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Original article

Frequency and predictors of bleeding events after 2nd generation drug-eluting stent implantation differ depending on time after implantation

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ABSTRACT

Background: Antiplatelet therapy is required after drug-eluting stent (DES) implantation, but bleeding events occur unexpectedly. We aimed to assess whether bleeding event predictors after 2nd generation DES (2nd DES) implantation differed by time after implantation.

Methods: We studied 1912 consecutive patients who underwent successful 2nd DES implantation (70 ± 10 years, 72% male). Bleeding events were recorded as early ($\leq$1 year) and late (>1 year). Major bleeding events were defined as a composite of type 5, 3, and 2 bleeding in the Bleeding Academic Research Consortium criteria. Predictors were assessed using a Cox proportional hazard model.

Results: Bleeding event rates were 3.3%, 5.1%, and 6.7% at 1, 2, and 3 years, respectively, with the highest 1-year rate in year 1 ($p < 0.001$). Cause and severity of bleeding events were similar between early and late bleeding events. Prior history of gastrointestinal bleeding, non-steroidal anti-inflammatory drug use, and triple antithrombotic therapy [adjusted risk ratio (RR): 3.68, 3.21, 4.57, respectively; $p < 0.01$] were independent predictors of early bleeding events. Age >80 years and severe renal dysfunction (adjusted RR: 2.27, 2.02, respectively; $p < 0.01$) were independent predictors of late bleeding events. Survival rate was significantly lower in patients with bleeding events compared with patients without bleeding events (82.4% vs 90.1%; $p < 0.001$).

Conclusion: Frequency and predictors of bleeding events after 2nd DES implantation differ by time after implantation. Treatment strategies corresponding to individual patients are required.

Introduction

Problems associated with percutaneous coronary intervention (PCI) were dramatically resolved with the appearance of drug-eluting stents (DES), especially 2nd generation DES [1–4]. Patients who undergo DES implantation are treated with dual antiplatelet therapy (DAPT) to prevent stent thrombosis (ST), which causes large myocardial infarction (MI) or sudden death. Discontinuation of both components of DAPT, but not discontinuation of thienopyridine therapy alone, is associated with an increased risk of stent thrombosis with 1st generation DES use [5]. Many studies have been performed to clarify the optimal DAPT duration after 2nd generation DES implantation, but optimal DAPT duration has remained controversial [6–10]. Prolongation of DAPT was common in previous studies and was closely related to an increase in bleeding events. Bleeding events after DES implantation were related to poor prognoses; thus, management of bleeding events was important for patients [11–14].

Although optimal DAPT duration remains an unsolved problem, predictors of bleeding events after PCI have been reported in

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various studies, and DAPT duration was not the sole factor correlated with bleeding events [15–18]. The frequency of bleeding events differed depending on time after implantation, and some patients experienced bleeding events immediately after DES implantation [19]. Little is known regarding the correlation between time and predictors of bleeding events after DES implantation. Our aim in this study was to assess whether bleeding event rates and predictors of bleeding events after DES implantation differed depending on the time after implantation.

Methods

Patient population

This study was a non-randomized, retrospective, single-center observational study (Saiseikai Yokohama City Eastern Hospital, Kanagawa, Japan). The study design is shown in Fig. 1. A total of 1947 consecutive patients underwent 2nd DES implantation in our hospital between April 2009 and April 2014. Successful PCI was defined as follows: (1) minimum stenosis diameter <20%; (2) grade thrombolysis in myocardial infarction (TIMI) 3 flow; and (3) no in-hospital major clinical complications [20]. Twenty-one patients died in the hospital due to causes that were unrelated to ST (14 patients, myocardial infarction; 6 patients, cardiopulmonary arrest on arrival; 1 patient, severe aortic valve stenosis). Fourteen patients experienced bleeding related to the procedure (2 patients, cardiac tamponade due to wire perforation; 2 patients, retroperitoneal bleeding; 10 patients, hematoma of puncture site). These 35 patients were excluded, and the remaining 1912 consecutive patients who underwent successful PCI with 2nd DES were included in the study.

Selection criteria were broad to reflect routine clinical practice. We did not set a limit with respect to lesion length or the number of treated lesions or vessels and did not exclude patients based on comorbid disorders or age; the exclusion criteria included contraindications with respect to antiplatelet therapy and patient decisions not to undergo treatment. The study protocol was approved by the ethics committee at our institution. All patients provided written informed consent prior to participation. We performed the study in accordance with the Declaration of Helsinki.

PCI procedures

Patients with ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI), or unstable angina pectoris were treated using early invasive treatment strategies.

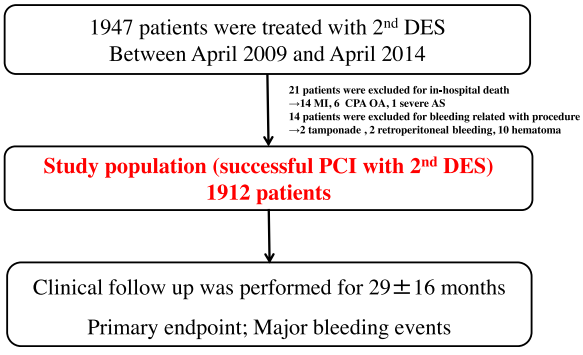

Fig. 1. Study design.
DES, drug-eluting stent; MI, myocardial infarction; CPA OA, cardiopulmonary arrest on arrival; AS, aortic valve stenosis; PCI, percutaneous coronary intervention.

Stent implantation was performed according to current standard techniques. The 2nd DES used included Xience V, Xience Prime, Xience Expedition (Abbott Vascular, Santa Clara, CA, USA), Promus, Promus Element, Promus Premier (Boston Scientific, Natick, MA, USA), Nobori (TERUMO, Tokyo, Japan), and Resolute Integrity (Medtronic, Minneapolis, MN, USA). Several details, including the approach site (radial versus femoral), type of guiding catheter, guide wire, and other technical issues, were left to the operator's discretion.

Antithrombotic therapy

All patients were treated with aspirin (200 mg loading dose) and clopidogrel (300 mg loading dose) prior to the initiation of PCI. The duration of dual antiplatelet therapy (DAPT) following stent implantation was scheduled for at least 1 year but was ultimately left to the doctor's discretion. Dates of discontinuation of aspirin and clopidogrel were reported separately during follow-up. If either aspirin or clopidogrel was restarted after discontinuation, the dates of restarting were also recorded.

Anticoagulation therapy was defined as the internal use of warfarin or non-vitamin K antagonist oral anticoagulants (NOAC). In this study, triple antithrombotic therapy (TAT) was defined as the combination use of anticoagulation therapy in addition to DAPT.

Endpoint and definition

The mean clinical follow-up duration was 29 ± 16 months. Follow-up data were obtained from hospital charts and by contacting patients. Information was collected regarding baseline clinical characteristics, procedural data, and clinical events. The primary endpoint was major bleeding events, which was defined as a composite of type 5, 3, and 2 bleeding in the Bleeding Academic Research Consortium criteria [21]. In this study, bleeding events were also recorded as early (within 1 year) and late (more than 1 year) bleeding events. Death was defined as all causes of intrinsic death, and sudden deaths with unknown causes were considered cardiac death.

Prior to the initiation of the PCI procedure, information regarding selected risk factors was obtained from hospital records made at discharge. The following data were collected to reflect baseline clinical characteristics: age, sex, hypertension (systolic blood pressure >140 mmHg), dyslipidemia (low-density lipoprotein cholesterol >140 mg/dl or high-density lipoprotein cholesterol <40 mg/dl), diabetes mellitus [fasting blood glucose >126 mg/dl, glycated hemoglobin (%, national glycohemoglobin standardization program) >7.0%, or casual blood glucose >200 mg/dl], past or current smoking status, renal function evaluated via estimated glomerular filtration rates (eGFR) (severe renal dysfunction was defined as eGFR <40 ml/min/1.73 m^2), and other past illnesses requiring hospitalization.

Statistical analysis

Continuous variables were expressed as mean ± SD, and categorical variables were expressed as numbers and percentages. A Cox proportional hazards model was used to identify independent predictors of the primary endpoint. To identify independent risk factors, we selected variables with p-values of <0.05 in the univariate Cox models and included them in the multivariate models simultaneously. Cumulative incidences of adverse events were estimated using the Kaplan–Meier method, and the curves were compared using the log-rank test.

All statistical analyses were performed using JMP® 10 (SAS Institute Inc., Cary, NC, USA). Values of $p < 0.05$ were considered statistically significant.

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