Catheterization and Cardiovascular Interventions 85:63–71 (2015)

Impact of In-Hospital Bleeding According to the Bleeding Academic Research Consortium Classification on the Long-Term Adverse Outcomes in Patients Undergoing Percutaneous Coronary Intervention

Yong-Hoon Yoon,[1] MD, Young-Hak Kim,[1] MD, PhD, Seon-Ok Kim,[2] MS, Jong-Young Lee,[1] MD, Duk-Woo Park,[1] MD, PhD, Soo-Jin Kang,[1] MD, PhD, Seung-Whan Lee,[1] MD, PhD, Cheol Whan Lee,[1] MD, PhD, Seong-Wook Park,[1] MD, PhD, and Seung-Jung Park,[1*] MD, PhD

Objectives: The aim of this study was to assess the impact of bleeding after percutaneous coronary intervention (PCI) with drug-eluting stents on long-term clinical events according to the newly proposed Bleeding Academic Research Consortium (BARC) classification. **Background:** Current evidence about the impact of the BARC classification is limited. **Methods:** Out of a total of 6,166 patients who underwent PCI in a prospective IRIS-DES registry, the impact of in-hospital bleeding defined as the BARC classification on major adverse cardiovascular events (MACE) comprising death, myocardial infarction (MI), or stroke was analyzed. **Results:** In-hospital bleeding occurred in 235 patients (3.8%) according to BARC classification. During the 2-year follow-up, MACE occurred in 599 patients (9.7%). The 2-year incidence of MACE was significantly higher in patients with bleeding (16.7% vs. 8.3%; adjusted hazard ratio [HR], 1.6; 95% confidence interval [CI], 1.2–2.3; $P = 0.002$) than in those without bleeding. We observed a higher risk of MI (12.4% vs. 6.4%; adjusted HR, 1.7; 95% CI, 1.2–2.6, $P = 0.005$), stroke (3.0% vs. 0.6%; adjusted HR, 2.9; 95% CI, 1.4–6.2, $P = 0.005$) in patients with bleeding. Death (3.8% vs. 1.6%; adjusted HR, 1.6; 95% CI, 0.9–3.0, $P = 0.120$) and target vessel revascularization (4.3% vs. 1.9%; adjusted HR, 1.6; 95% CI, 0.9–2.9, $P = 0.108$) were statistically insignificant. Incidence, adjusted HR and *P*-value were similar between BARC and TIMI classification. **Conclusions:** In-hospital bleeding events according to the newly proposed BARC definition were significantly associated with an increased risk of adverse long-term events in patients undergoing PCI with drug-eluting stents.

Key words: coronary artery disease; stent; bleeding; prognosis

INTRODUCTION

Advances in antithrombotic therapy have improved clinical outcomes in patients with acute coronary syndromes (ACS) and those undergoing percutaneous coronary intervention (PCI). However, the combination of multiple pharmacotherapies including aspirin, platelet P_2Y_{12} inhibitors, heparin, glycoprotein IIb/IIIa inhibitors, and direct thrombin inhibitors has increased bleeding events. Furthermore, popular use of invasive procedures in the treatment of ACS has also been associated with an increased risk of bleeding. Unfortunately, bleeding complications have led to subsequent

[1]Department of Cardiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea
[2]Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Conflict of interest: Nothing to report.

Contract grant sponsor: CardioVascular Research Foundation, Seoul, Korea, Korea Health 21 R&D Project, Ministry of Health & Welfare, Korea; grant number: A120711; Grant sponsor: Asan Medical Center, and Abbott and Cordis.

*Correspondence to: Dr. Seung-Jung Park, Department of Cardiology, University of Ulsan College of Medicine, Asan Medical Center, 388-1 Poongnap-dong, Songpa-gu, Seoul.
E-mail : sjpark@amc.seoul.kr

Received 10 October 2013; Revision accepted 22 November 2013

DOI: 10.1002/ccd.25308
Published online 27 November 2013 in Wiley Online Library (wileyonlinelibrary.com)

adverse events such as death, myocardial infarction (MI), stent thrombosis, or stroke [1–5]. In many clinical trials, the incidence and clinical impact of bleeding during hospitalization were investigated mainly in ACS patients who could be more serious than real world population. Therefore, in spite of several studies assessing the consequences of post-PCI bleeding complications, the real incidence and impact of bleeding on adverse outcomes in daily practice are still not well known.

In 2011, a consensus report from the Bleeding Academic Research Consortium (BARC) proposed standardized bleeding definitions using a hierarchical approach to describe the bleeding severity grade in patients receiving antithrombotic therapy for cardiovascular clinical trials [6]. However, the BARC definition was not created from a data-based analysis and few validation studies were performed to evaluate the impact of bleeding as defined by the BARC classification [7]. For widespread use of the BARC definition in clinical trials and daily practices, it is necessary to validate the newly proposed definition in different temporal and geographical data sets, particularly based on a design of the real world registries and prospective trials. Therefore, we assessed the impact of in-hospital bleeding on adverse outcomes in patients undergoing PCI using the new BARC definition, and we compared it to the grading system previously used in a prospective multicenter registry.

TABLE I. Definition of Bleeding Complications and Incidence of Events

				In-hospital bleeding	
	Class		Definition	Overall (No, %)	Detailed (No)
BARC	2		Any overt, actionable sign of hemorrhage	27 (11.5)	Procedure site (26) Gastrointestinal (1)
	3			207 (88.1)	
		3a			
			Hb level drop 3 to <5 g/dL	184 (78.3)	Procedure site (159)
			Any transfusion		Gastrointestinal (10)
					Genitourinary (8)
					Pulmonary (4)
					Retroperitoneal (1)
					Pharynx, oral (1)
					Trauma-related (1)
		3b	Hb level drop $\geq$ 5 g/dL	23 (9.8)	Procedure site (12)
			Requiring surgical intervention		Gastrointestinal (5)
			Requiring vasoactive agents		
			Cardiac tamponade		Hemopericardium(4)
					Genitourinary (1)
					Retroperitoneal (1)
		3c	Intracranial or intraocular hemorrhage	0	•
	4 (CABG-related)		Intracranial bleeding	1 (0.4)	Massive chest tube bleeding (1)
			Transfusion $\geq$ 5 U within 48 hr		
			Chest tube output $\geq$ 2 L within 24 hr		
	5		Fatal bleeding	0	•
	Total			235	•
TIMI	Major		Intracranial bleeding	32 (16.4)	Procedure site (18)
			Hb level drop $\geq$ 5 g/dL		Gastrointestinal (8)
			Fatal bleeding		Hemopericardium(3)
					Retroperitoneal (1)
					Genitourinary (1)
					Pharynx, oral (1)
	Minor		Hb level drop 3–5 g/dL	163 (83.6)	Procedure site (147)
					Genitourinary (7)
					Pulmonary (4)
					Gastrointestinal (3)
					Retroperitoneal (1)
					Hemopericardium(1)
	Total			195	•

[a]Values are *n* (%).

BARC, Bleeding Academic Research Consortium; TIMI, Thrombolysis in Myocardial Infarction; CABG, coronary artery bypass surgery; Hb, hemoglobin.

TABLE II. Baseline Clinical, Angiographic, and Procedural Characteristics

	In-hospital bleeding (235 patients)	No bleeding (5931 patients)	*P* value
Age, y	65.9± 11.8	63.5± 10.8	0.001
Male	150 (63.8)	3981 (67.1)	0.293
BMI, kg/m^2	24.3± 3.1	24.7± 3.1	0.059
Diabetics	79 (33.6)	2070 (34.9)	0.685
Hypertension	154 (65.5)	3693 (62.3)	0.311
Hyperlipidemia	80 (34.2)	2317 (39.1)	0.121
Current smoker	75 (31.9)	1654 (27.4)	0.178
Previous PCI	23 (9.8)	1012 (17.1)	0.003
Previous CABG	2 (0.9)	141 (2.4)	0.127
Previous MI	18 (7.7)	366 (6.2)	0.354
Previous heart failure	9 (3.8)	132 (2.2)	0.107
Left ventricular ejection fraction, %	55.4± 11.5	59.4± 9.9	<0.001
Cerebrovascular disease	30 (12.8)	439 (7.4)	0.002
Peripheral vascular disease	5 (2.1)	62 (1.0)	0.117
Chronic lung disease	4 (1.7)	170 (2.9)	0.291
Renal failure	8 (3.4)	215 (3.6)	0.859
Family history of coronary arterial disease	17 (7.3)	253 (4.3)	0.029
NSTEMI or STEMI	120 (51.1)	1308 (22.1)	<0.001
Angiographic characteristics			
Lesion number, n	1.7 ± 0.8	1.4± 0.7	<0.001
Multi-vessel disease	152 (64.7)	3096 (52.2)	<0.001
Left main disease	25 (10.6)	419 (7.1)	0.038
LAD disease	151 (64.3)	3809 (64.2)	0.992
Bifurcation disease	89 (37.9)	1800 (30.3)	0.014
Total obstruction	67 (28.6)	840 (14.2)	<0.001
Restenotic lesions	13 (5.5)	390 (6.6)	0.525
Long lesion	191 (81.3)	4521 (76.2)	0.074
Procedural characteristics			
Stent number, n	2.2 ± 1.3	1.8 ± 1.1	<0.001
Stent length, mm	53.0± 33.5	43.2 ± 28.8	<0.001
Stent diameter, mm	3.1 ± 0.4	3.2 ± 0.4	0.155
Stent type			0.032
EES	134 (56.8)	2947 (49.7)	
SES	101 (43.2)	2984 (50.3)	
Transfemoral approach	192 (82.1)	4531 (76.9)	0.067
Any transfusion	63 (26.8)	33 (0.6)	<0.001
Red blood cell	61 (26.0)	29 (0.5)	<0.001
Others	5 (2.1)	3 (0.1)	<0.001
In-hospital antithrombotics			
Aspirin	235 (100.0)	5931 (100.0)	
Clopidogrel	235 (100.0)	5931 (100.0)	
Cilostazol	26 (11.1%)	501 (8.5%)	0.160
Glycoprotein IIb/IIIa	5 (2.1)	123 (2.1)	0.352
Antithrombotics at discharge			
Aspirin	233 (99.1)	5864 (98.9)	0.690
Clopidogrel	233 (99.1)	5863 (98.9)	0.675
Cilostazol	71 (30.2)	1372 (23.1)	0.012

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

BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass surgery; MI, myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction; LAD, left anterior descending; EES, everolimus-eluting stent; SES, sirolimus-eluting stent.

MATERIALS AND METHODS

Population

This study represents a patient-level pooled analysis of patients from the IRIS-DES (Interventional Cardiology Research In-Cooperation Society-Drug-Eluting Stents) registry. Study design and primary results of the IRIS-DES trial were published previously [8]. In brief, the IRIS-DES registry involves a prospective, multicenter recruitment of consecutive consenting patients undergoing elective or urgent PCI with drug-eluting stents (DES) from 46 academic and community hospitals in Korea between April 1, 2008 and June 30,

2010. For these patients complete follow-up data were available for at least 1 year, up to 3 years. The analysis of the registry included patients treated simultaneously with everolimus-eluting stents (EES, Xience V, Abbott Vascular) or sirolimus-eluting stents (SES, Cypher Select, Cordis, Johnson & Johnson). Exclusion criteria were minimal: patients with cardiogenic shock, malignant disease, or other comorbid conditions with a life expectancy less than 12 months, those treated with a mixture of different types of DES, and those with a planned surgery requiring interruption of antiplatelet drugs within 6 months of the procedure. The study protocol was approved by the ethics committee at each participating center and all patients provided written, informed consent.

Procedure and Data Collection

In the IRIS-DES registry, all interventions were performed according to the current practice guidelines for PCI. Before or during the procedure, all patients received at least 200 mg of aspirin and a 300–600 mg loading dose of clopidogrel. Heparin was administered throughout the procedure to maintain an activated clotting time of 250 sec or longer. Administration of glycoprotein IIb/IIIa inhibitors was at the discretion of the operator. After the intervention, all patients were prescribed 100–200 mg/day of aspirin and 75 mg/day of clopidogrel for at least 12 months. Clinical follow-up was conducted during hospitalization and at 30 days, 6 months, 12 months, and every 6 months thereafter. Monitoring and verification of registry data was periodically performed in participating hospitals by members of the coordinating center (CardioVascular Research Foundation, Seoul, Korea).

Outcomes and Definition

The primary outcome of interest in this study was the 2-year incidence of major adverse cardiovascular events (MACE). MACE was defined by the composite of all-cause mortality, MI, and stroke. The secondary outcomes of interest were individual components of MACE comprising mortality, MI, stroke, and target vessel revascularization (TVR). The definitions of MI and TVR were based on standardized definitions in coronary stent trials [9]. Procedure related MI was defined as the presence of new Q waves or an elevation of creatine kinase-myocardial band isoenzyme or troponin I concentration > 3 times the normal upper

TABLE III. Adverse Outcomes Over 2 Years

	BARC bleeding		TIMI bleeding	
Bleeding definition	BARC $\geq$ grade 2	BARC $\geq$ grade 3	Major + Minor	Major
Death, MI, or stroke				
Bleeding, *n* (%)	44 (16.7)	41 (17.4)	37 (17.5)	7 (21.9)
No bleeding, *n* (%)	555 (8.3)	558 (8.3)	562 (8.4)	592 (8.6)
Adjusted HR (95% CI)	1.6 (1.2–2.3)	1.7 (1.2–2.4)	1.7 (1.2–2.3)	1.7 (0.8–3.6)
p value	0.002	0.001	0.004	0.164
Death				
Bleeding, n (%)	12 (3.8)	12 (4.3)	10 (4.1)	4 (12.5)
No bleeding, n (%)	118 (1.6)	118 (1.6)	120 (1.6)	126 (1.6)
Adjusted HR (95% CI)	1.6 (0.9–3.0)	1.8 (1.0–3.4)	1.6 (0.8–3.1)	3.7 (1.3–10.1)
p value	0.120	0.054	0.159	0.012
MI				
Bleeding, n (%)	29 (12.4)	27 (12.5)	25 (12.3)	3 (9.6)
No bleeding, n (%)	392 (6.4)	394 (6.4)	396 (6.5)	418 (6.6)
Adjusted HR (95% CI)	1.7 (1.2–2.6)	1.8 (1.2–2.7)	1.8 (1.2–2.7)	1.2 (0.4–3.7)
p value	0.005	0.003	0.006	0.759
Stroke				
Bleeding, n (%)	8 (3.0)	7 (2.9)	7 (3.1)	1 (3.1)
No bleeding, n (%)	51 (0.6)	52 (0.6)	52 (0.6)	58 (0.7)
Adjusted HR (95% CI)	2.9 (1.4–6.2)	2.8 (1.3–6.3)	3.0 (1.4–6.8)	2.3 (0.3–16.8)
P value	0.005	0.011	0.006	0.410
Target vessel revascularization				
Bleeding, *n* (%)	12 (4.3)	10 (3.9)	10 (4.2)	2 (6.5)
No bleeding, *n* (%)	171 (1.9)	173 (1.9)	173 (1.9)	181 (1.9)
Adjusted HR (95% CI)	1.6 (0.9–2.9)	1.5 (0.8–2.9)	1.6 (0.8–3.0)	2.0 (0.5–8.2)
P value	0.108	0.207	0.151	0.318

Percentage of events are based on Kaplan-Meier estimates. BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; HR, hazard ratio.

Catheterization and Cardiovascular Interventions DOI 10.1002/ccd.
Published on behalf of The Society for Cardiovascular Angiography and Interventions (SCAI).

limit. Spontaneous MI was defined as any creatine kinase-myocardial band isoenzyme or troponin increase above the upper range limit with or without the development of Q waves on electrocardiography. TVR was defined as any percutaneous or surgical revascularization procedure in the treated vessels. Stroke was defined as a neurologic deficit lasting more than 24 hr and confirmed by both imaging and a neurologist. Adverse events were considered to be meaningful if they occurred chronologically after bleeding.

Every in-hospital bleeding event during follow-up was adjudicated by two different classifications, the BARC [6] and the Thrombolysis in Myocardial Infarction (TIMI) classification [10]. The BARC criteria is composed of five hierarchical grades, 1 to 5, with grade 4 being coronary arterial bypass graft (CABG)-related bleeding as shown in Table I. BARC grade 2, 3, 4, and 5, and TIMI major and minor bleeding were considered clinically significant and were assessed in our study.

Statistical Analysis

Patient baseline characteristics and procedural findings were presented as mean ± standard deviation (SD) and number (percentage). Differences between the in-hospital bleeding group and the no bleeding group were evaluated by the Student *t*-test for continuous variables and by the chi-square test for categorical variables. All patients were censored at the time of an event or at a fixed interval of 2 years. Cumulative event curves were constructed using Kaplan-Meier estimates and compared with the log-rank test. For multivariable analysis, we selected covariates among several clinical, angiographic, and procedural characteristics that were statistically significant (P value < 0.05) on univariable Cox proportional hazard model. Using these covariates, the multivariable Cox proportional hazard model was used to investigate adjusted hazards ratio (HR) of in-hospital bleeding on adverse outcomes. The subgroups of patients sorted according to various clinical and angiographic characteristics were analyzed after adjustment by the multivariable Cox model with clinical factors as covariates. A backward stepwise Cox proportional hazard model was also used to identify independent predictors of in-hospital bleeding. The discriminatory power of the multivariable models with different bleeding definitions and grades was assessed by performing a receiver operating characteristic curve analysis and calculating the C-index. BARC grade 4 (CABG-related) was included in the multivariable analysis and in the Kaplan-Meyer cumulative event curves. All reported P values were 2-sided, and P values < 0.05 were considered statistically significant. SPSS software, version 18, and R programming language were used for statistical analyses.

RESULTS

Baseline Characteristics

Between April 2008 and June 2010, a total of 6,166 patients were treated with EES ($N = 3{,}081$) and SES ($N = 3{,}085$) and entered into the database. In-hospital bleeding events occurred in 235 patients (3.8%) according to the BARC definition and in 195 patients (3.2%) according to the TIMI definition (Table I). The intervention access site was the most common bleeding site (198 patients, 84.3%). Table II shows the differences in baseline clinical, angiographic, and procedural characteristics of the study population according to in-hospital bleeding events. Patients with in-hospital bleeding were older and more likely to have prior stroke, lower left ventricular

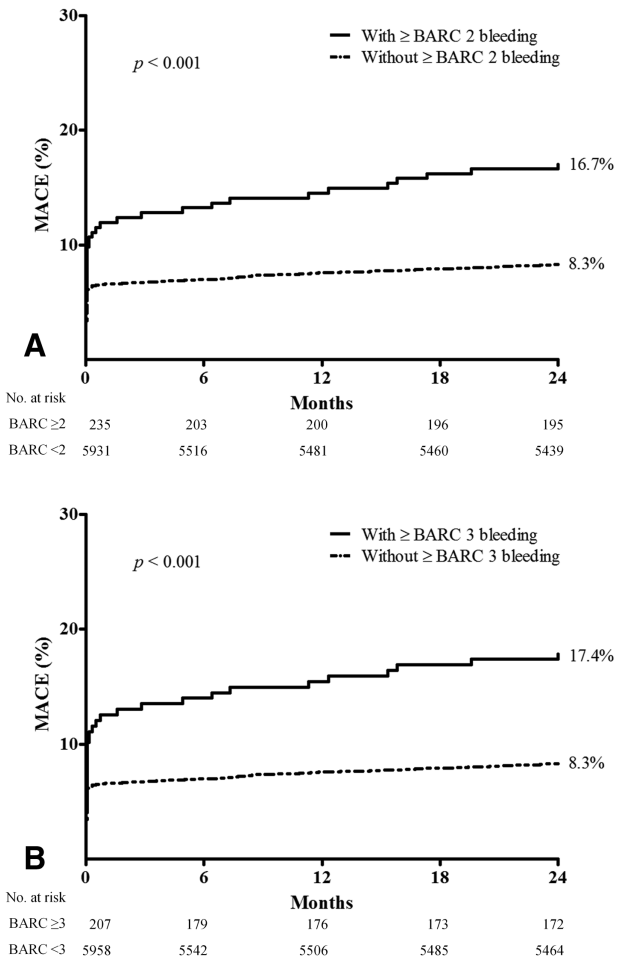

Fig. 1. Kaplan-Meier curves of the major adverse cardiovascular events comprising all-cause death, myocardial infarction, stroke between patients with and without a Bleeding Academic Research Consortium (BARC) grade ≥2 (A) and those with and without a BARC grade ≥3 (B).

ejection fraction, multi-vessel disease, total obstruction, bifurcation lesions, and a family history of coronary arterial disease. They often presented with myocardial infarction and are less likely to have prior PCI.

Adverse Outcomes Over 2 Years

During the 2-year follow-up on 6,166 patients in the IRIS-DES registry, MACE occurred in 599 patients (9.7%). Table III shows the incidence of adverse events between patients with and without in-hospital bleeding. Figure 1 shows the cumulative 2-year incidence of events in patients with in-hospital bleeding according to BARC grade. The 2-year incidence of MACE was 16.7% in patients with bleeding $\geq$ BARC grade 2 and 8.3% in those without bleeding ($P < 0.001$) (Fig. 1A). When comparing patients with- $\geq$ BARC 3 to those without, MACE occurred in 17.4% of patients with $\geq$ BARC 3 and in 8.3% of patients without $\geq$ BARC 3 ($P < 0.001$) (Fig. 1B).

Secondary outcomes of interest including all-cause mortality, MI, stroke, and TVR are shown in Fig. 2. Two-year mortality was higher in the BARC in-hospital bleeding group than in the no bleeding group (3.8% vs. 1.6%; $P < 0.001$). MI (12.4% vs. 6.4%, $P < 0.001$), stroke (3.0% vs. 0.6%, $P < 0.001$), and TVR (4.3% vs. 1.9%, $P = 0.037$) were also higher in the in-hospital bleeding group.

Adjusted Risk of Adverse Events in Patients With In-Hospital Bleeding

A multivariable Cox proportional hazard models revealed that in-hospital bleeding was significantly associated with MACE (adjusted HR, 1.6; 95% confidence interval [CI], 1.2–2.3; $P = 0.002$). In the analysis of individual end points, in-hospital bleeding increased the risk of MI (adjusted HR, 1.7; 95% CI, 1.2–2.6; $P = 0.005$) and stroke (adjusted HR, 2.9; 95% CI, 1.4–6.2; $P = 0.005$). However, after adjustment, the association between bleeding complications, the risk of mortality (adjusted HR, 1.6; 95% CI, 0.9–1.6; $P = 0.12$) and TVR (adjusted HR, 1.6; 95% CI, 0.9 to 2.9; $P = 0.108$) lost statistical significance (Table III).

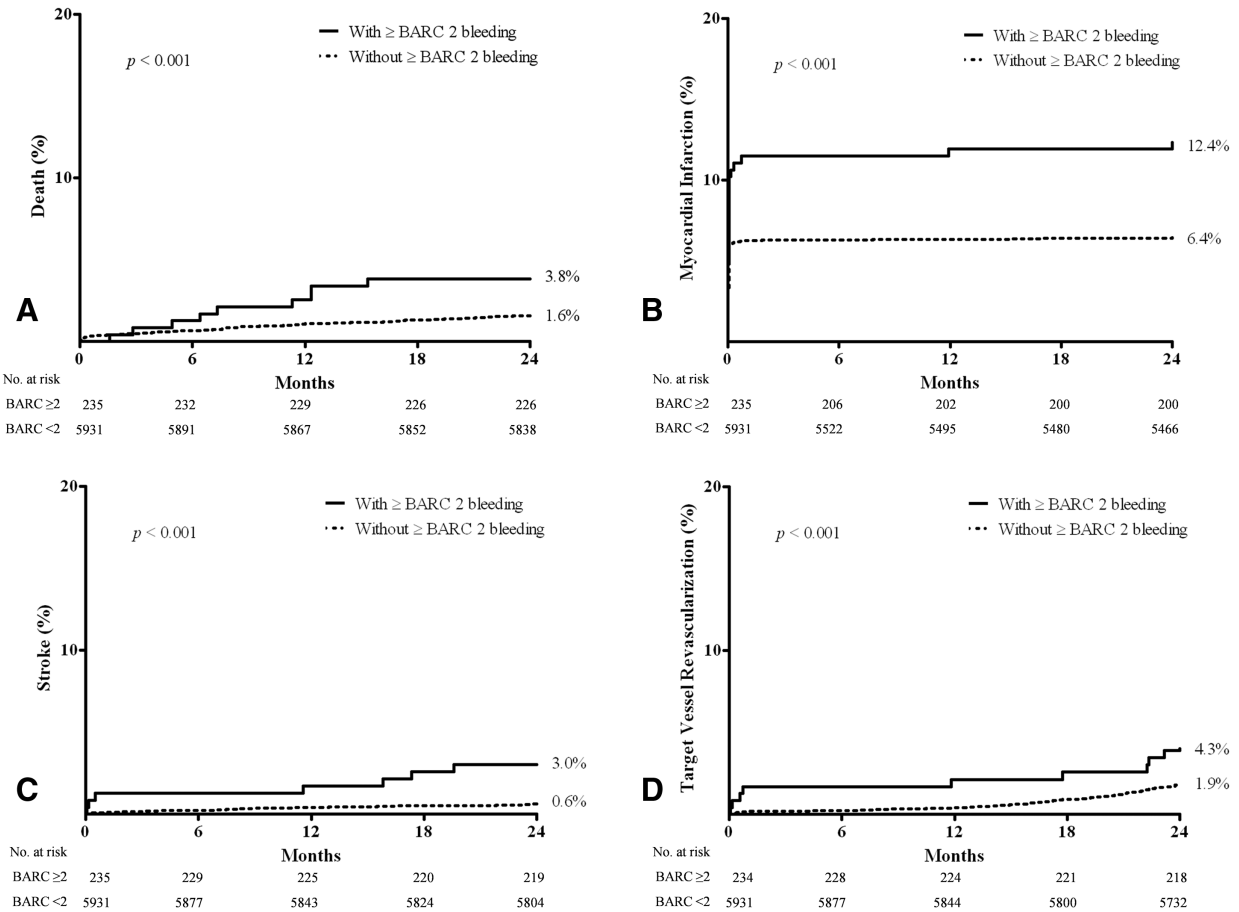

Fig. 2. Kaplan-Meier curves for adverse events of all-cause death (A), myocardial infarction (B), stroke (C), and target vessel revascularization (D).

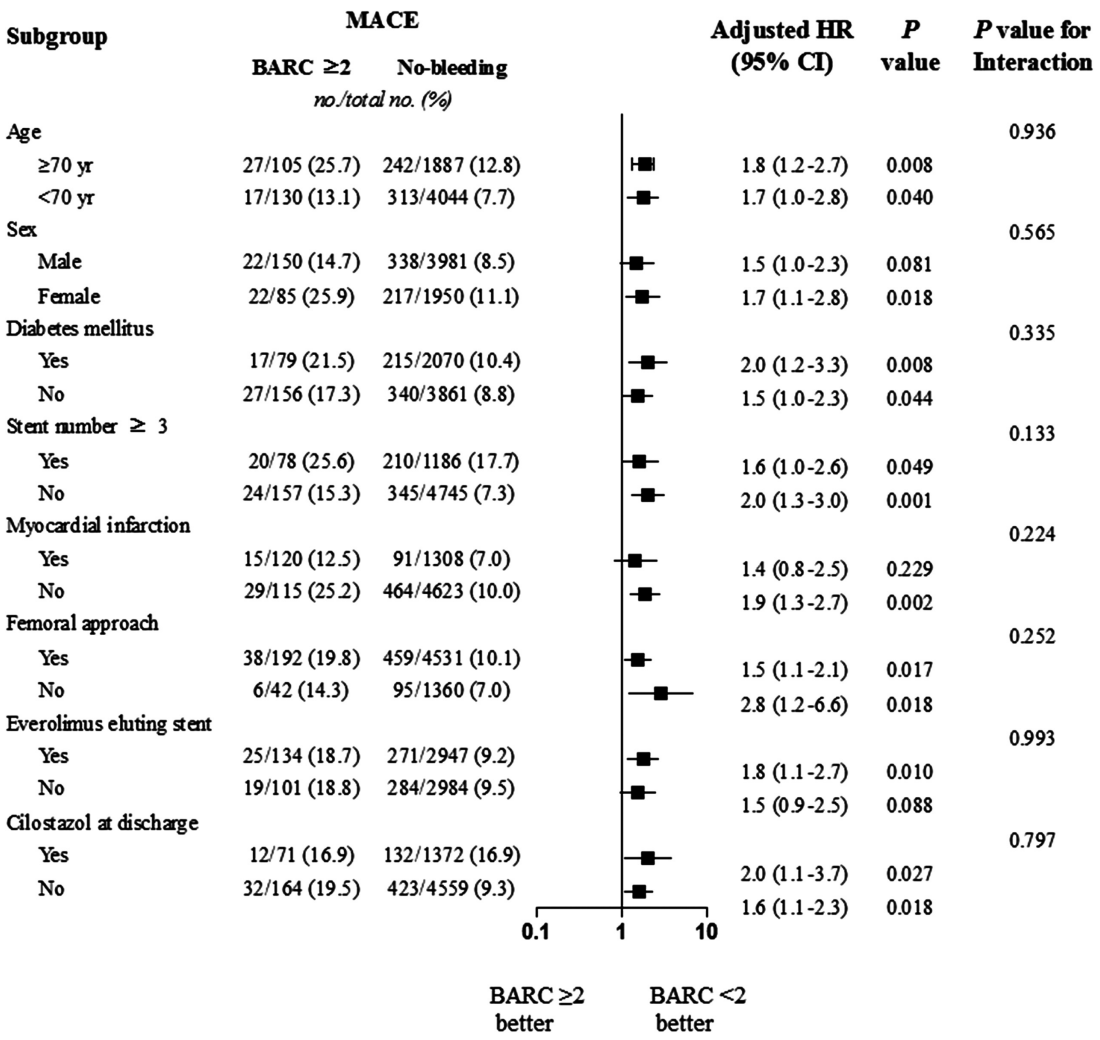

Fig. 3. Adjusted hazard ratios (HRs) for major adverse cardiovascular events (MACE) in subgroups. Interactions were not significant in any subgroup.

Figure 3 shows the adjusted risk of in-hospital bleeding for MACE according to variously categorized subgroups. An increased risk of MACE was found in all subgroups without a significant interaction.

Patients with TIMI major or minor bleeding also had a higher risk of MACE, MI, and stroke (Table III). When the receiver operating characteristic curves were calculated according to different bleeding definitions and grades, the C-index was similar. (BARC $\geq 2 = 0.707$, TIMI major or minor $= 0.707$) (Fig. 4).

Table IV shows the results of the multivariable Cox proportional hazards model presenting several independent clinical and angiographic factors for in-hospital bleeding.

DISCUSSION

In our study, in-hospital bleeding occurred in 3.8% of patients according to a BARC grade ≥ 2 in a real world registry enrolling 6,166 consecutive patients who underwent PCI with DES. Such patients were associated with a 1.6-fold increased risk of MACE comprising death, MI, or stroke, and individual end points of MI (1.7-fold) and stroke (2.9-fold) over 2 years after adjusting for nonrandomized bias. Bleeding complications defined by the traditional TIMI criteria also increased the risk of MACE with a similar risk to the BARC definition. This finding is significant as it suggests that in-hospital bleeding independently leads to a poor long-term prognosis after daily PCI even at 2 years.

In previous studies, bleeding events in patients presenting with ACS or undergoing PCI were independent risk factors for early and late adverse outcomes, such as mortality, MI, stent thrombosis, and stroke [1–5,11,12]. In the acute stage of bleeding, hypovolemia and anemia may reduce oxygen delivery to major

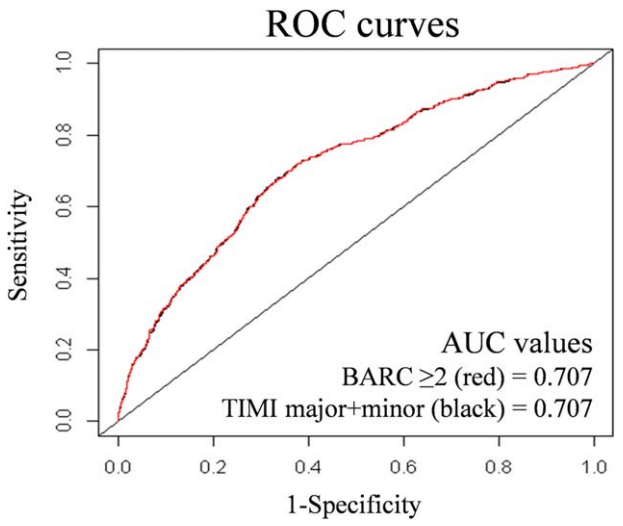

Fig. 4. Receiver operating characteristic (ROC) curves of BARC ≥2 and TIMI major + minor model for predicting major adverse cardiovascular events (MACE). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

organs, including the heart and brain. The action of neurohormones such as catecholamine to maintain blood flow to vital organs is also associated with adverse cardiac events [13]. Blood transfusions after bleeding have also been related to death or MI [14]. In the later stages of bleeding, physicians are likely to discontinue effective antithrombotic drugs, which in turn may increase the potential risk of MI, stent thrombosis, stroke, and cardiovascular death [15–18].

The unified BARC definition facilitates communication regarding bleeding complications after PCI across physicians, investigators, and research groups. The clinical impact of bleeding complications has been highlighted in the current practice due to the introduction of strong antithrombotics and the widespread use of complex procedures. Our results supported a study by Ndrepepa et al. on the validation of the BARC definition [7], in which BARC-defined bleeding was the significant risk factor for mortality. However, the study population was affected by direct thrombin inhibitors and IIb/IIIa inhibitors, which may have caused bleeding events. In addition, the primary outcome in Ndrepepa's study was mortality alone at 1 year. Other clinical outcomes such as MI, TVR, and stroke were not taken into consideration. Other studies have focused on bleeding events in ACS patients undergoing emergency procedures [1–5]. In this respect, our study has several strong points because we analyzed a real world registry largely composed of elective procedures, and we included other important outcomes that may occur after PCI. MACE, MI, and stroke were statistically significant factors even after adjusting important confounding factors, for example, such as presentation with MI and total obstructive lesion. In addition, we performed a subgroup analysis to assess the risks for MACE according to different clinical situations. Of interest is that bleeding complications inflated the risk of adverse events across all subgroups.

TABLE IV. Independent Predictors of In-Hospital Bleeding

Variables	Adjusted HR (95% CI)	*P* value
Age	1.02 (1.01–1.03)	0.002
Prior history of cerebrovascular disease	1.7 (1.2–2.5)	0.007
Left ventricular ejection fraction	0.98 (0.97–1.0)	0.029
Myocardial infarction	2.9 (2.1–3.89)	<0.001
Aspirin loading	1.5 (1.1–2.1)	0.006
Total obstruction	1.4 (1.1–2.0)	0.021
Stent number	1.3 (1.2–1.5)	<0.001

CI, confidence interval; HR, hazard ratio.

We did not find that the BARC bleeding definition was a better surrogate to predict adverse outcomes than the traditional TIMI definition. When major and minor TIMI bleeding was combined, the HR of MACE was almost identical between TIMI and BARC ≥ 2 bleedings. However, even though BARC classification did not provide stronger predictability for adverse outcomes compared with the previous definition, unified BARC classification can be useful and accurate tools to classify bleeding events occurred in coronary intervention.

This study has several limitations. First, it was a retrospective analysis of a nonrandomized registry. Therefore, in spite of statistical adjustments, bias cannot be completely ruled out. Nonetheless, because a randomized study to assess the clinical impact of bleeding is impossible, this study still provides valuable information for physician. Second, in spite of aggressive monitoring and auditing activity, minor bleeding episodes might have been under-reported. In fact, bleeding defined as BARC grade 1 is not frequently reported and was omitted from this study. In addition, because the clinical scenarios of subsequent clinical events after bleeding are complicated, a future study with more vigorous protocols to pursue temporal bleeding events is warranted. Third, the 3.8% incidence of in-hospital bleeding was relatively low compared with previous studies. Therefore, it may be underpowered to detect significant differences in the risk of mortality and revascularization after adjustment. However, it should be noted that the tendency of higher risk was consistently observed in any end points of our study. Fourth, to reflect current real-world practice better, higher proportion of radial approach and more use of new antiplatelet agents such as prasugrel and ticagrelor should have been included in IRIS-DES registry. Finally, we used the TIMI definition as the sole comparator. Further

studies may be required to validate the role of the BARC definition compared with other definitions.

CONCLUSIONS

We investigated and validated the clinical impact of in-hospital bleeding events defined by the newly proposed BARC definition on the likelihood of MACE in patients undergoing PCI. In-hospital bleeding events defined by the BARC criteria increased the risk of subsequent MACE at 2 years. Therefore, clinicians should pay particular attention to bleeding complications in coronary intervention and clinical practice.

REFERENCES

1. Rao SV, O'Grady K, Pieper KS, et al. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. Am J Cardiol 2005;96:1200–1206.
2. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006;114:774–782.
3. Spencer FA, Moscucci M, Granger CB, et al. Does comorbidity account for the excess mortality in patients with major bleeding in acute myocardial infarction? Circulation 2007;116:2793–2801.
4. Hochholzer W, Wiviott SD, Antman EM, et al. Predictors of bleeding and time dependence of association of bleeding with mortality: insights from the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38). Circulation 2011;123:2681–2689.
5. Mehran R, Pocock S, Nikolsky E, et al. Impact of bleeding on mortality after percutaneous coronary intervention results from a patient-level pooled analysis of the REPLACE-2 (randomized evaluation of PCI linking angiomax to reduced clinical events), ACUITY (acute catheterization and urgent intervention triage strategy), and HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trials. JACC Cardiovasc Interv 2011;4:654–664.
6. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: A consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736–2747.
7. Ndrepepa G, Schuster T, Hadamitzky M, et al. Validation of the Bleeding Academic Research Consortium definition of bleeding in patients with coronary artery disease undergoing percutaneous coronary intervention. Circulation 2012;125:1424–1431.
8. Park DW, Kim YH, Song HG, et al. Outcomes after unrestricted use of everolimus-eluting and sirolimus-eluting stents in routine clinical practice: A multicenter, prospective cohort study. Circ Cardiovasc Interv 2012;5:365–371.
9. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–2351.
10. Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. Circulation 1987;76:142–154.
11. Budaj A, Eikelboom JW, Mehta SR, et al. Improving clinical outcomes by reducing bleeding in patients with non-ST-elevation acute coronary syndromes. Eur Heart J 2009;30:655–661.
12. Kim YH, Lee JY, Ahn JM, et al. Impact of bleeding on subsequent early and late mortality after drug-eluting stent implantation. JACC Cardiovasc Interv 2011;4:423–431.
13. Ferrari R, Ceconi C, Curello S, Visioli O. The neuroendocrine and sympathetic nervous system in congestive heart failure. Eur Heart J 1998;19 Suppl F:F45–51.
14. Rao SV, Jollis JG, Harrington RA, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA 2004;292:1555–1562.
15. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126–2130.
16. Ferrari E, Benhamou M, Cerboni P, Marcel B. Coronary syndromes following aspirin withdrawal: a special risk for late stent thrombosis. J Am Coll Cardiol 2005;45:456–459.
17. Wang TY, Xiao L, Alexander KP, et al. Antiplatelet therapy use after discharge among acute myocardial infarction patients with in-hospital bleeding. Circulation 2008;118:2139–2145.
18. Mangano DT, Multicenter Study of Perioperative Ischemia Research G. Aspirin and mortality from coronary bypass surgery. N Engl J Med 2002;347:1309–1317.