Long-Term Incidence and Details of Bleeding Events After Everolimus-Eluting Stent Implantation — 7–8-Year Outcomes —

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Background: To date, the long-term incidence and details of major bleeding (MB) and coronary thrombotic events (CTE) in patients with everolimus-eluting stent (EES) implantation have not been made clear.

Methods and Results: The study population comprised 1,193 patients treated with EES without in-hospital events between 2010 and 2011. MB was defined as the occurrence of a Bleeding Academic Research Consortium type 3 or 5 bleeding event. The mean follow-up period was 2,996±433 days. Cumulative rate of MB was 7.4% and 10.8% at 5 and 8 years, respectively. Of 46 patients with intracranial bleeding, 20 had trauma-related intracranial bleeding. Cumulative rates of definite stent thrombosis and CTE at 8 years were 0.4% and 5.9%, respectively. Multivariate analysis revealed low body mass index (<23) (hazard ratio (HR), 1.57; 95% confidence interval (CI), 1.03–2.36; P=0.03) and concomitant use of oral anticoagulants (HR, 2.17; 95% CI, 1.30–3.50; P=0.004) as independent risk factors of MB and previous PCI (HR, 2.47; 95% CI, 1.29–1.00; P=0.006) as the factor for CTE.

Conclusions: MB is not uncommon and is a long-term hazard, but the occurrence of stent thrombosis is very low after EES implantation. Approximately half of the cases involving intracranial bleeding were associated with trauma.

Key Words: Bleeding; Drug-eluting stents; Dual antiplatelet therapy; Stent thrombosis

The introduction of current-generation drug-eluting stents (DES) has greatly improved the clinical outcomes of percutaneous coronary intervention (PCI)1,2 However, the optimal duration of dual antiplatelet therapy (DAPT) after 2nd-generation DES implantation remains controversial3,4 Although prolonged DAPT therapy reduces the risk of a thrombotic event, it is associated with higher risk of bleeding events3,5 The current guidelines recommend assessment of individual patients based on their risk scores to decide the duration of DAPT.7 To date, the incidence and risk factors for very long-term (>5 years) thrombotic and bleeding events after 2nd-generation DES implantation are unclear. Accordingly, we aimed to investigate these issues in patients who underwent everolimus-eluting stent (EES) implantation.

Methods

Patient Population
This study was a retrospective single-center study. A total of 1,787 consecutive patients undergoing EES (Xience V, Abbott Vascular, Santa Clara, CA, USA) implantaion between January 2010 and December 2011 were enrolled. After excluding patients with repeat EES implantation (n=288), combined use of EES and other types of stent (n=280), and in-hospital events (in-hospital death: n=17, in-hospital definite stent thrombosis (ST): n=1, in-hospital ischemic stroke: n=2, in-hospital major bleeding (MB): n=6), we analyzed 1,193 patients (Figure 1). Informed consent was given by all patients for both the procedure and subsequent data collection and analysis for research purposes, and the study was approved by the institutional ethics committee.

Study Definitions and Outcomes
Bleeding events were classified according to the Bleeding Academic Research Consortium (BARC) criteria. MB was defined as the occurrence of a BARC type 3 or 5 bleeding event, and a major thrombotic event was defined as a coronary thrombotic event (CTE), a composite of ST and myocardial infarction (MI). Endpoints of the present study included all-cause death, cardiac death, MI, definite or...
probable ST, target lesion revascularization, and ischemic stroke. MI was defined according to the Academic Research Consortium definitions. ST was defined as definite or probable according to the Academic Research Consortium definitions.\(^8\)

**Follow-up**

Two angiographic follow-ups were routinely scheduled at 8 and 20 months after the procedure. The clinical follow-up information was obtained at the time of office visit or by telephone contact or letter with primary care physicians or patients.

**Antiplatelet Therapy**

All the patients were pretreated with aspirin (100 mg daily) and ticlopidine (200 mg daily)/clopidogrel (75 mg daily).
### Table 1. Patient, Lesion, and Procedural Characteristics

|                                | Overall | Absent | Present | P value | Absent | Present | P value |
|--------------------------------|---------|--------|---------|---------|--------|---------|---------|
| n                              | 1,193   | 1,093  | 100     | 0.16    | 1,140  | 53      |         |
| Age, years                     | 70.1±11.2 | 69.9±11.3 | 71.6±9.7 | 0.17 | 70.1±11.1 | 69.5±13.2 | 0.69 |
| Male                           | 861 (72.2) | 795 (72.7) | 68 (6.0) | 0.17 | 820 (71.9) | 41 (77.4) | 0.39 |
| BMI, kg/m²                     | 24.3±3.5 | 24.4±3.5 | 23.6±4.1 | 0.04 | 24.3±3.6 | 24.6±3.5 | 0.49 |
| Hypertension                   | 848 (71.1) | 776 (71.0) | 72 (72.0) | 0.78 | 808 (70.9) | 40 (75.5) | 0.47 |
| Diabetes mellitus              | 467 (39.2) | 421 (38.5) | 46 (46.0) | 0.24 | 440 (38.6) | 27 (50.9) | 0.07 |
| Insulin therapy                | 130 (10.9) | 117 (10.7) | 13 (13.0) | 0.48 | 121 (10.6) | 9 (17.0) | 0.15 |
| Dyslipidemia                   | 745 (62.4) | 686 (62.8) | 59 (59.0) | 0.46 | 707 (62.0) | 38 (71.7) | 0.15 |
| Male                           | 166 (13.9) | 157 (14.4) | 9 (9.0) | 0.13 | 158 (13.9) | 8 (15.1) | 0.79 |
| Male                           | 60.9±25.7 | 61.9±25.7 | 54.6±25.8 | 0.02 | 61.7±27.7 | 53.1±23.6 | 0.03 |
| Male                           | 24.3±3.6 | 24.6±3.5 | 23.6±4.1 | 0.04 | 24.3±3.6 | 24.6±3.5 | 0.49 |
| Male                           | 224.4    |         |         |         |         |         |         |

**Values are mean±SD or n (%), unless otherwise specified. ACC, American College of Cardiology; ACEI, angiotensin-converting enzyme inhibitors; AHA, American Heart Association; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CCr, creatinine clearance; CKD, chronic kidney disease; CTE, coronary thrombotic event; eGFR, estimated glomerular filtration rate; MB, major bleeding; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; SAP, stable angina; STEMI, ST-elevation myocardial infarction; UAP, unstable angina.**
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Variables entered into the multivariable model were those that reached significance (P<0.10) after univariable analysis and judged to be of clinical significance. All P-values <0.05 were considered to be significant. Statistical analyses were performed using JMP 9.0 (SAS Institute, Cary, NC, USA).

Results

Baseline Characteristics
Baseline patient, lesion, and procedural characteristics in the overall study population and subset with and without MB and CTE are summarized in Table 1. Patients who experienced MB had lower body mass index, estimated glomerular filtration rate (eGFR), and higher rates of anemia and concomitant use of oral anticoagulants (OAC) at discharge.

Statistical Analysis
Categorical variables were compared using the chi-square test. Continuous variables are expressed as mean±SD and compared using Student’s t-test or the Wilcoxon rank-sum test based on the distributions. The cumulative incidence was estimated using the Kaplan-Meier method, and differences were assessed using the log-rank test. Cox proportional hazard model was used to identify the independent risk factors of MB and CTE. Continuous variables were dichotomized by clinically meaningful reference values. Variables entered into the multivariable model were those that reached significance (P<0.10) after univariable analysis and judged to be of clinical significance. All P-values <0.05 were considered to be significant. Statistical analyses were performed using JMP 9.0 (SAS Institute, Cary, NC, USA).
Incidence and Details of Bleeding Events
Mean follow-up was 2,996±433 days and the cumulative incidence of bleeding and thrombotic event within and beyond 5 years is summarized in Figure 2. The cumulative rate of DAPT discontinuation at 5 and 8 years was 44.6% and 69.4%, respectively. During follow-up, 222 patients had any bleeding events and 100 patients had MB. The annual rate of MB within and beyond 5 years was 1.5% and 1.2%, respectively. Table 2 is a summary of bleeding events. The most common cause of any bleeding was gastrointestinal (GI) bleeding (36.5%), whereas that of MB was intracranial bleeding (46.0%). Among those with intracranial bleeding, 20 patients (20.0% among those with MB) experienced trauma-related bleeding. A summary of patients with trauma-related intracranial bleeding is shown in Table 3. A total of 81 patients experienced GI bleeding, and the proportions of upper GI and lower GI bleeding were 43.2% and 46.9%, respectively. Among patients with MB, 76 patients experienced a bleeding event while on DAPT treatment (Supplementary Table).

Incidence of Thrombotic Events
The cumulative incidence of cardiovascular events at 1, 5, and 8 years is summarized in Table 4. CTE occurred in 32 patients (3.0%) at 5 years and in 51 patients (5.9%) at 8 years. Definite or probable ST occurred in 4 patients (0.4%) at 5 years and in 5 patients (0.5%) at 8 years. The annual rate of CTE within and beyond 5 years was 0.6% and 1.0%, respectively.

Risk Factors of MB and CTE
We performed a multivariate analysis to identify the risk factors of MB and found that low body mass index (BMI <23) (hazard ratio (HR), 1.57; 95% confidence interval (CI), 1.03–2.36; P=0.03) and concomitant use of OAC (HR, 2.17; 95% CI, 1.30–3.50; P=0.004) were independent risk factors of MB throughout the follow-up (Table 5). Cumulative incidence of MB and DAPT discontinuation in subgroups of each risk factor is summarized in Figure 3. The cumulative rate of MB was higher in patients with lower BMI and concomitant use of OAC than in those without. However, the rate of DAPT discontinuation was not significantly different during follow-up. Previous PCI was identified as the risk factor for CTE (HR, 2.47; 95% CI, 1.29–4.87; P=0.006) in multivariate analysis.

| Table 4. Cumulative Incidence of Cardiovascular and Bleeding Events |
|-------------------|-----------------|-----------------|
|                   | Cumulative rate |
|                   | 1 year          | 5 years         | 8 years         |
| All-cause death   | 57 (4.8)        | 223 (18.9)      | 316 (28.1)      |
| Cardiac death     | 20 (1.7)        | 68 (6.2)        | 101 (10.2)      |
| Myocardial infarction | 10 (0.9)    | 32 (3.0)        | 51 (6.0)        |
| Definite/probable ST | 1 (0.1)       | 4 (0.4)         | 5 (0.5)         |
| Definite ST       | 1 (0.1)         | 3 (0.3)         | 4 (0.4)         |
| Any TLR           | 90 (7.8)        | 147 (13.1)      | 165 (15.8)      |
| Clinically-indicated TLR | 48 (4.2)   | 83 (7.7)        | 101 (10.7)      |
| CTE                | 11 (1.9)        | 32 (3.0)        | 51 (5.9)        |
| Ischemic stroke   | 10 (0.9)        | 24 (2.2)        | 42 (4.0)        |
| MB                 | 21 (1.8)        | 77 (7.4)        | 97 (10.8)       |

Values are number of patients with event (cumulative incidence). Event rates estimated using Kaplan-Meier analysis. CTE, coronary embolic event; MB, major-bleeding; ST, stent thrombosis; TLR, target lesion revascularization.

| Table 5. Risk Factors of MB and CTE |
|------------------------------------|
| Risk factors                        | Univariate | Multivariate |
|                                    | HR (95% CI) | P value      | HR (95% CI) | P value      |
| Risk factors of MB                 |            |              |            |              |
| BMI <23                            | 1.64 (1.06–2.43) | 0.02        | 1.57 (1.03–2.36) | 0.03          |
| eGFR (for each increase of 1 unit) | 0.98 (0.98–0.99) | 0.001       | 0.99 (0.98–1.00) | 0.13          |
| Peripheral artery disease           | 1.78 (0.90–3.48) | 0.09        | 1.33 (0.65–2.47) | 0.41          |
| Anemia (Hb <11 g/dL)                | 1.79 (1.11–2.90) | 0.02        | 1.48 (0.86–2.47) | 0.15          |
| Platelet count <10^10/μL            | 2.34 (0.87–6.28) | 0.08        | 2.01 (0.70–4.59) | 0.18          |
| Concomitant use of OACs             | 2.23 (1.35–3.68) | 0.001       | 2.17 (1.30–3.50) | 0.004         |
| Risk factors of CTE                 |            |              |            |              |
| Diabetes mellitus                   | 1.65 (0.95–2.87) | 0.07        | 1.47 (0.85–2.54) | 0.17          |
| eGFR (for each increase of 1 unit)  | 0.98 (0.97–0.99) | 0.03        | 0.99 (0.98–1.00) | 0.11          |
| Previous PCI                        | 3.31 (1.80–6.09) | <0.0001     | 2.47 (1.29–4.87) | 0.006         |
| Anemia (Hb <11 g/dL)                | 2.09 (1.12–3.88) | 0.02        | 1.83 (0.90–3.57) | 0.09          |
| In-stent restenosis                 | 2.58 (1.41–4.70) | 0.001       | 1.41 (0.73–2.64) | 0.30          |

CI, confidence interval; Hb, hemoglobin; HR, hazard ratio; OAC, oral anticoagulant. Other abbreviations as in Table 1.
Long-Term Bleeding Events After EES Implantation

Discussion

The main findings of this study were as follows. (1) Bleeding events after EES implantation occurred at a relatively constant rate up to 8 years. (2) Although MI occurred at a constant rate during follow-up, the cumulative rate of ST was very low up to 8 years. (3) Low BMI and concomitant use of OAC were independent risk factors of MB in this cohort. (4) Approximately half of the cases of intracranial bleeding were associated with trauma.

DAPT reduces ischemic recurrence in patients undergoing after PCI with DES, but the benefit of DAPT is counterbalanced by an increase in bleeding events that occurs over time, and affects morbidity and mortality and quality of life. Multiple studies have investigated the patient or procedural features of bleeding and ischemic events that affect DAPT duration and current guidelines recommend risk stratification of individual patients based on their risk.
scores to decide the duration of DAPT. However, the risk scores were based on bleeding events occurring no longer than 5 years after the procedure. This is the first report on the very long-term incidence of bleeding and thrombotic events and the status of antithrombotic therapy in the 2nd-generation DES era.

Notably, bleeding events occurred at a relatively constant rate without attenuation up to 8 years, although the rate of DAPT discontinuation increased gradually during follow-up. There are several possible explanations for this clinically important finding. The first is the rate of DAPT discontinuation in this study. Because most of the MB occurred while on DAPT treatment, prolonged DAPT is considered to be the cause of constant bleeding events. With the appearance of current-generation DES, the risk of ST has been reduced, and warrants investigation of short-term DAPT. The occurrence of ST in the present study was extremely low and in line with previous reports on 2nd-generation DES. However, the rate of DAPT discontinuation in this study was relatively low compared with the current guidelines, although it increased gradually during follow-up. This tendency might have been influenced by clinicians’ fear of ST in the 1st-generation DES era, which lasted until this study period.

The second factor was temporal change in bleeding risk with aging. Aging itself is a well-known risk factor for bleeding and several bleeding risk scores include age as a risk parameter. Moreover, some patient features related to bleeding events (e.g., renal dysfunction, anemia, and atrial fibrillation) are associated with aging. Therefore, increased bleeding risk during long-term follow-up, which eclipsed the effect of DAPT discontinuation, was related to the constant bleeding events.

Surprisingly, 43% of cases of intracranial bleeding, which is the most common cause of MB, were associated with trauma. Because it was reported that fall-related deaths increase 1% over 5 years from 65 to 85 years old, increasing frailty with aging might lead to a severe bleeding event. Therefore, periprocedural assessment of frailty might be useful to prevent a postoperative trauma-related bleeding event.

GI bleeding was most common cause of bleeding in this study and 47% of cases were in the lower GI tract. Although routine use of proton-pomip inhibitors is recommended to avoid bleeding complications, especially in patient with OACs as stated in the current guideline, it might not be always sufficient prevention for GI bleeding.

The difference in the risk factors for bleeding events across studies might be related to differences in race, patient populations, and antiplatelet drugs. However, the risk factors for bleeding in this study were in line with those in previous studies. Rao et al reported BMI as a risk factor for in-hospital bleeding. and in the PARIS registry, it was linked to 2-year bleeding events. We suggest it be extended to a longer term bleeding risk of up to 8 years. Concomitant OACs is a well-known risk factor for bleeding after PCI and was also identified as an independent risk factor in this study. In the current guideline, DAPT with concomitant use of OACs is limited to patients with high thrombotic risk, and duration is recommended to be short. However, the duration of DAPT therapy in patients with concomitant use of OACs was obviously longer in this study cohort compared with the recommendation in the current guideline, which might lead to a high rate of bleeding events. There is increasing evidence about direct OACs in patients undergoing PCI; widespread use of these drugs might reduce bleeding events in patient with indications for OACs.

Study Limitations
In this study, almost all patients were treated with clopidogrel, thereby limiting generalizability to other P2Y12 inhibitors. Duration of DAPT was not based on the current worldwide guideline. In addition, this study was conducted as a retrospective single-center study. As the treatment strategy and management of patients were relatively homogeneous, this reduces the generalizability of our findings to populations with different therapeutic strategies.

Conclusions
MB is not uncommon and is a long-term hazard, although the occurrence of ST was very low, after EES implantation. About half of the cases of intracranial bleeding were associated with trauma.

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