHED BY ELSEVIER INC.
DOI: 10.1016/j.jcin.2008.06.011

Stent Thrombosis, Clinical Events, and Influence of Prolonged Clopidogrel Use After Placement of Drug-Eluting Stent

Data From an Observational Cohort Study of Drug-Eluting Versus Bare-Metal Stents

Duk-Woo Park, MD,* Sung-Cheol Yun, PHD,† Seung-Whan Lee, MD,* Young-Hak Kim, MD,* Cheol Whan Lee, MD,* Myeong-Ki Hong, MD,* Sang-Sig Cheong, MD,‡ Jae-Joong Kim, MD,* Seong-Wook Park, MD,* Seung-Jung Park, MD*

Seoul and GangNeung, Korea

Objectives The purpose of this study was to evaluate the risk of stent thrombosis (ST), clinical outcomes, and the benefits of extended clopidogrel use after drug-eluting stent (DES) implantation.

Background Data are limited regarding uniform evaluation of ST and the influence of clopidogrel continuation beyond 12 months on late events after DES treatment.

Methods We identified 7,221 patients who received DES implantation (n = 3,160) or bare-metal stent (BMS) implantation (n = 4,061), and compared long-term adverse outcomes. Additionally, 2,851 patients with DES surviving 12 months without major events were analyzed according to clopidogrel continuation.

Results The adjusted-risk of overall ST was similar in the 2 groups. After 1 year, however, DES patients showed a higher risk of ST; definite/probable (hazard ratio [HR]: 3.55, 95% confidence interval [CI]: 1.26 to 9.99). The adjusted-risk of death (HR: 0.60, 95% CI: 0.46 to 0.79), death/myocardial infarction (HR: 0.63, 95% CI: 0.49 to 0.81), and target lesion revascularization (HR: 0.32, 95% CI: 0.24 to 0.43) were significantly lower in the DES group than in the BMS group. Continuing clopidogrel beyond 12 months was not associated with a reduced risk for ST (HR: 0.54, 95% CI: 0.07 to 4.23), death (HR: 1.20, 95% CI: 0.55 to 2.66), or death/myocardial infarction (HR: 1.16, 95% CI: 0.56 to 2.42) after DES implantation.

Conclusions As compared with BMS, DES showed a similar risk of overall ST, but a higher risk of very late ST. The rates of death, death/myocardial infarction, and target lesion revasuclarization were significantly lower in the DES group. Clopidogrel continuation beyond 1 year did not appear to reduce ST and clinical events after DES implantation. (J Am Coll Cardiol Intv 2008;1:494–503)

From the *Department of Cardiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea; ‡Department of Cardiology, Asan Medical Center, GangNeung, Korea; and the †Division of Biostatistics, Center for Medical Research and Information, University of Ulsan College of Medicine, Seoul, Korea. This study was partly supported by the Cardiovascular Research Foundation, Seoul, Korea, and a grant from the Korea Health 21 R&D Project, Ministry of Health and Welfare, Korea (0412-CR02-0704-0001).

Manuscript received January 22, 2008; revised manuscript received May 23, 2008, accepted June 12, 2008.

Based on clinical trials, the use of drug-eluting stents (DES) has been associated with a significant decrease in restenosis and subsequent revascularization (1–3). The application of DES has rapidly extended to the "real-world" population with more complicated clinical and lesion subsets (4–6). Concerns have increased, however, about the long-term safety of these DES platforms (7,8). In particular, DES have been associated with a higher risk of late stent thrombosis (ST) compared to bare-metal stents (BMS) (9), a phenomenon not recognized in the initial clinical studies owing to few events and limited durations of follow-up (10,11). Furthermore, premature discontinuation of thienopyridine was associated with a marked increase in the risk of ST (12,13). The advisory panel of the U.S. Food and Drug Administration (FDA) recommended dual antiplatelet therapy for at least 12 months after DES implantation (14).

However, there have been limited data applying uniform definitions for the safety profiles of these devices in routine practice. Also, the role of extended use of clopidogrel beyond 12 months after DES implantation was uncertain. We, therefore, evaluated the long-term safety of DES and the influence of long-term continuation of clopidogrel on late events in an unselected, real-world population.

Methods

Study population and procedures. This study included consecutive patients who underwent coronary artery stent implantation at 2 academic hospitals in Korea between January 3, 1998, and February 28, 2006. The DES has been adopted as the default treatment for percutaneous coronary intervention (PCI) since February 2003 at Asan Medical Center, Seoul, and since May 2003 at Asan Medical Center, GangNeung. The choice of the specific type of DES (i.e., sirolimus-eluting stent [Cypher, Cordis, Johnson & Johnson, Miami Lakes, Florida] or paclitaxel-eluting stent [Taxus, Boston Scientific, Natick, Massachusetts]) was left to the physician's discretion. Patients who underwent coronary brachytherapy were excluded. Patients who received both a BMS and at least 1 DES at the same or different times were regarded as those with DES. All patients were prescribed clopidogrel (loading dose, 300 or 600 mg) or ticlopidine (loading dose, 500 mg) plus aspirin before or during PCI. After the procedure, aspirin was continued indefinitely for all patients. Patients were prescribed clopidogrel for at least 6 months, regardless of DES type (13). Treatment beyond this duration was at the discretion of the physician. Patients receiving BMS were prescribed clopidogrel or ticlopidine for at least 1 month.

This study was approved by the local Ethics Committees at Asan Medical Center, Seoul and GangNeung, and written informed consent was obtained from all patients for the use of clinical and PCI data.

Outcome variables and definitions. The end points of the study were ST, death (all-cause, cardiac, or noncardiac), myocardial infarction (MI), the composite of death or MI, the composite of cardiac death or MI, and target lesion revascularization. Stent thrombosis was assessed by the Academic Research Consortium (ARC) definitions (14) and was classified by the level of certainty (definite, probable, or possible) and by the timing of the event (early [0 to 30 days], late [31 days to 1 year], or very late [>1 year]). Definite ST was defined as an angiographically or pathologically confirmed thrombus, along with ischemic symptoms or signs. Probable ST was defined as any unexplained deaths within 30 days or acute MI of the target vessel territory without angiographic evidence. Possible ST included any unexplained deaths more than 30 days. All deaths were considered cardiac unless an unequivocal noncardiac cause could be established. The diagnosis of acute MI was established in the presence of ischemic symptoms and cardiac enzyme elevation (creatine kinase-myocardial band elevation >3× or creatine kinase elevation >2× the upper limit of normal value) (15). Target lesion revascularization was defined as revascularization for a stenosis within the stent or within the 5-mm borders adjacent to the stent. During the adjudication of outcomes, subsequent events occurring after repeated revascularization were included in the analysis. All clinical outcomes of interest were adjudicated by independent clinicians.

Abbreviations and Acronyms

ARC = Academic Research Consortium
BMS = bare-metal stent(s)
CI = confidence interval
DES = drug-eluting stent(s)
HR = hazard ratio
MI = myocardial infarction
PCI = percutaneous coronary intervention
ST = stent thrombosis

Clinical follow-up and data verification. Baseline clinical and PCI data were recorded into the dedicated database of each institution by independent research personnel. Clinical follow-up was performed by office visit or telephone contact at 1, 6, and 12 months after the procedure, and every 6 months thereafter. Detailed information on antiplatelet therapy was collected at each follow-up period for patients treated with DES, as previously reported (13). Briefly, at the time of follow-up contact, patients were asked to provide a medication list, especially regarding antiplatelet therapy. In cases with discontinuation, detailed information (time and reason for stopping) was obtained. Also, in cases of uncertainty, general practitioners, referring cardiologists, and patients were contacted as necessary.

To make the clinical follow-up of the 2 sequential cohorts of patients (BMS and DES) comparable and reduce follow-up bias, clinical outcomes were censored at 3 years in both groups.

For validation of complete follow-up data, information about vital records was obtained through March 31, 2007, from the National Registration System of the Ministry of

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 1, NO. 5, 2008
OCTOBER 2008:494–503

Table 1. Baseline Clinical and Procedural Characteristics

Variable	DES (n = 3,160)	BMS (n = 4,061)	p Value
Age (yrs)	60.5 ± 10.3	59.2 ± 10.1	<0.001
Male	2,229 (70.5)	2,903 (71.5)	0.38
Diabetes mellitus	865 (27.4)	835 (20.6)	<0.001
Hypertension	1,599 (50.6)	1,674 (41.2)	<0.001
Current smoker	920 (29.1)	1,642 (40.4)	<0.001
Hypercholesterolemia	759 (24.0)	1,469 (36.2)	<0.001
Previous myocardial infarction	297 (9.4)	304 (7.5)	0.004
Previous coronary angioplasty	544 (17.2)	373 (9.2)	<0.001
Previous coronary artery bypass graft	84 (2.7)	65 (1.6)	0.002
Renal failure	80 (2.5)	82 (2.0)	0.13
Acute coronary syndrome	1,637 (51.8)	2,932 (72.2)	<0.001
Multivessel disease	1,865 (59.0)	1,656 (40.8)	<0.001
Left ventricular ejection fraction (%)	58.4 ± 8.8	59.2 ± 9.6	0.001
Treated lesions, n	4,491	5,702	
Vessels treated			
Left anterior descending artery	2,216 (49.3)	2,840 (49.8)	0.64
Left circumflex artery	721 (16.1)	928 (16.3)	0.76
Right coronary artery	1,219 (27.1)	1,643 (28.8)	0.06
Left main coronary artery	307 (6.8)	264 (4.6)	<0.001
Coronary graft	28 (0.6)	27 (0.5)	0.31
Lesion characteristics			
ACC/AHA type B2 or C lesion	3,338 (74.3)	3,250 (57.0)	<0.001
Bifurcation lesion	732 (16.3)	602 (10.6)	<0.001
Restenotic lesion	251 (5.6)	175 (3.1)	<0.001
Ostial lesion	475 (10.6)	427 (7.5)	<0.001
Chronic total occlusion	251 (5.6)	217 (3.8)	<0.001
Procedural characteristics			
Direct stenting without pre-dilation	727 (16.2)	378 (6.6)	<0.001
Intervention with intravascular ultrasound guidance	2,897 (64.5)	2,676 (46.9)	<0.001
Maximal balloon pressure (atm)	15.9 ± 3.9	12.8 ± 3.8	<0.001
Balloon-to-vessel ratio	1.3 ± 0.2	1.1 ± 0.1	<0.001
Number of stents per patient	1.9 ± 1.1	1.4 ± 0.7	<0.001
Total stent length per patient (mm)	48.0 ± 31.0	26.6 ± 15.1	<0.001
Average stent diameter per patient (mm)	3.2 ± 0.7	3.4 ± 0.9	<0.001
Glycoprotein IIb/IIIa inhibitors	93 (2.9)	232 (5.7)	<0.001

Data are mean ± SD or n (%).
ACC/AHA = American College of Cardiology/American Heart Association classification; BMS = bare-metal stent(s); DES = drug-eluting stent(s).

Government Administration and Home Affairs in Korea using a personal identification number. Also, data regarding rehospitalization for follow-up MI were obtained from the Hospital Disease Code Registration System (categorized according to the International Classification of Diseases-10th Revision), which was merged for reimbursement in the Health Insurance Review Agency in Korea.

Statistical methods. Continuous variables were compared with the *t* test or Wilxocon rank sum test, and categorical variables were compared with the chi-square test or Fisher exact test as appropriate. Cumulative event curves were generated using the Kaplan-Meier method and compared by the log rank test. Univariate and multivariable Cox proportional hazards models were used to examine the association of stent type with the risks of clinical events (16). Additionally, selection bias for the choice of stent was examined with the use of a propensity model (17). The propensity scores were estimated without regard to outcomes, using a multiple logistic-regression model including all the variables listed in Table 1 (18). This score ranged from 0.01 to 0.99, and the *c* statistic for the propensity score model was 0.87, indicating a strong discrimination. The individual propensity score was incorporated into Cox proportional hazards regression models as a covariate as well as stent group to calculate the adjusted hazard ratios (HR). Also, the propensity scores were grouped into quintiles, and

Table 2. Unadjusted and Adjusted Hazard Ratios of Stent Thrombosis for Use of DES Compared With BMS in Entire Study Population

	Outcome Rates (%)*		Crude		Multivariable Adjusted†		Adjusted for Propensity	
Outcome	DES	BMS	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
ARC definite								
Overall at 3 yrs	1.0	0.9	1.10 (0.67–1.81)	0.71	1.20 (0.64–2.26)	0.56	1.11 (0.58–2.09)	0.76
≤1 yr after PCI	0.5	0.7	0.64 (0.34–1.19)	0.16	0.71 (0.32–1.57)	0.39	0.64 (0.29–1.42)	0.27
>1–3 yrs after PCI	0.5	0.1	4.17 (1.54–11.29)	0.01	4.83 (1.50–15.57)	0.01	4.35 (1.32–14.30)	0.02
ARC definite or probable								
Overall at 3 yrs	1.3	1.3	0.97 (0.63–1.49)	0.88	0.97 (0.55–1.71)	0.91	1.07 (0.60–1.91)	0.90
≤1 yr after PCI	0.5	1.0	0.53 (0.30–0.93)	0.03	0.63 (0.30–1.31)	0.21	0.58 (0.28–1.21)	0.15
>1–3 yrs after PCI	0.7	0.2	3.64 (1.60–8.27)	0.002	3.29 (1.18–9.17)	0.02	3.55 (1.26–9.99)	0.02
Any ARC criteria								
Overall at 3 yrs	2.5	1.9	1.30 (0.94–1.80)	0.11	1.21 (0.80–1.83)	0.38	1.20 (0.79–1.84)	0.39
≤1 yr after PCI	1.1	1.3	0.83 (0.54–1.27)	0.38	0.86 (0.50–1.49)	0.59	0.86 (0.49–1.51)	0.60
>1–3 yrs after PCI	1.4	0.6	2.70 (1.60–4.57)	< 0.001	2.25 (1.16–4.36)	0.02	2.28 (1.17–4.43)	0.02

*Outcome rates were derived from Kaplan-Meier curves. †Adjusted for all variables listed in Table 1.
ARC = Academic Research Consortium; CI = confidence interval; PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

HR was compared across quintiles. To evaluate very late occurring events, a landmark analysis was performed with a pre-specified landmark time point at 12 months (19). A new propensity score for DES versus BMS at the landmark point was incorporated for each analysis.

To determine the association between extended continuation of dual antiplatelet therapy beyond 1 year and late events among patients receiving DES, we used a landmark analysis based on continuing clopidogrel at last follow-up contact beyond 1 year. Patients who received DES and survived without MI or revascularization during the initial 12 months were included in this analysis. A Cox proportional hazards model and a propensity score analysis were used to determine whether the long-term outcomes differed significantly between patients taking clopidogrel and patients not taking clopidogrel beyond 1 year after controlling for the patient's risks (17,20). In addition, we calculated Aalen-Nelson estimates of the cumulative hazard function for patients on a regimen of double antiplatelet therapy and for patients who discontinued thienopyridine therapy at a certain point in time.

All p values were 2-sided, and a probability value of <0.05 was considered significant. Statistical analysis was performed using SPSS version 12.0 for Windows (SPSS Inc., Chicago, Illinois).

Results

Baseline characteristics. From February 2003 to February 2006, a total of 3,160 patients (4,491 lesions) were treated with 6,171 DES at the 2 institutions, with 2,513 patients (80%) receiving sirolimus-eluting stents and 647 patients (20%) receiving paclitaxel-eluting stents. During 1998 and 2003, before the adoption of DES as the default strategy, 4,061 patients (5,702 lesions) received 5,867 BMS. When the follow-up period was truncated at 3 years, mean length of follow-up was 30.5 ± 9.0 months in the DES group and 33.7 ± 6.7 in the BMS group.

Baseline and procedural characteristics according to stent type are summarized in Table 1. As compared with patients who received BMS, patients who received DES were significantly older and had a higher prevalence of diabetes mellitus, hypertension, and a history of MI, coronary angioplasty, or bypass surgery. Also, patients with DES had significantly lower mean ejection fractions and were more likely to have multivessel disease. Patients treated with DES had more complex lesions and procedural characteristics than did patients with BMS.

Stent thrombosis. During the 3 years, 66 patients in the DES group (definite: 27 [41%], probable: 7 [11%], and possible: 32 [48%]) and 77 in the BMS group (definite: 35 [45%], probable: 15 [20%], and possible: 27 [35%]) had ST. In the DES group, 9 patients (14%) had early ST, 26 (39%) had late ST, and 31 (47%) had very late ST. In the BMS group, 29 patients (38%) had early ST, 25 (32%) had late ST, and 23 (30%) had very late ST.

Table 2 and Figure 1 summarize the risk of ST based on stent type. In a crude and risk-adjusted analysis, the overall rate of ST was similar in the two groups, whereas after the first year, the incidence of ST was more common in the DES group than in the BMS group. This finding is graphically presented in Figure 1, which shows that event rates for patients with DES increase more steeply over time than they do for patients with BMS. For each ARC criteria, the adjusted HR for very late ST across cohort quintiles was

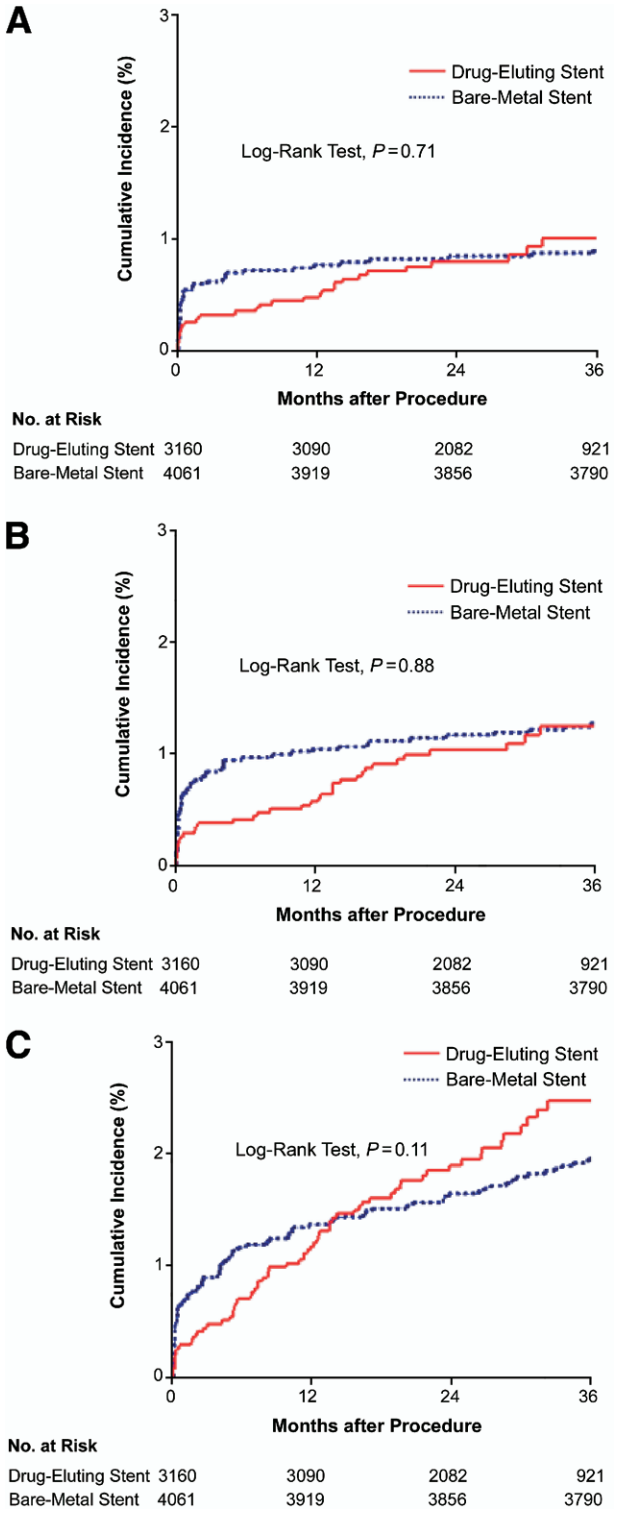


Figure 1. Kaplan-Meier Curves of Cumulative Incidence of Stent Thrombosis

Kaplan-Meier curves showing the cumulative incidence of stent thrombosis over 3 years according to Academic Research Consortium (ARC) definitions: **(A)** definite; **(B)** definite or probable; **(C)** any ARC criteria.

consistently higher in patients receiving DES compared to patients receiving BMS.

Death, MI, and revascularization. During the 3 years of follow-up, 351 patients died (111 in the DES group and 240 in the BMS group) and 123 had MI (41 in the DES group and 82 in the BMS group). Table 3 and Figure 2 summarize clinical events according to stent type. In a crude and multivariable adjusted analysis, mortality rate was significantly lower in the DES group than in the BMS group. The adjusted risks of death/MI and cardiac death/MI were also significantly lower in the DES group.

In the landmark analysis after 1 year, the rates of all-cause and noncardiac mortality were consistently lower in the DES group than in the BMS group, whereas there was no difference in risk of cardiac death. The adjusted risk of death/MI in the DES group was lower after 1 year, whereas the risk of cardiac death/MI after 1 year did not significantly differ between the 2 groups.

During the 3 years of follow-up, target lesion revascularization was performed in 208 patients receiving DES and in 578 receiving BMS (8.1% vs. 15.0%, $p < 0.001$). In the propensity score adjusted Cox regression analysis, the adjusted risk of target lesion revascularization was significantly lower in the DES group (HR: 0.32, 95% CI: 0.24 to 0.43; $p < 0.001$).

Long-term use of clopidogrel and outcomes after DES implantation. Among patients receiving DES, the mean duration of clopidogrel use was 11.8 ± 8.0 months. Among 2,873 eligible patients who received DES and survived the first 12 months without nonfatal MI and revascularization, detailed information about clopidogrel treatment was available for 2,851 patients (99.2%). Baseline and procedural characteristics according to continuation of clopidogrel at the time of last follow-up are summarized in Table 4. More patients continuing clopidogrel were older and had diabetes, a history of angioplasty or bypass surgery, renal failure, and multivessel disease, and presented with an acute coronary syndrome. Also, procedural characteristics were more complex for patients taking clopidogrel than for patients not taking clopidogrel at last follow-up.

Among 467 patients taking clopidogrel at last follow-up beyond 1 year, ST occurred in 3 patients (0.6%; definite: 2 [0.4%] and definite or probable: 2 [0.4%]). In 2,384 patients not taking clopidogrel, ST occurred in 28 patients (1.2%; definite: 10 [0.4%] and definite or probable: 14 [0.6%]). The median interval from clopidogrel discontinuation to the occurrence of ST was 12.7 months (interquartile range 6.9 to 21.8 months).

Table 5 summarizes ST and clinical events based on continuing clopidogrel at last follow-up. In a crude analysis and multivariable analysis after adjusting confounders and propensity, there was no significant association between clopidogrel continuation and outcomes. Figure 3 represents the association between the timing of clopidogrel discon-

Table 3. Unadjusted and Adjusted Hazard Ratios of Clinical Outcomes for Use of DES Compared With BMS in the Entire Study Population

Outcome	Outcome Rates (%)*		Crude		Multivariable Adjusted†		Adjusted for Propensity	
	DES	BMS	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Death (all causes)								
Overall at 3 yrs	4.2	5.9	0.68 (0.54–0.84)	0.001	0.57 (0.43–0.75)	<0.001	0.60 (0.46–0.79)	<0.001
≤1 yr after PCI	1.8	2.9	0.62 (0.45–0.85)	0.003	0.51 (0.32–0.80)	0.003	0.53 (0.34–0.82)	0.005
>1–3 yrs after PCI	2.4	3.1	0.74 (0.54–1.00)	0.05	0.64 (0.45–0.92)	0.02	0.65 (0.46–0.93)	0.02
Cardiac death								
Overall at 3 yrs	2.1	2.5	0.83 (0.60–1.14)	0.24	0.66 (0.42–1.03)	0.07	0.66 (0.42–1.02)	0.06
≤1 yr after PCI	1.1	1.7	0.68 (0.45–1.01)	0.06	0.65 (0.36–1.19)	0.16	0.63 (0.35–1.16)	0.14
>1–3 yrs after PCI	0.9	0.9	1.18 (0.70–1.98)	0.54	0.74 (0.38–1.43)	0.37	0.74 (0.39–1.40)	0.35
Noncardiac death								
Overall at 3 yrs	2.1	3.4	0.59 (0.43–0.80)	0.001	0.50 (0.35–0.73)	<0.001	0.55 (0.38–0.79)	0.001
≤1 yr after PCI	0.6	1.2	0.54 (0.32–0.92)	0.02	0.37 (0.18–0.76)	0.006	0.42 (0.21–0.82)	0.01
>1–3 yrs after PCI	1.5	2.2	0.61 (0.42–0.90)	0.01	0.59 (0.38–0.92)	0.02	0.60 (0.39–0.93)	0.02
MI								
Overall at 3 yrs	1.5	2.1	0.76 (0.52–1.09)	0.13	0.66 (0.41–1.05)	0.08	0.66 (0.42–1.05)	0.08
≤1 yr after PCI	0.7	1.4	0.51 (0.31–0.84)	0.008	0.56 (0.29–1.05)	0.07	0.54 (0.29–1.02)	0.06
>1–3 yrs after PCI	0.8	0.7	1.33 (0.77–2.31)	0.31	0.92 (0.46–1.86)	0.82	0.98 (0.49–1.93)	0.94
Death or MI								
Overall at 3 yrs	5.3	7.3	0.71 (0.58–0.86)	<0.001	0.62 (0.48–0.79)	<0.001	0.63 (0.49–0.81)	<0.001
≤1 yr after PCI	2.4	3.8	0.61 (0.47–0.81)	<0.001	0.55 (0.37–0.80)	0.002	0.54 (0.37–0.79)	0.001
>1–3 yrs after PCI	3.0	3.6	0.82 (0.62–1.08)	0.15	0.71 (0.51–0.98)	0.047	0.72 (0.52–0.99)	0.046
Cardiac death or MI								
Overall at 3 yrs	3.3	4.0	0.83 (0.64–1.07)	0.14	0.72 (0.51–1.00)	0.05	0.70 (0.50–0.97)	0.04
≤1 yr after PCI	1.7	2.7	0.65 (0.47–0.90)	0.009	0.65 (0.41–1.03)	0.07	0.61 (0.39–0.97)	0.04
>1–3 yrs after PCI	1.6	1.4	1.25 (0.83–1.87)	0.28	0.89 (0.54–1.49)	0.67	0.89 (0.54–1.46)	0.64

*Outcome rates were derived from Kaplan-Meier curves. †Adjusted for all variables listed in Table 1.
MI = myocardial infarction; other abbreviations as in Tables 1 and 2.

tinuation and the risk of ST among the overall population. Although the prevalence of ST was higher among patients not taking clopidogrel before 1 year, the incidence of ST was similar after 1 year.

Discussion

In this study, we found that the overall rates of ST were not significantly different for patients receiving DES versus BMS. However, DES was associated with a small but significant increase of very late ST. In addition, DES was associated with lower rates of death, death or MI, and repeat revascularization. Continuing clopidogrel beyond 1 year did not seem to be associated with reduced risks of subsequent ST and clinical events after DES implantation.

Pooled analyses of clinical trials showed no evidence for an increase in mortality or MI, and inconsistent evidence for an increased risk of late thrombosis with DES compared with BMS (21–24). A large observational study from Sweden, however, found evidence for an increased risk of death, or the composite of death or MI associated with DES after 6 months (25). In the present study, the 3-year rate of ST was similar in the DES and BMS groups, but there were significant increases in very late ST associated with DES, still raising concerns about the long-term safety.

Recent studies have used all-cause mortality as a surrogate clinical marker for late ST with DES (25,26). However, noncardiac mortality accounted for more than 50% of all-cause mortality in other studies (27,28) and in our results. Also, death from ST in these studies accounted for about 10% of all-cause mortality (22). Therefore, to represent the biological and clinical relevance of infrequent thrombosis, these clinical outcomes may need to be sufficiently defined and classified (29). In contrast to a recent study reporting an increased rate of noncardiac mortality with DES relative to BMS (28), we found that noncardiac mortality was significantly lower among patients with DES. When assessing the specific cause of noncardiac mortality, we found that the risk of noncardiac death due to ischemic vascular causes (ischemic stroke or other arterial embolism) was lower for patients receiving DES than for those receiving BMS (HR: 0.33, 95% CI: 0.11 to 0.98; p = 0.04). This

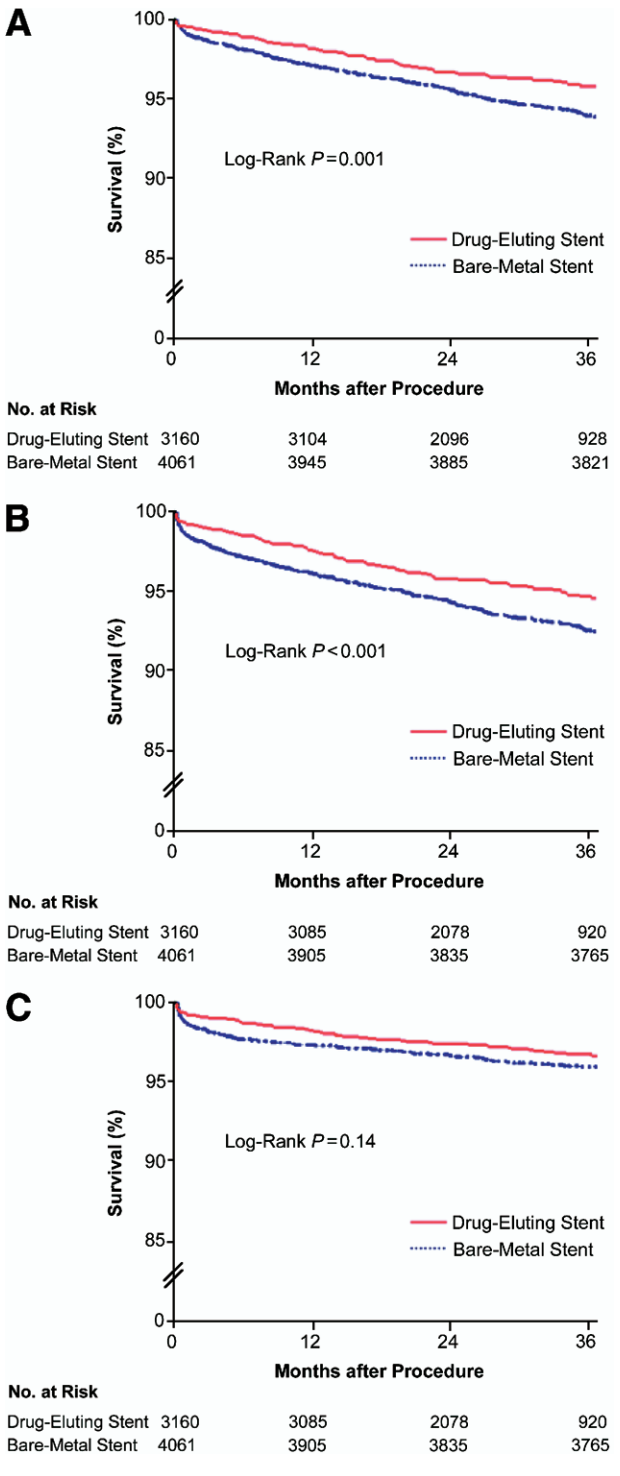


Figure 2. Kaplan-Meier Survival Curves

Kaplan-Meier survival curves of **(A)** all-cause mortality, **(B)** death or myocardial infarction, and **(C)** cardiac death or myocardial infarction.

finding may have been due, at least in part, to the extended duration of clopidogrel treatment with DES. Also, the unchecked paradigm shifts in general health care for individual patients over time might have been related to the difference in noncardiac mortality.

In contrast to previous studies (25,28), our study showed that the adjusted risk of death and death/MI were significantly lower in the DES group compared to the BMS group. These findings are consistent with recent results of large registries (30,31). Given that the risk of ST was similar up to 1 year, significant decreases of in-stent restenosis, which could present as acute MI (32,33), and repeat revascularization, which could lead to subsequent thrombosis and cardiac mortality (24), with DES may contribute to the reduced risk of death or MI. Also, the rapid changes within cardioprotective drugs such as statin and increased or extended use of clopidogrel could be responsible for these differences.

In our study, the cumulative incidence of ST or mortality was relatively lower than it was in recent reports from large registries (25,34). These discrepancies may be partially explained by differences in patient populations, lesion characteristics, interventional practice, and ethnic groups.

Recent study suggested that the prolonged use of clopidogrel was significantly associated with a reduced risk for death or MI in patients treated with DES (26). In contrast, our study showed that continuing clopidogrel beyond 1 year was not associated with decreased risks of ST and clinical events. These findings are similar to those of other investigators, who have suggested that discontinuation of clopidogrel beyond 6 months after DES implantation was not related to subsequent risk of ST (35). The lack of randomization regarding discontinuation of thienopyridine therapy at a certain time point and the low number of events that occurred more than 12 months after the procedure may weaken the power to make a firm statement about the safety of thienopyridine discontinuation during long-term follow-up. Nonsignificant trends toward lower event rates (any ARC criteria) were seen among patients continuing clopidogrel after 12 months; these trends might have been significant with a larger cohort of patients. However, the time interval (median 12.7 months) between clopidogrel discontinuation and thrombosis might be too long to speculate on the cause and effect of discontinuation on very late thrombosis. Therefore, considering the risk-benefit ratio of long-term use of clopidogrel, our findings warrant further investigation and should be confirmed or refuted through large, randomized clinical trials with long-term follow-up.

Study limitations. Although we used an unselected control group to reduce potential selection bias, there are inherent limitations about using the historical control. Because of changes over time in risks and concomitant medical treatment, there may be a risk of bias due to systematic

Table 4. Baseline Characteristics of Patients Continuing and Not Continuing Clopidogrel at Time of Last Follow-Up After 12 Months

Variable	Continuing Clopidogrel (n = 467)	Not Continuing Clopidogrel (n = 2,384)	p Value
Age (yrs)	61.6 ± 10.3	60.4 ± 10.3	0.02
Male	343 (73.4)	1,671 (70.1)	0.15
Diabetes mellitus	143 (30.6)	618 (25.9)	0.04
Hypertension	256 (54.8)	1,196 (50.2)	0.07
Current smoker	118 (25.3)	715 (30.0)	0.04
Hypercholesterolemia	92 (19.7)	579 (24.3)	0.03
Previous myocardial infarction	48 (10.3)	204 (8.6)	0.23
Previous coronary angioplasty	96 (20.6)	383 (16.1)	0.02
Previous coronary artery bypass graft	25 (5.4)	52 (2.2)	<0.001
Renal failure	20 (4.3)	45 (1.9)	0.002
Acute coronary syndrome	263 (56.3)	1,208 (50.7)	0.03
Multivessel disease	295 (63.2)	1,350 (56.6)	0.01
Left ventricular ejection fraction (%)	58.3 ± 8.6	58.7 ± 8.8	0.49
Duration of clopidogrel use (months)	22.4 ± 7.9	9.1 ± 5.0	<0.001
Lesion characteristics			
Left anterior descending artery	232 (49.7)	1,349 (56.6)	0.01
Left main coronary artery	47 (10.1)	187 (7.8)	0.11
ACC/AHA type B2 or C lesion	359 (76.9)	1,876 (78.7)	0.38
Bifurcation lesion	93 (19.9)	461 (19.3)	0.77
Restenotic lesion	32 (6.9)	165 (6.9)	0.96
Ostial lesion	64 (13.7)	236 (9.9)	0.01
Chronic total occlusion	28 (6.0)	161 (6.8)	0.55
Procedural characteristics			
Direct stenting without pre-dilation	53 (11.3)	291 (12.2)	0.60
Intervention with intravascular ultrasound guidance	305 (65.3)	1,670 (70.1)	0.04
Number of stents per patient	2.0 ± 1.2	1.9 ± 1.1	0.01
Total stent length per patient (mm)	51.8 ± 32.1	46.9 ± 30.3	0.002
Average stent diameter per patient (mm)	3.2 ± 0.5	3.2 ± 0.7	0.49
Glycoprotein IIb/IIIa inhibitors	30 (6.4)	40 (1.7)	<0.001

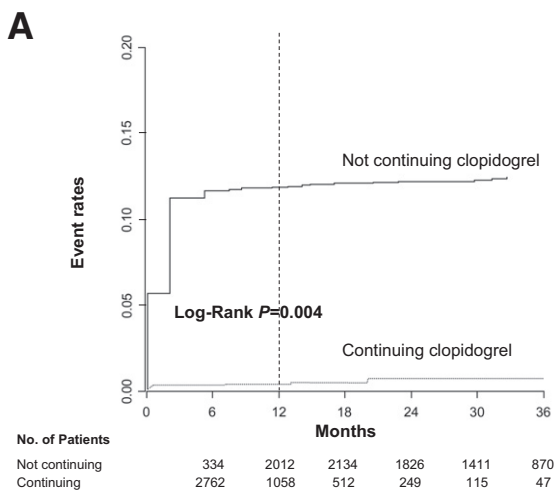
Data are mean ± SD or n (%).
Abbreviations as in Table 1.

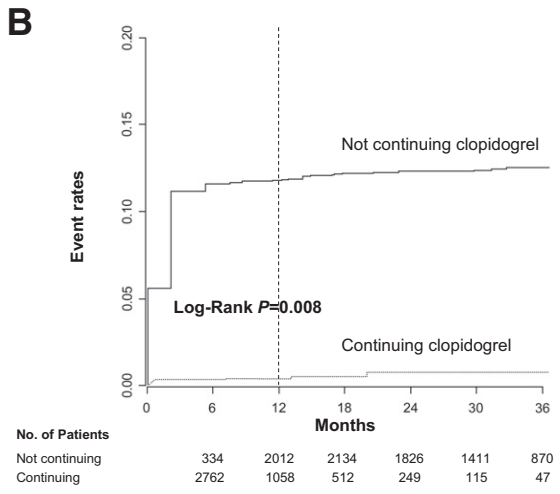
Table 5. Unadjusted and Adjusted Hazard Ratios of Stent Thrombosis and Clinical Events Among Patients Continuing and Not Continuing Clopidogrel at Time of Last Follow-Up After 12 Months

	Crude		Multivariable Adjusted*		Adjusted for Propensity	
Outcome	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Stent thrombosis						
Definite	0.86 (0.11–6.86)	0.89	1.41 (0.17–11.97)	0.75	1.38 (0.17–11.21)	0.77
Definite or probable	0.62 (0.15–2.65)	0.56	0.52 (0.06–4.23)	0.54	0.54 (0.07–4.23)	0.55
Any ARC criteria	0.55 (0.07–4.22)	0.52	0.45 (0.10–1.97)	0.29	0.45 (0.10–1.97)	0.29
Clinical events						
Death	1.62 (0.75–3.47)	0.22	1.23 (0.56–2.70)	0.61	1.20 (0.55–2.66)	0.65
MI	0.52 (0.07–3.98)	0.53	0.55 (0.07–4.34)	0.57	0.53 (0.07–4.11)	0.54
Death or MI	1.40 (0.68–2.85)	0.36	1.16 (0.56–2.42)	0.69	1.16 (0.56–2.42)	0.69
Cardiac death or MI	0.55 (0.13–2.30)	0.41	0.41 (0.10–1.79)	0.24	0.41 (0.10–1.79)	0.24

*Adjusted for all variables listed in Table 4.
Abbreviations as in Tables 2 and 3.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 1, NO. 5, 2008
OCTOBER 2008:494–503





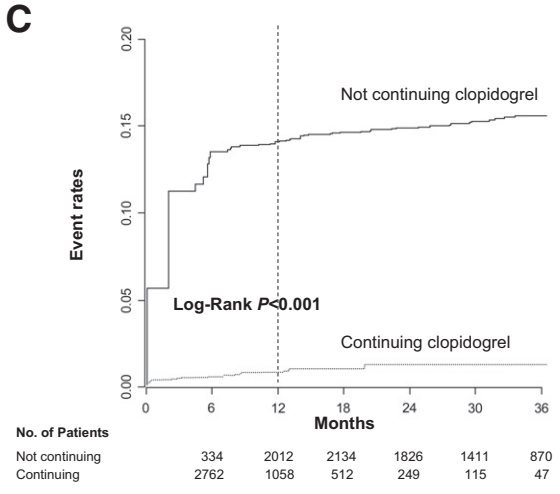


Figure 3. Aalen-Nelson Estimate Curves of Cumulative Hazard Function for Stent Thrombosis

Aalen-Nelson estimate curves of cumulative hazard function for stent thrombosis in patients who continued and in patients who discontinued clopidogrel during follow-up: **(A)** definite; **(B)** definite or probable; **(C)** any Academic Research Consortium criteria.

differences between the groups. To reduce any baseline differences or confounding factors, we performed propensity analysis to more rigorously adjust for these biases. Nonetheless, observational studies may fail to identify all confounders, and propensity analyses cannot account for selection bias related to unmeasured characteristics (36).

Conclusions

Our study suggests that, compared with BMS, DES was associated with a similar risk of overall ST, but increased rates of very late ST. Patients with DES had significantly better risk-adjusted clinical outcomes for death, death or MI, and target lesion revascularization. An obvious relationship between late-occurring (>1 year) events and clopidogrel continuation beyond 1 year was not found. Further studies are required to determine the long-term safety of DES and the impact on late ST of the extended use of clopidogrel.

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.

REFERENCES

1. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.
2. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221–31.
3. Babapulle MN, Joseph L, Belisle P, Brophy JM, Eisenberg MJ. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. Lancet 2004;364:583–91.
4. Lemos PA, Serruys PW, van Domburg RT, et al. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. Circulation 2004;109:190–5.
5. Cosgrave J, Agostoni P, Ge L, et al. Clinical outcome following aleatory implantation of paclitaxel-eluting or sirolimus-eluting stents in complex coronary lesions. Am J Cardiol 2005;96:1663–8.
6. Rao SV, Shaw RE, Brindis RG, et al. Patterns and outcomes of drug-eluting coronary stent use in clinical practice. Am Heart J 2006;152:321–6.
7. Shuchman M. Trading restenosis for thrombosis? New questions about drug-eluting stents. N Engl J Med 2006;355:1949–52.
8. Wijns WC, Krucoff MW. Increased mortality after implantation of first generation drug-eluting stents: seeing the smoke, where is the fire? Eur Heart J 2006;27:2737–9.
9. Bavry AA, Kumbhani DJ, Helton TJ, Borek PP, Mood GR, Bhatt DL. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. Am J Med 2006;119:1056–61.
10. Bavry AA, Kumbhani DJ, Helton TJ, Bhatt DL. Risk of thrombosis with the use of sirolimus-eluting stents for percutaneous coronary intervention (from registry and clinical trial data). Am J Cardiol 2005;95:1469–72.
11. Moreno R, Fernandez C, Hernandez R, et al. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. J Am Coll Cardiol 2005;45:954–9.

12. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126–30.
13. Park DW, Park SW, Park KH, et al. Frequency of and risk factors for stent thrombosis after drug-eluting stent implantation during long-term follow-up. Am J Cardiol 2006;98:352–6.
14. Laskey WK, Yancy CW, Maisel WH. Thrombosis in coronary drug-eluting stents: report from the meeting of the Circulatory System Medical Devices Advisory Panel of the Food and Drug Administration Center for Devices and Radiologic Health, December 7–8, 2006. Circulation 2007;115:2352–7.
15. Mehilli J, Kastrati A, Dirschinger J, Bollwein H, Neumann FJ, Schomig A. Differences in prognostic factors and outcomes between women and men undergoing coronary artery stenting. JAMA 2000; 284:1799–805.
16. Cain KC, Lange NT. Approximate case influence for the proportional hazards regression model with censored data. Biometrics 1984;40: 493–9.
17. Rubin DB. Estimating causal effects from large data sets using propensity scores. Ann Intern Med 1997;127:757–63.
18. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998;17:2265–81.
19. Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response. J Clin Oncol 1983;1:710–9.
20. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70:41–55.
21. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:989–97.
22. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. N Engl J Med 2007;356:998–1008.
23. Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007; 356:1030–9.
24. 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;356:1020–9.
25. 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;356:1009–19.
26. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. JAMA 2007;297:159–68.
27. Holmes DR Jr., Moses JW, Schofer J, Morice MC, Schampaert E, Leon MB. Cause of death with bare metal and sirolimus-eluting stents. Eur Heart J 2006;27:2815–22.
28. Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: a meta-analysis. Eur Heart J 2006;27:2784–814.
29. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
30. Tu JV, Bowen J, Chiu M, et al. Effectiveness and safety of drug-eluting stents in Ontario. N Engl J Med 2007;357:1393–402.
31. Hannan EL, Racz M, Holmes DR, et al. Comparison of coronary artery stenting outcomes in the eras before and after the introduction of drug-eluting stents. Circulation 2008;117:2071–8.
32. 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;151:1260–4.
33. Walters DL, Harding SA, Walsh CR, Wong P, Pomerantsev E, Jang IK. Acute coronary syndrome is a common clinical presentation of in-stent restenosis. Am J Cardiol 2002;89:491–4.
34. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667–78.
35. Airoldi F, Colombo A, Morici N, et al. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. Circulation 2007;116:745–54.
36. Rosenbaum PR. Discussing hidden bias in observational studies. Ann Intern Med 1991;115:901–5.

Key Words: coronary disease ■ stents ■ thrombosis.