Impact of Bleeding on Subsequent Early and Late Mortality After Drug-Eluting Stent Implantation

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Objectives The aim of this study was to assess the impact of early and late bleeding on subsequent mortality after drug-eluting stent (DES) implantation.

Background Little is known about the impact of late bleeding after DES implantation.

Methods With a time-updated Cox model, the impact of bleeding and myocardial infarction (MI) on 3-year mortality was analyzed in 3,148 consecutive patients who underwent DES implantation for coronary disease.

Results Bleeding, defined according to STEEPLE (Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation) minor or major criteria, occurred in 6.5% of patients over 3 years. Patients with bleeding were older; were more likely to be female; had higher rates of diabetes mellitus, hypertension, and extensive coronary disease and lower ventricular function; and underwent more complex procedures than those without bleeding. The 3-year adjusted hazard ratios (HRs) for mortality were 5.81 (95% confidence interval [CI]: 3.92 to 8.60; $p < 0.001$) for patients with bleeding and 2.53 (95% CI: 1.62 to 3.96; $p < 0.001$) for patients with MI. When the timings of events were separated, the HRs for mortality were 4.89 (95% CI: 3.08 to 7.78; $p < 0.001$) and 7.81 (95% CI: 4.39 to 13.89; $p < 0.001$) for patients with bleeding within and after 30 days, respectively. By contrast, the HRs for mortality were 1.85 (95% CI: 1.09 to 3.14, $p = 0.022$) and 10.33 (95% CI: 4.91 to 21.75, $p < 0.001$) for patients with MI within and after 30 days, respectively.

Conclusions Bleeding is closely associated with mortality during both the early and late periods after DES implantation. Therefore, in addition to carefully assessing bleeding after stenting, evidence-based treatment should be implemented to offer the best balance of benefit and harm. (J Am Coll Cardiol Intv 2011;4:423–31) © 2011 by the American College of Cardiology Foundation

Advancements in pharmaceutical agents have improved the outcomes of patients undergoing percutaneous coronary intervention (PCI) for coronary artery disease. In particular, drug-eluting stents (DES) have reduced rates of restenosis and the subsequent need for repeat revascularization compared with bare-metal stents. However, long-term dual antiplatelet therapy with aspirin and clopidogrel is required to prevent the late occurrence of stent thrombosis, although it increases the risks of bleeding (1). The incidence of bleeding complications is higher in patients treated with clopidogrel plus aspirin than in those treated with aspirin alone (2). Bleeding, in turn, has been associated with an increased risk of mortality (3–7). Most studies of bleeding complications and mortality, however, have focused on the effects of early bleeding related directly to the procedure in patients with acute coronary syndrome (ACS), with few studies assessing the association between bleeding complications and late mortality. Therefore, we assessed the impact of bleeding on early and late mortality in patients undergoing DES implantation in daily practice. Furthermore, the relative risks of mortality among patients with bleeding were compared with those among patients with myocardial infarction (MI) during each period.

Abbreviations and Acronyms

ACS = acute coronary syndrome

CI = confidence interval

DES = drug-eluting stent(s)

HR = hazard ratio

MI = myocardial infarction

PCI = percutaneous coronary intervention

Methods

Population. The study population consisted of all patients who received at least 1 DES for coronary artery stenosis between February 2003 and February 2006 at 2 centers in Korea (8). Patients who underwent coronary brachytherapy were excluded. The institutional review board of each hospital approved the study, and informed consent was obtained from all patients. The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Procedure and data collection. Stenting procedures were performed according to general guidelines (9). Because our protocol did not specify the method of stenting, the use of intravascular ultrasound or any other adjunctive coronary device was at the discretion of the operator. During the study period, DES was the default stent in both institutions for patients with coronary artery stenosis, but the choice of DES was at the discretion of each operator. Each patient was administered a loading dose of 200 mg aspirin and 300 mg clopidogrel before the procedure. During the procedure, a single bolus (100 U/kg) and subsequent boosters (2,000 U) of heparin were injected to achieve an activated clotting time >250 s. Administration of glycoprotein IIb/IIIa inhibitor before or during the procedure was at the discretion of the physician. After DES implantation, standard dual antiplatelet therapy, consisting of 100 mg/day aspirin and 75 mg/day clopidogrel, was recommended for at least 6 months, with a longer period of clopidogrel use recommended for patients at high risk of ischemic complications. Patients at high risk of ischemic events were also administrated cilostazol 200 mg/day for 1 month after stenting at the discretion of the physician (10).

Baseline and procedural information was collected into a dedicated database by independent research nurses. All patients were followed-up by office visit or telephone contact at 1 month and 6 and 12 months after the procedure and every 6 months thereafter. To validate complete follow-up data, information about vital records was obtained from the National Registration System of the Ministry of Government Administration and Home Affairs in Korea with a personal identification number. In addition, data regarding repeat hospital stay for follow-up MI were obtained from the Hospital Disease Code Registration system.

Endpoints and definitions. The primary end point was the occurrence of any-cause mortality. Myocardial infarction was diagnosed by the presence of ischemic symptoms or signs plus cardiac enzyme elevation (creatine kinase-muscle brain elevation >3× or creatine kinase elevation >2× the upper limit of normal). Among all MIs, small MI was defined as elevation of creatine kinase-muscle brain elevation ≤8× the upper limit of normal. Major and minor bleeding were defined as described in STEEPLE (Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation) (11). Major bleeding was defined as fatal bleeding; retroperitoneal, intracranial, or intraocular bleeding; bleeding that caused hemodynamic compromise requiring specific treatment; bleeding that required intervention (surgical or endoscopic) or decompression of a closed space to stop or control the event; clinically overt bleeding; requirement for any transfusion of ≥1 U packed red cells or whole blood; and clinically overt bleeding causing a decrease in hemoglobin of ≥3 g/dl (or if hemoglobin level not available, a ≥10% decrease in hematocrit). Minor bleeding was defined as bleeding that did not meet any of the criteria of major bleeding and that met at least 1 of the following criteria: gross hematuria not associated with trauma; epistaxis that was prolonged, repeated, or required plugging or intervention; gastrointestinal hemorrhage; hemoptysis; subconjunctival hemorrhage; hematoma >5 cm or leading to prolonged or new hospital stay; clinically overt bleeding causing a decrease in hemoglobin of 2 to 3 g/dl; and uncontrolled bleeding requiring protamine sulfate administration. The cause and time of events were independently adjudicated on the basis of the source documents. When the cause of bleeding was not certain, the date of bleeding was declared when the clinically overt bleeding was identified or blood component was transfused.

Statistical analysis. Patient baseline characteristics and procedural findings were presented by mean ± SD and number

(percentage). All patients were censored at the time of an event or at a fixed interval of 3 years. Time-to-event was assessed by the Kaplan-Meier incidence curves, which were compared with the log-rank test. Differences in baseline clinical, angiographic, and procedural characteristics between groups of patients with and without bleeding were compared with the univariate Cox proportional hazard models. To separately evaluate the impact of early and late

Table 1. Baseline and Procedural Characteristics of Patients With and Without Bleeding 3 Years Post-Procedure

	Bleeding (n = 207)	No Bleeding (n = 2,941)	HR (95% CI)	p Value*
Clinical features				
Age, yrs	63.9 ± 9.9	60.3 ± 10.3	1.03 (1.02–1.05)	<0.001
Male	131 (63.3)	2,091 (71.1)	0.71 (0.54–0.95)	0.02
Hypertension	129 (62.3)	1,463 (49.7)	1.64 (1.24–2.17)	<0.001
Smoking	48 (23.2)	868 (29.5)	0.73 (0.53–1.01)	0.058
Hypercholesterolemia	42 (20.3)	714 (24.3)	0.81 (0.58–1.14)	0.23
Diabetes mellitus	76 (36.7)	786 (26.7)	1.54 (1.16–2.04)	0.003
Chronic renal failure	18 (8.7)	62 (2.1)	4.06 (2.50–6.59)	<0.001
Prior PCI	19 (9.2)	521 (17.7)	0.48 (0.30–0.77)	0.002
Prior CABG	8 (3.9)	76 (2.6)	1.46 (0.72–2.96)	0.29
Acute MI	44 (21.3)	391 (13.3)	1.77 (1.27–2.47)	<0.001
Stable angina	99 (47.8)	1,420 (48.3)		
Unstable angina	64 (30.9)	1,130 (38.4)		
LV ejection fraction, %	56.1 ± 10.3	58.6 ± 8.7	0.97 (0.96–0.99)	<0.001
Baseline hemoglobin, g/dl	12.4 ± 2.1	13.4 ± 1.7	0.77 (0.71–0.82)	<0.001
Baseline platelet, 10^3/mm^3	226.6 ± 91.4	229.0 ± 63.0	0.999 (0.997–1.002)	0.54
Angiographic features				
Multivessel disease	141 (68.1)	1,717 (58.4)	1.51 (1.12–2.02)	0.006
2 vessels	62 (30.0)	948 (32.2)		
3 vessels	76 (36.7)	709 (24.1)		
Left main involvement	3 (1.4)	60 (2.0)	0.72 (0.47–1.12)	0.15
ACC/AHA type B2/C	168 (81.2)	2,319 (78.9)	1.15 (0.81–1.62)	0.45
Bifurcation lesion	40 (19.3)	575 (19.6)	0.98 (0.70–1.39)	0.20
Restenotic lesion	7 (3.4)	216 (7.3)	0.45 (0.21–0.95)	0.037
Chronic total occlusion	7 (3.4)	206 (7.0)	0.47 (0.22–1.00)	0.050
Procedures				
Use of IVUS	115 (55.6)	2,047 (69.6)	0.56 (0.42–0.73)	<0.001
Multiple DES	120 (58.0)	1,548 (52.6)	1.14 (0.93–1.62)	0.14
Number of DES	2.2 ± 1.4	1.9 ± 1.1		
Total length of DES, mm	54.8 ± 37.1	47.6 ± 30.5	1.01 (1.00–1.01)	0.001
Multivessel PCI	85 (41.1)	966 (32.8)	1.41 (1.07–1.86)	0.015
Glycoprotein IIb/IIIa inhibitor	16 (7.7)	77 (2.6)	3.13 (1.88–5.21)	<0.001
Medication at discharge				
Warfarin	7 (3.4)	22 (0.7)	4.02 (1.89–8.54)	<0.001
Statin	95 (45.9)	1,597 (54.3)	0.72 (0.55–0.95)	0.018
Beta blocker	138 (66.7)	2,219 (75.5)	0.66 (0.49–0.88)	0.004
Calcium channel blocker	140 (67.6)	2,237 (76.1)	0.66 (0.49–0.88)	0.005
ACE inhibitor	61 (29.5)	847 (28.8)	1.03 (0.76–1.38)	0.87
Cilostazol	69 (33.3)	800 (27.2)	1.33 (0.99–1.77)	0.056
Dual antiplatelet therapy†				
At 6 months	172 (83.1)	2,565 (87.2)	1.41 (0.98–2.03)	0.063
At 1 yr	66 (31.9)	1,008 (34.3)	1.12 (0.84–1.50)	0.45

Values are mean ± SD or n (%) unless otherwise indicated.

*The p values were drawn by univariate Cox models. †Dual antiplatelet therapy includes aspirin and clopidogrel.

ACC/AHA = American College of Cardiology/American Heart Association lesion classification; ACE = angiotensin converting enzyme; CABG = coronary artery bypass graft; CI = confidence interval; DES = drug-eluting stent(s); IVUS = intravascular ultrasound; LV = left ventricular; MI = myocardial infarction; PCI = percutaneous coronary intervention.

bleeding on mortality after the procedure, we compared event curves for patients with and without bleeding and for bleeding that occurred within or after 30 days of stent implantation. Multivariable Cox proportional hazard models were developed to identify the independent predictors of 3-year bleeding and MI with covariates having p values ≤0.1. The multivariable model considered 19 potential covariates: age, sex, hypertension, smoking history, diabetes mellitus, chronic renal failure, hypercholesterolemia, prior history of PCI or coronary artery bypass graft, left ventricular ejection fraction, acute myocardial infarction, multivessel disease, multivessel PCI, multiple DES, use of glycoprotein IIb/IIIa inhibitor, use of warfarin or statin at discharge, baseline hemoglobin, and platelet count. The proportional hazards assumption was confirmed by examination of log (-log [survival]) curves and by testing of partial (Schoenfeld) residuals, and no relevant violations were found.

Furthermore, to investigate the interactive impact of MI and bleeding on mortality, a time-updated Cox model was created with adjustment of the aforementioned covariates (12). To further estimate the time-dependent risk of major bleeding and MI on mortality rate, additional Cox models were developed with different time-updated binary covariates for discrete time intervals (i.e., 0 to 30 days and ≥31 days after the event) which

are clinical relevant point. All reported p values are 2-sided, and p values <0.05 were considered statistically significant. The SAS software (version 9.1, SAS Institute, Cary, North Carolina) was used for all statistical analyses.

Results

Baseline and procedural characteristics. Of the 3,160 patients who underwent DES implantation at the 2 institutions between February 2003 and February 2006 (8), information on bleeding complications was available for 3,148 patients. Table 1 shows their baseline and procedural characteristics. Compared with patients without bleeding, those with bleeding at 3 years were more likely to be female and of advanced age and to have hypertension, diabetes mellitus, chronic renal failure, MI at presentation, low ventricular ejection fraction, low hemoglobin, and extensive coronary artery disease. Therefore, patients with bleeding were more likely to be treated with multiple stents and glycoprotein IIb/IIIa inhibitors. Dual antiplatelet therapy with aspirin and clopidogrel was administered to 87% of patients at 6 months and 34% at 1 year and was similar between the 2 groups.

Unadjusted outcomes. Figure 1 shows the Kaplan-Meier
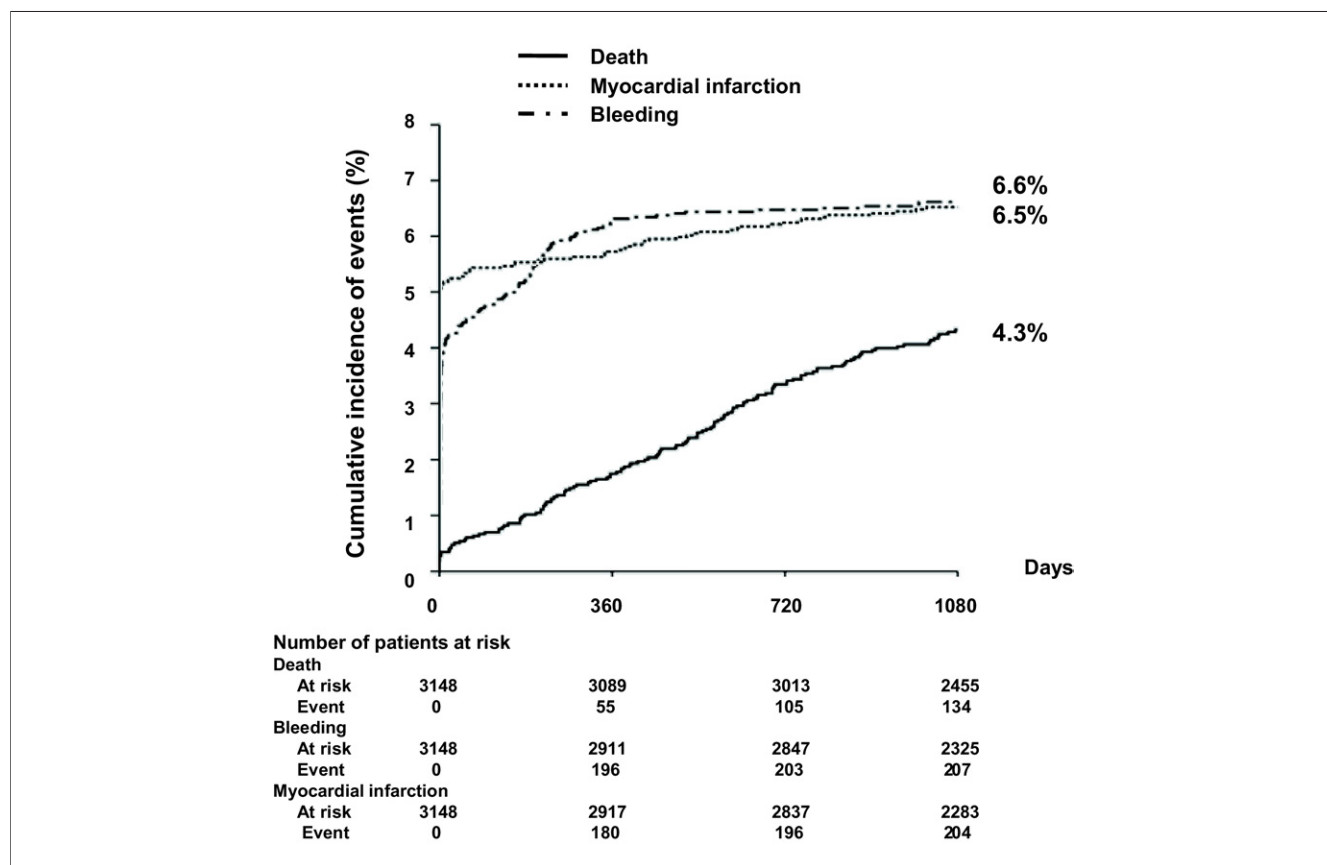
Figure 1. Incidence Curves of Events

Three-year Kaplan-Meier curves of adverse events in patients with and without bleeding events.
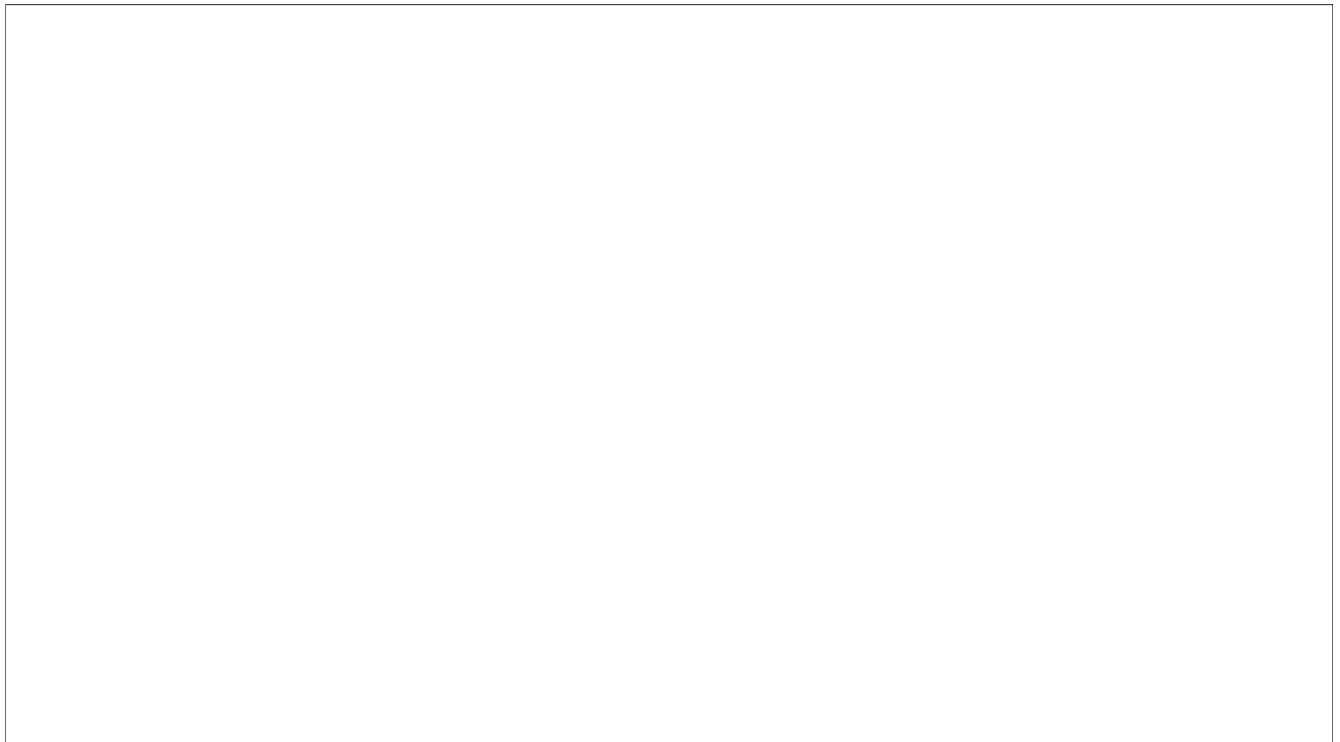
Figure 2. Incidence Curves of Events After 30 Days Post-Procedure

Three-year Kaplan-Meier curves of adverse events in patients with and without bleeding events occurring within and after 30 days post-procedure.
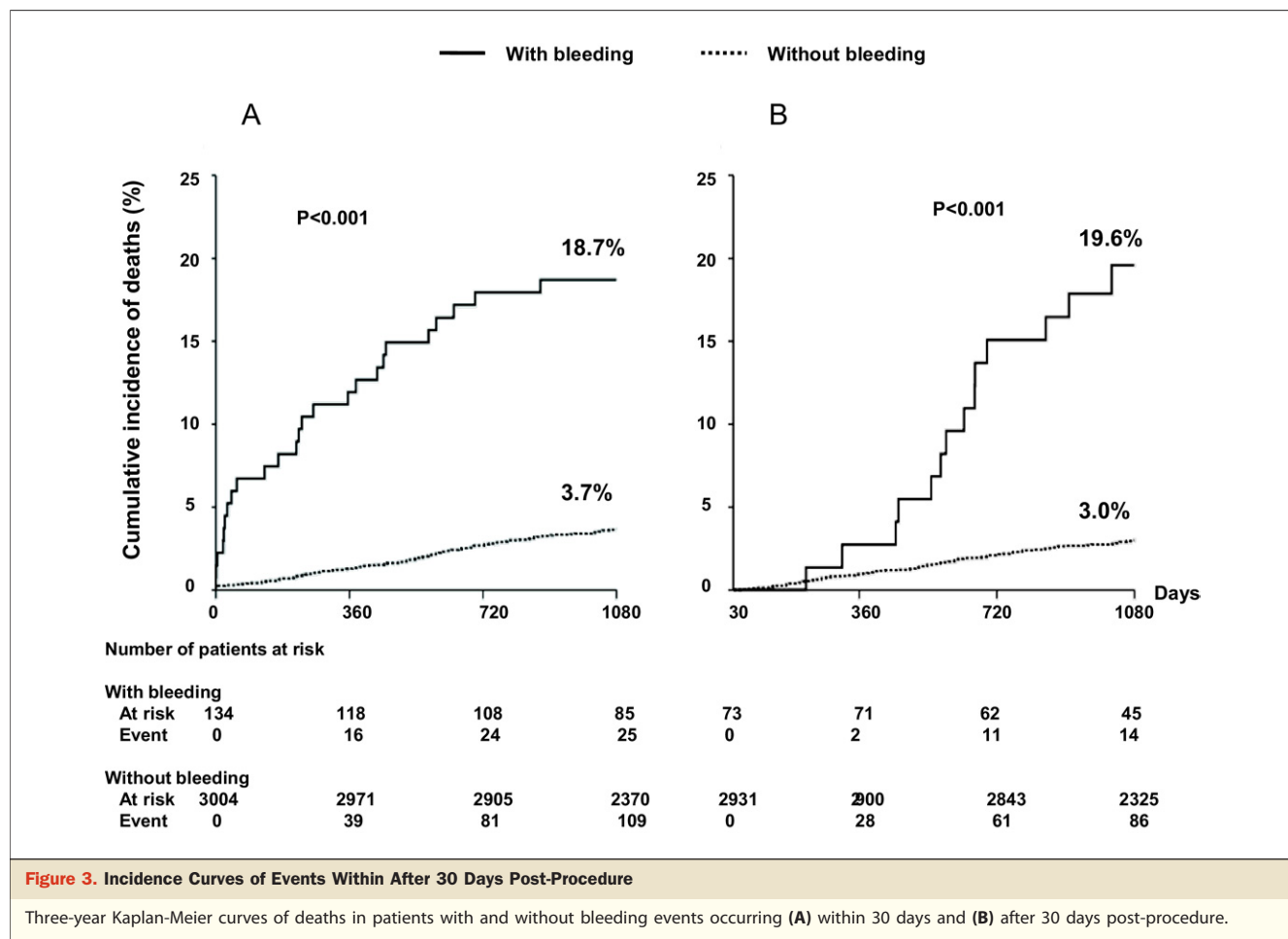
incidences of adverse outcomes for 3 years. Figure 2 shows the separate incidences of events within 30 days and 30 days after procedure. Although the occurrence of bleeding and MI were mostly clustered within 30 days after DES implantation, there were some incidences of bleeding after 30 days, mostly within 1 year. The incidence of mortality gradually increased over the 3-year study period. Figure 3 shows that the mortality rates were higher in patients with than without bleeding, both within 30 days and after 30 days post-procedure. Over 3 years, 134 patients died with cardiac (71 patients) and noncardiac (63 patients) causes. Bleeding by 3 years occurred in 207 patients comprising 123 major and 84 minor episodes. The causes of bleeding according to the STEEPLE criteria were listed in Table 2. After bleeding, 8 (3.9%) patients experienced MI (median of 127 days, interquartile range 6 to 496 days) and 31 (15.0%) patients died (median of 262 days, interquartile range 54 to 490 days). At the time of bleeding, 113 (54.6%) were receiving dual antiplatelets including aspirin plus clopidogrel, and 77 (37.2%) were receiving triple antithrombotics, including dual antiplatelets with either cilostazol in 51 or warfarin in 26. After bleeding episodes, 40 (19.3%) patients discontinued all antithrombotic medications. Myocardial infarction at 3 years occurred in 204 patients, including 97 (47.5%) patients having a small MI (CK-MB ≤8× the upper normal limit). Definite angiographic stent thrombosis occurred in 31 patients (median of 386 days, interquartile range 18 to 623 days).

Independent predictors of bleeding or MI. Table 3 shows the independent predictors of bleeding and MI. We found that advanced age, hypertension, chronic renal failure, the first PCI, low ejection fraction, anemia, acute MI at presentation, multivessel PCI, and use of glycoprotein IIb/III inhibitor or warfarin were independent predictors of bleeding.

Adjusted hazard ratios for mortality. Figure 4 shows the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality among patients with bleeding or MI. When the incidences of bleeding were separated according to the timing of events, the HRs for mortality were significantly higher in patients with than without bleeding, both within and after 30 days. These findings were similar in patients who had suffered an MI (Fig. 5). When bleeding events were separated, both major (HR: 11.10; 95% CI: 7.42 to 16.62; p < 0.001) and minor (HR: 2.10; 95% CI: 1.06 to 4.16; p = 0.033) bleedings were significantly associated with 3-year mortality after adjustment. The occurrence of small MI also increased the adjusted risk of 3-year mortality (HR: 2.32; 95% CI: 1.43 to 3.76; p = 0.001).

Discussion

Our results indicate that bleeding complications in patients undergoing DES implantation for coronary artery stenosis was associated with a 6-fold increased risk of death over 3 years. Although two-thirds of bleeding

Figure 3. Incidence Curves of Events Within After 30 Days Post-Procedure

Three-year Kaplan-Meier curves of deaths in patients with and without bleeding events occurring **(A)** within 30 days and **(B)** after 30 days post-procedure.

complications occurred within 30 days after the procedure, the remaining one-third occurred after 30 days, mostly within 1 year. The association between bleeding and subsequent death was consistently observed, both during the early and late periods after stenting, as indicated by the increased risks of mortality among patients with bleeding within and after 30 days.

Table 2. Causes of Bleeding Events According to the STEEPLE Definitions

Overall	207
Retroperitoneal bleeding	3 (1.4%)
Intracranial bleeding	2 (1.0%)
Bleeding in the closed space	3 (1.4%)
Genitourinary bleeding	4 (1.9%)
Prolonged epistaxis	2 (1.0%)
Gastrointestinal bleeding	28 (13.5%)
Hemoptysis	3 (1.4%)
Vascular access complication	52 (25.1%)
Bleeding related to repeat revascularization	5 (2.4%)
Bleeding related with noncardiac surgery	13 (6.3%)
Bleeding related with cancer	7 (3.4%)
Clinically overt bleeding causing hemoglobin drop or transfusion	85 (41.1%)

STEEPLE = Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation.

Table 3. Multivariate Predictors of 3-Year Bleeding and MI

	Bleeding			MI		
	HR	95% CI	p Value	HR	95% CI	p Value
Age, yrs	1.02	1.01–1.04	0.002	—	—	—
Hypertension	1.42	1.06–1.90	0.018	—	—	—
Previous PCI	0.52	0.32–0.84	0.007	—	—	—
Chronic renal failure	1.93	1.12–3.31	0.018	2.40	1.34–4.31	0.003
LV ejection fraction, %	0.98	0.97–0.996	0.011	—	—	—
Acute MI	1.56	1.09–2.23	0.016	—	—	—
Baseline hemoglobin, g/dl	0.84	0.77–0.90	<0.001	—	—	—
Multivessel PCI	1.35	1.02–1.79	0.034	—	—	—
Multivessel disease	—	—	—	1.82	1.29–2.56	<0.001
Glycoprotein IIb/IIIa inhibitor	3.30	1.97–5.51	<0.001	2.22	1.26–3.90	0.006
Warfarin	3.03	1.42–6.49	0.004	—	—	—
Multiple stents	—	—	—	1.88	1.36–2.60	<0.001

Abbreviations as in Table 1.
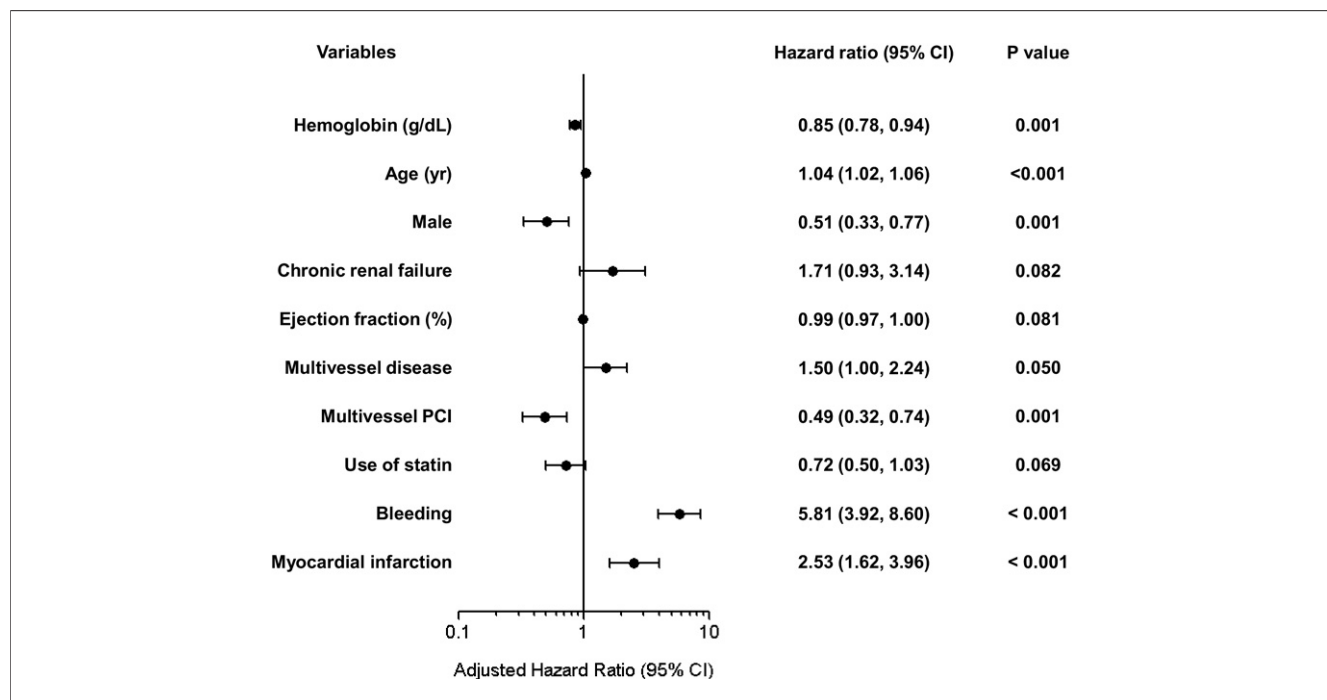
Figure 4. Adjusted Hazard Ratios With Covariates, Bleeding, and MI

Adjusted with covariates, bleeding, and myocardial infarction (MI) for 3-year mortality with the time-updated Cox model. CI = confidence interval; PCI = percutaneous coronary intervention.
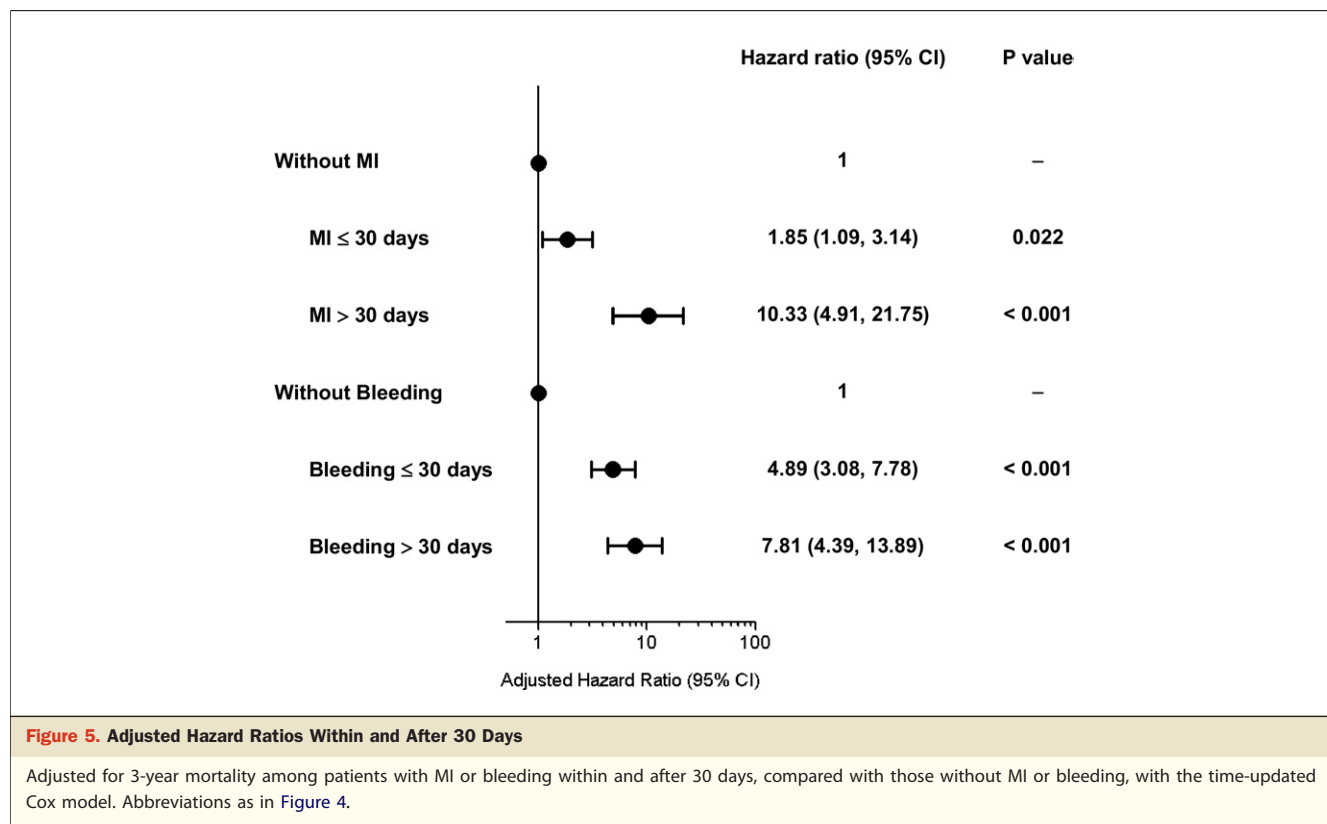
Several clinical trials have shown that bleeding complications increased the risk of mortality during treatment for acute coronary syndrome (3–7). A recent analysis of the ACUITY (Acute Catheterization and Urgent intervention Triage strategy) trial of patients with ACS showed that the occurrence of bleeding within 30 days post-procedure increased the 1-year mortality risk 3.5-fold, whereas the occurrence of MI within 30 days increased the 1-year mortality risk 3.1× (3). The GRACE registry (Global Registry of Acute Coronary Events) of ACS patients also reported that in-hospital bleeding complications increased mortality risk 1.9-fold (4). Nevertheless, the long-term clinical impact of time of bleeding has not been well-evaluated, and most previous studies limited enrollment to patients with ACS (3–7). Therefore, our study had the advantages of enrolling all patients treated with DES and its extended clinical follow-up.

We found that, over 3 years, bleeding complication occurred in approximately 7% of patients who underwent DES implantation for coronary artery stenosis. Because bleeding was closely related with procedural complication, two-thirds of bleeding episodes occurred within 30 days after the procedure. Mortality was less closely related with procedures, and 47% of the deaths during follow-up were noncardiac deaths. The rate of periprocedural bleeding at 30 days was lower than in studies enrolling patients with ACS but similar to studies of patients treated with PCI (3–7,13). The incidences of bleeding, in fact, were dependent on patient risk profiles, treatment strategies, assessment times, and definitions. Of the various definitions of bleeding, we adopted the STEEPLE criteria, because others—such as Thrombolysis in Myocardial Infarction and GUSTO (Global Use of Strategies to Open Coronary arteries) bleeding criteria (14,15)—primarily focused on severe and moderate bleeding during early stages of treatment (16). Bleeding criteria focusing on periprocedural events might underscore the importance of long-term bleeding, because the severity of bleeding in the late period after PCI seems to differ (17).

The increased risk of death among patients who developed bleeding remained evident after adjustment for baseline and procedural characteristics with time-updated Cox models, in agreement with previous studies showing an association between bleeding and subsequent death (3–7). Death after bleeding episodes might be due to hypotension, anemia, the adverse effects of blood product transfusion, ineffective oxygen delivery, vasoconstriction, platelet dysfunction, or—in some patients—the discontinuation and/or reversal of essential antithrombotic or antiplatelet therapy (18,19). By contrast, death after MI after PCI might be due to distal embolization, side branch occlusion, flow limiting dissection, or vasospasm in the early period or to a thromboembolic event, fatal arrhythmia, or pump failure in the late period (20,21).

Our study highlighted the long-term clinical impact of bleeding beyond 30 days post procedure on mortality. Although there are few studies evaluating the impact of late bleeding after DES implantation, the GRACE registry, conducted before the introduction of DES, showed that

Figure 5. Adjusted Hazard Ratios Within and After 30 Days

Adjusted for 3-year mortality among patients with MI or bleeding within and after 30 days, compared with those without MI or bleeding, with the time-updated Cox model. Abbreviations as in Figure 4.

patients with bleeding after discharge were not at increased risk of mortality compared with patients without bleeding (4). Likewise, pooled data from 3 large studies, which included 34,146 patients with ACS, suggested that the association of bleeding after 30 days post-procedure with subsequent death was not strong (7). Although an analysis from the ACUITY trial showed an association between bleeding within 30 days and 1-year mortality, the impact of late bleeding was not evaluated (3,5). By contrast, we found that the hazard for death among patients with bleeding after 30 days was not lower than that among those with bleeding within 30 days. Moreover, the risk of death after bleeding was similar to the risk of death after MI, both within and after 30 days. A recent large dataset supported our finding that bleeding after discharge increases the risk of 1-year death or MI after PCI in elderly patients (22). However, the data were limited due to the selective inclusion of elderly patients >65 years of age and heterogeneous inclusion of PCI with either bare-metal stent or DES (22).

The mechanisms linking bleeding and subsequent death might be more complicated in the late than in the early period. Prolonged use of dual antiplatelet therapy, consisting of aspirin and clopidogrel, after DES implantation might contribute, at least in part, to the occurrence of late bleeding. We found that 87% and 34% of our patients remained on dual antiplatelet therapy at 6 months and 1 year, respectively. By contrast, in the PREMIER study

(Prospective Registry Evaluating Myocardial Infarction: Events and Recovery), which compared the patterns of antiplatelet medication after discharge among patients with acute MI, approximately 40% of patients remained on thienopyridine at 6 months (19). In the randomized CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial, the incidence of major bleeding was higher among patients taking dual antiplatelet therapy than those taking aspirin alone (2). Moreover, results of the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial suggested that dual antiplatelet therapy might paradoxically increase morality in asymptomatic patients, via an unknown mechanism (23). More recently, dual antiplatelet therapy over 1 year was found to increase the risk of bleeding, (24) but not reduce the incidence of ischemic events (24,25). We found that the incidences of bleeding and subsequent death were negligible after 1 year post-procedure, when fewer patients were adherent to dual antiplatelet therapy. Alternatively, discontinuation of dual antiplatelet therapy after bleeding might potentially contribute to death through recognized or unrecognized thrombotic episodes.

Study limitations. First, although we used rigorous statistical adjustment, unmeasured confounders might have influenced the outcomes. For example, patients at high risk of ischemic complications might have been prescribed a more intensive regimen of antiplatelet agents, for a longer period,

which might have increased the risk of bleeding complication. Second, a merge of major and minor criteria into the definition of bleeding might overestimate the strength of hazard. Conversely, however, the current definition of major bleeding might underestimate the true impact of bleeding on clinical outcomes, especially in the late period after PCI. Third, because the definition of MI included periprocedural enzyme elevation with any ischemic symptom, the relative impact of MI on death might have been diluted. Fourth, owing to the limited numbers of subjects and events, complicated interactions among adverse events could not be determined. Therefore, the plausible mechanisms linking the events of bleeding and death could not be completely evaluated. Large-scale studies are needed to assess the causal relationships among bleeding, MI, and subsequent death.

Conclusions

Our results indicate that bleeding complications in the early and late periods after DES placement are closely associated with death. Therefore, in addition to carefully assessing bleeding complications after stenting, evidence-based medical treatment should be implemented after PCI to offer the best balance between benefit and harm, thus optimizing patient outcomes.

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