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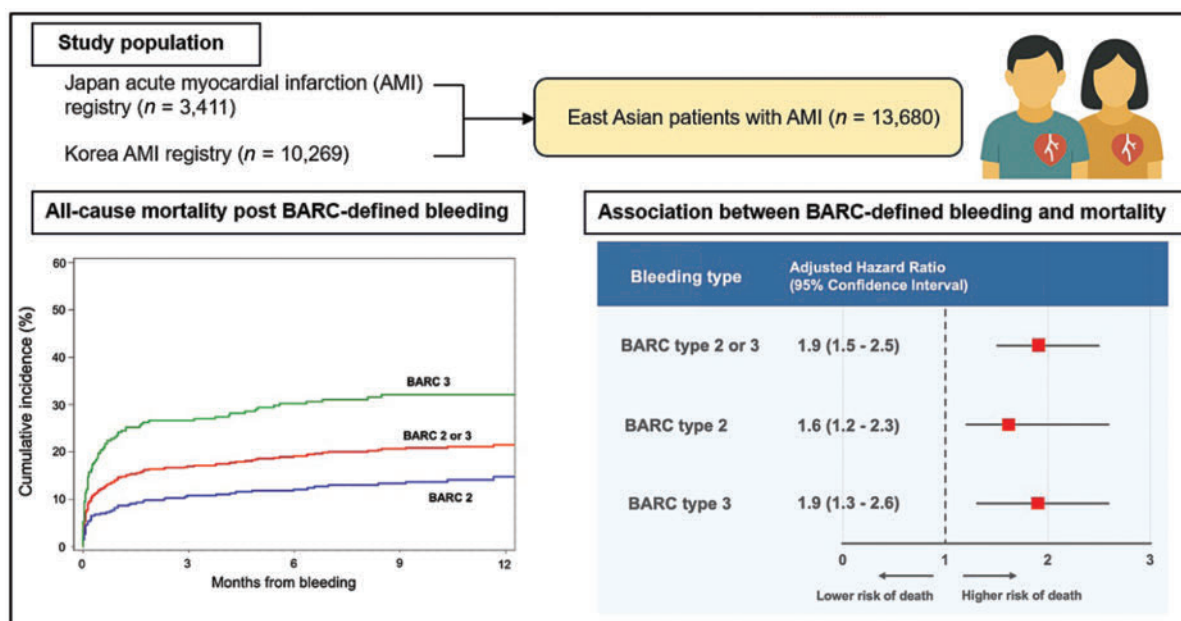
Prognostic Value of BARC-defined Bleeding in East Asian Acute Myocardial Infarction Patients: Evidence from Multicentre Registries in Korea and Japan

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GRAPHICAL ABSTRACT



ABSTRACT

Background The Bleeding Academic Research Consortium (BARC) classification was proposed to standardize bleeding endpoint definitions and reports in cardiovascular clinical trials. However, its prognostic value has not been fully validated in East Asian patients with acute myocardial infarction (AMI) who have a higher bleeding risk than Western populations do.

Methods We analyzed bleeding events (types 2 or 3) based on the BARC classification in 13,657 patients with AMI (mean age 64.9 ± 12.7 years) from nationwide prospective registries in Japan and Korea. The primary endpoint was all-cause mortality during the 1-year clinical follow-up.

Results During the 1-year follow-up, BARC type 2 or 3 bleeding occurred in 5.5% of the patients ($n = 759$). Patients who experienced BARC type 2 or 3 bleeding had a significantly higher risk of mortality compared with those without bleeding (hazard ratio [HR] 4.1, 95% confidence interval [CI] 3.4–4.8, $p < 0.001$). The risk of mortality was higher in BARC type 3 (HR 6.4, 95% CI 5.1–7.9) than in type 2 bleeding (HR 2.4, 95% CI 1.8–3.1). BARC type 2 or 3 bleeding remained significantly associated with increased mortality after adjustment (adjusted HR 1.9, 95% CI 1.5–2.5, $p < 0.001$). Similar associations with mortality were observed when each BARC classification (type 2 and 3) was analyzed individually.

Conclusion In East Asian patients with AMI, BARC-defined bleeding events were significantly associated with increased mortality. These findings support the adoption of the BARC classification to predict mortality, particularly in East Asian patients with AMI.

Keywords BARC, East Asians, acute myocardial infarction, bleeding event, mortality

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Introduction

Bleeding complications are critical concerns in the management of acute myocardial infarction (AMI). Although advances in percutaneous coronary intervention (PCI) and antithrombotic therapy have significantly reduced ischaemic events following AMI,^{1–3} they have also increased the risk of bleeding events, which can adversely impact short- and long-term outcomes.^{3–5} A standardized approach to defining and classifying bleeding events is essential for improving patient care and enabling reliable comparisons across studies. However, the assessment of bleeding in clinical trials and registries has often been inconsistent, leading to challenges in evaluating its clinical impact.⁶

The Bleeding Academic Research Consortium (BARC) classification proposed a standardized hierarchical bleeding classification system aimed at improving the consistency and reliability of bleeding definitions in cardiovascular research.⁷ This bleeding classification has been validated in Western populations^{8–10} and has been widely adopted in contemporary clinical trials.^{11,12} Importantly, it has also been increasingly utilized in clinical studies and registries across East Asia, including in Japan and South Korea.^{13,14} However, the prognostic utility of BARC-defined bleeding events in these populations has not been fully established. Given that East Asian patients are known to have higher bleeding risk compared with Western populations, partly due to ethnic differences such as greater predisposition to hemorrhagic complications relative to thrombotic events,¹⁵ further validation of the BARC classification in this population is warranted.

Therefore, this study aimed to evaluate the prognostic significance of BARC-defined bleeding in a large cohort of East Asian patients with AMI, using data from nationwide registries in Japan and South Korea. The prospective multinational design of this study, incorporating data from two distinct East Asian populations, provides a unique opportunity to assess the applicability of the BARC classification in a region with a higher bleeding risk than that in Western populations.

Methods

Study Population

This study used a combined dataset from nationwide registries in Japan and South Korea. The Japan Acute Myocardial Infarction Registry (JAMIR) is a prospective multicentre registry that

consecutively enrolled patients with AMI from 50 hospitals in Japan between December 2015 and May 2017 ($n = 3,411$).^{16,17} In the JAMIR, AMI was diagnosed according to the universal definition.¹⁸ The Korea Acute Myocardial Infarction Registry–National Institutes of Health (KAMIR-V) is a multicentre prospective registry that consecutively enrolled patients with AMI from 43 hospitals across Korea.¹⁹ Here, data from patients enrolled between

January 2016 and June 2017 were included ($n = 10,269$). In KAMIR-V, AMI was diagnosed based on a universal definition.¹⁸ Data on patient outcomes up to 1 year after hospitalization were extracted from both registries. To address the heterogeneity in data structure and differences in variable definitions, a combined dataset was created by aligning patient demographics, angiographic findings, and procedural details across both sources (**Supplementary Table S1**, available in the online version only). Standardization involves aligning registry-specific codes and classifications in a unified format to ensure consistency in diagnostic criteria, laboratory measurements, and procedural terminology. Differences in measurement units and data formats were resolved through systematic conversion, and variable definitions were harmonized to minimize inconsistencies across datasets. Informed consent was obtained from all participants of KAMIR-V. In the JAMIR, written informed consent was not required in accordance with Japanese Ethical Guidelines for Medical and Health Research involving Human Subjects. Instead, an opt-out approach was employed, whereby a summary of the study protocol was publicly disclosed on the registry Web site to inform patients of their right to refuse participation. In addition, the research secretariat confirmed compliance with opt-out procedures at each study site. The ethics committees at each participating centre in both JAMIR and KAMIR-V approved the study protocol (approval numbers M27–019–13 and KCT-0008355). This study was conducted in accordance with the principles of the Declaration of Helsinki.

Study Endpoints

The primary endpoint of the analysis was all-cause mortality. Actionable bleeding events (BARC type 2, 3, or 5), excluding those related to coronary artery bypass grafting (CABG), were identified by the site investigator in the case report form and prospectively assessed according to the BARC classification.⁷ The definition of bleeding events according to the BARC classification is provided in **Supplementary Table S2** (available in the online version only).

Statistical Analysis

Patients who experienced BARC type 5 bleeding (fatal bleeding) ($n=23$) were excluded because the primary outcome of this analysis was all-cause mortality. Patient characteristics for those with and without BARC type 2 or 3 bleeding events are presented as mean $\pm$ standard deviation for continuous variables and as frequency and percentage for categorical variables. The cumulative incidence of various bleeding events post-admission was estimated using the Kaplan–Meier method. Patients who experienced multiple bleeding events of different BARC types were counted in all relevant categories. Furthermore, the cumulative event rates of mortality following bleeding were estimated using the Kaplan–Meier method.

To evaluate the association between BARC-defined bleeding events and mortality, hazard ratios (HRs) and 95% confidence intervals (95% CIs) for mortality were estimated using Cox regression models, adjusted for age, sex, ST-elevation myocardial infarction, Killip class, atrial fibrillation, previous cerebrovascular disease, estimated glomerular filtration rate (eGFR), use of potent P2Y12 inhibitors (standard-dose prasugrel or ticagrelor), left main coronary artery culprit lesion, radial artery approach, and use of mechanical circulatory support devices. These variables were selected based on previous studies reporting their association with mortality and bleeding.²⁰ Furthermore, variables demonstrating significant differences ($p < 0.05$) between patients with and without BARC type 2 or 3 bleeding events, including hypertension, body mass index (BMI), haemoglobin level, left ventricular ejection fraction (LVEF), use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and use of β -blockers, were incorporated into the adjusted model.

Associations between all-cause mortality and BARC type 2 or 3 bleeding events, as well as between all-cause mortality and BARC type 2 and 3 bleeding events, were analyzed separately. To specifically evaluate the prognostic impact of late bleeding events, a 30-day landmark analysis was performed by re-setting time zero at day 30 after admission. Patients who died or experienced bleeding within the first 30 days were excluded from this analysis.

Furthermore, short- and long-term mortality risks following a bleeding event were assessed using a piecewise hazard function, categorizing time periods as <30 days, days 30 to 89, and ≥ 90 days post-bleeding.

Cox proportional hazard models were used to identify the determinants of BARC type 2 or 3 bleeding after admission. All statistical analyses were performed using complete case analysis, and missing data were not imputed. All the statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Differences were considered statistically significant at a two-tailed p -value of 0.05.

Results

Patient Demographics

After excluding patients who experienced BARC type 5 bleeding (fatal bleeding) during the follow-up period ($n=23$), a total of 13,657 patients were included in the final analysis. Among the study population, 742 patients (5.5%) experienced BARC type 2 or 3 bleeding during the 1-year follow-up period. Specifically, 465 patients (3.4%) had BARC type 2 bleeding and 324 patients (2.4%) had BARC type 3 bleeding (Fig. 1). Overall, 0.2% ($n=25$) of patients experienced more than one type of bleeding event.

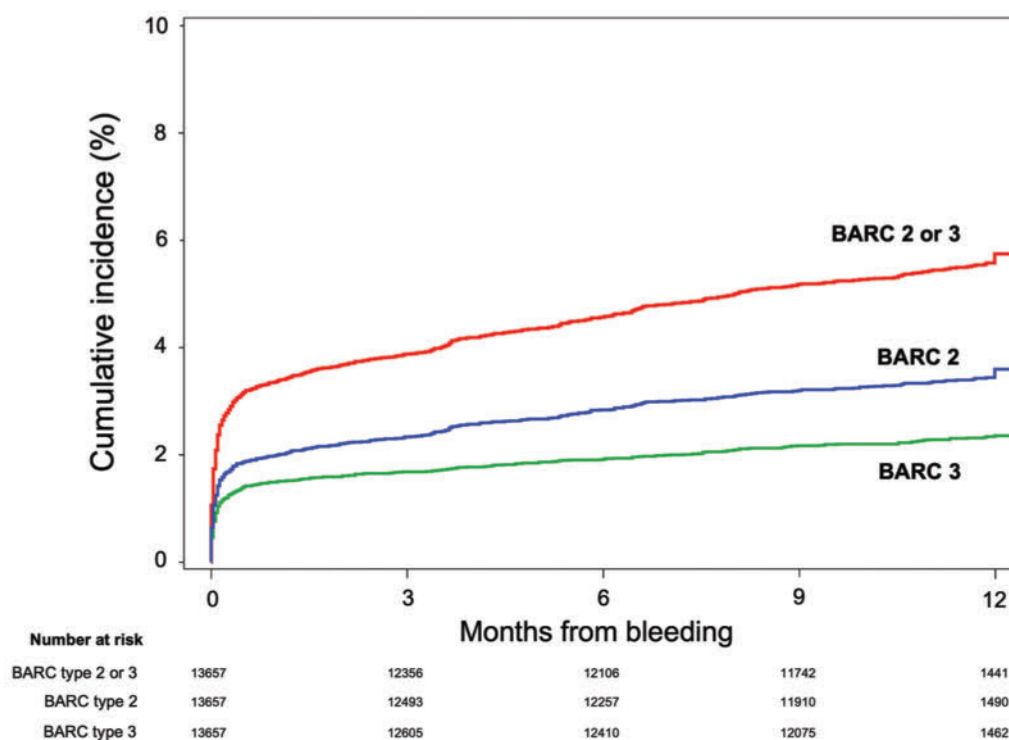


Fig. 1 Incidence of bleeding events based on the Bleeding Academic Research Consortium (BARC) classification.

Table 1 Patient characteristics

	Overall	BARC type 2 or 3 Bleeding (+)	BARC type 2 or 3 Bleeding (-)	p-value
	n = 13,657	n = 742	n = 12,915	
Age (year)	64.9 ± 12.7	69.6 ± 12.8	64.7 ± 12.7	<0.001
Female	3,163 (23.2)	240 (32.4)	2,923 (22.6)	<0.001
BMI (kg/m ²)	24.2 ± 3.5	23.3 ± 3.5	24.3 ± 3.5	<0.001
STEMI	7,523 (55.1)	449 (60.5)	7,074 (54.8)	0.002
Killip class ≥2	2,699 (19.8)	259 (35)	2,440 (19)	<0.001
Hypertension	7,537 (55.2)	448 (60.4)	7,089 (54.9)	0.004
Diabetes	3,978 (29.1)	233 (31.4)	3,745 (29)	0.162
Previous myocardial infarction	1,004 (9.8)	62 (10.7)	942 (9.8)	0.467
Previous PCI	1,372 (10.1)	82 (11.1)	1,290 (10)	0.349
Previous CABG	131 (1)	8 (1.1)	123 (1)	0.733
Previous cerebrovascular disease	998 (7.3)	82 (11.1)	916 (7.1)	<0.001
Atrial fibrillation	749 (5.7)	82 (11.4)	667 (5.4)	<0.001
eGFR (mL/min/1.73 m ²)	62.2 ± 27.8	54.5 ± 27	62.6 ± 27.8	<0.001
Haemoglobin (g/dL)	13.9 ± 2.1	12.9 ± 2.5	13.9 ± 2	<0.001
Peak CK (IU/L)	1,433.8 ± 2,456.7	2,180.5 ± 4,942.3	1,387.3 ± 2,203.4	<0.001
LVEF (%)	52.4 ± 11.4	48.6 ± 12.4	52.6 ± 11.3	<0.001
Medication during hospitalization				
Prasugrel				0.248
3.75 mg	2,637 (19.3)	144 (19.4)	2,493 (19.3)	
10 mg	542 (4)	38 (5.1)	504 (3.9)	
Ticagrelor	5,345 (39.2)	285 (38.4)	5,060 (39.2)	0.671
Clopidogrel	6,423 (47)	382 (51.5)	6,041 (46.8)	0.013
Aspirin	13,399 (98.1)	724 (97.6)	12,675 (98.1)	0.269
ACE inhibitors/ARBs	10,001 (73.2)	501 (67.5)	9,500 (73.6)	<0.001
Beta-blockers	9,803 (71.8)	493 (66.4)	9,310 (72.1)	<0.001
Oral anticoagulants	920 (6.7)	78 (10.5)	842 (6.5)	<0.001

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blocker; BARC, Bleeding Academic Research Consortium; BMI, body mass index; CABG, coronary artery bypass grafting; CK, creatinine kinase; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

Note: Data are presented as mean ± standard deviation, median [interquartile range], or number (percentage).

The baseline demographics of the patients with and without BARC type 2 or 3 bleeding are summarized in **Table 1**. Patients with bleeding were older, more likely to be female, and more frequently presented with ST-elevation myocardial infarction than those without; moreover, these patients had higher rates of hypertension, cerebrovascular disease, and atrial fibrillation. Compared with those without bleeding, patients with bleeding exhibited a lower BMI, eGFR, and LVEF; in contrast, peak creatine kinase (CK) levels were higher.

Regarding medication use, patients with bleeding were more likely to receive clopidogrel and oral anticoagulants than those without bleeding. In contrast, aspirin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers were less frequently used in patients with bleeding than in those without.

The procedural characteristics are shown in **Table 2**. Patients with bleeding were more likely to undergo procedures via radial

access and had a higher frequency of culprit lesions in the left main coronary artery compared with patients without. The use of glycoprotein IIb/IIIa inhibitors and mechanical circulatory support devices such as intra-aortic balloon pumping or venoarterial extracorporeal membrane oxygenation was also more common in patients with bleeding than in those without.

Bleeding and Mortality

Among the 13,657 patients included in the analysis, 890 died within 1 year. The cumulative all-cause mortality rates according to the BARC bleeding classification are shown in **Fig. 2**. The unadjusted and adjusted HRs for all-cause mortality according to BARC-defined bleeding are summarized in **Table 3**. Patients who experienced BARC type 2 or 3 bleeding had a significantly higher risk of all-cause death compared with those without (HR

Table 2 Procedure and angiographic characteristics

	Overall	BARC type 2 or 3 Bleeding (+)	BARC type 2 or 3 Bleeding (-)	p-value
	n = 13,657	n = 742	n = 12,915	
PCI	12,290 (92.7)	671 (93.3)	11,619 (92.7)	0.498
Puncture site				
Radial	6,426 (50.2)	415 (59.8)	6,011 (49.7)	<0.001
Femoral	6,306 (49.3)	272 (39.2)	6,034 (49.9)	
Brachial	67 (0.5)	7 (1)	60 (0.5)	
Culprit lesion				
LMT	328 (2.6)	33 (4.7)	295 (2.4)	<0.001
LAD	5,995 (46.5)	305 (43.3)	5,690 (46.7)	
LCX	2,223 (17.3)	105 (14.9)	2,118 (17.4)	
RCA	4,304 (33.4)	251 (35.6)	4,053 (33.3)	
Use of glycoprotein IIb/IIIa inhibitors	977 (11)	68 (14.4)	909 (10.8)	0.013
Thrombolysis	108 (0.8)	4 (0.6)	104 (0.8)	0.435
Use of IABP	578 (12.9)	93 (26.4)	485 (11.7)	<0.001
Use of V-A ECMO	183 (4.1)	58 (16.4)	125 (3.0)	<0.001
CABG during hospitalization	197 (4.4)	15 (4.3)	182 (4.4)	0.901

Abbreviations: BARC, Bleeding Academic Research Consortium; CABG, coronary artery bypass grafting; IABP, intra-aortic balloon pumping; LAD, left anterior descending artery; LCX, left circumflex artery; LMT, left main coronary artery; PCI, percutaneous coronary intervention; RCA, right coronary artery; V-A ECMO, venoarterial extracorporeal membrane oxygenation.

Note: Data are shown as number (percentage).

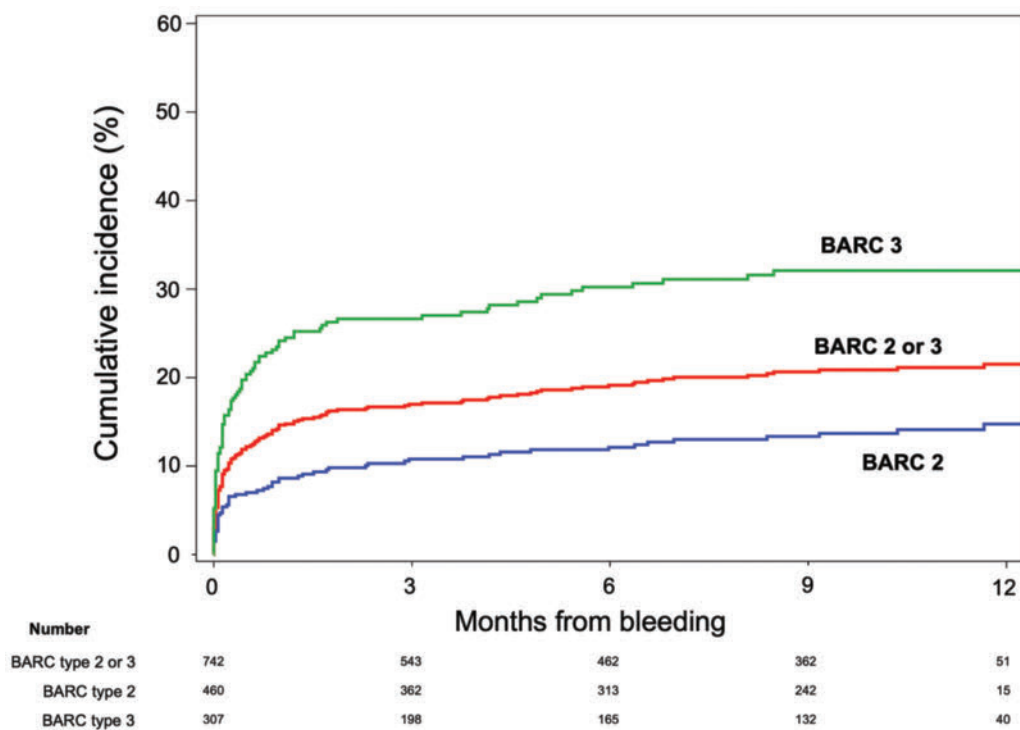
**Fig. 2** Cumulative mortality rate post-bleeding by the Bleeding Academic Research Consortium (BARC) classification.

Table 3 Impact of BARC bleeding events on all-cause mortality

	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)*	p-value
BARC type 2 or 3	4.1 (3.4–4.8)	<0.0001	1.9 (1.5–2.5)	<0.0001
BARC type 2	2.4 (1.9–3.1)	<0.0001	1.6 (1.2–2.3)	0.005
BARC type 3	6.4 (5.1–7.9)	<0.0001	1.9 (1.3–2.6)	<0.0001

Abbreviations: BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio.

*Variables for adjustment: age, sex, ST-elevation myocardial infarction, Killip class, atrial fibrillation, previous cerebrovascular disease, estimated glomerular filtration rate, peak creatinine kinase level, use of potent P2Y12 inhibitors, left main coronary artery culprit lesion, radial artery approach, and use of a mechanical circulatory support device, hypertension, body mass index, haemoglobin level, left ventricular ejection fraction, use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers, and use of β -blockers.

Table 4 Association of BARC bleeding and mortality according to time from bleeding

	HR (95% CI) for all-cause death		
	<30 days post-bleeding	30–89 days post-bleeding	≥90 days post-bleeding
BARC type 2 or 3	3.5 (2.7–4.4)	4.6 (2.9–7.3)	3.8 (2.5–5.6)
BARC type 2	2.1 (1.5–3.0)	3.1 (1.6–5.9)	2.7 (1.6–4.6)
BARC type 3	7.1 (5.5–9.1)	5.3 (2.7–10.4)	4.9 (2.9–8.4)

Abbreviations: BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio.

4.1, 95% CI 3.4–4.8; $p < 0.001$). After adjustment for baseline and procedural characteristics, BARC type 2 or 3 bleeding remained significantly associated with increased all-cause mortality (adjusted HR 1.9, 95% CI 1.5–2.5; $p < 0.001$). When analyzed separately, both type 2 and type 3 bleeding were significantly associated with higher mortality, with type 3 bleeding showing a greater hazard (BARC type 2: adjusted HR 1.6, 95% CI 1.2–2.3; BARC type 3: adjusted HR 1.9, 95% CI 1.3–2.6).

In a supplementary analysis including BARC type 5 bleeding events, the association between bleeding and all-cause mortality remained robust: patients with BARC type 2, 3, or 5 bleeding, as well as those with BARC type 3 or 5 bleeding, had a significantly higher adjusted risk of mortality compared with patients without bleeding (**Supplementary Table S3**, available in the online version only).

Table 4 details the associations between BARC-defined bleeding and all-cause mortality stratified by the time elapsed since the bleeding event. All bleeding types were significantly associated with increased mortality risk within 29 days, between 30 and 90 days, and beyond 90 days after the bleeding event.

We further investigated whether late-phase bleeding events (≥ 30 days after AMI onset) were associated with mortality. The unadjusted and adjusted HRs for all-cause mortality according to late-phase BARC-defined bleeding are summarized in **Supplementary Table S4** (available in the online version only). After adjustment, late-phase BARC type 2 or 3 bleeding events were significantly associated with increased risk of all-cause mortality (adjusted HR 3.9, 95% CI 2.2–6.8; $p < 0.001$). A similar pattern was observed when BARC type 2 and type 3

bleeding events were analyzed separately (BARC type 2: adjusted HR 3.6, 95% CI 1.6–8.3; BARC type 3: adjusted HR 3.0, 95% CI 1.5–6.2).

Determinants of Bleeding Events

The results of multivariate analysis of the factors associated with BARC type 2 or 3 bleeding are presented in **Table 5**. Significant determinants of these bleeding events included lower BMI, lower haemoglobin levels, higher peak CK levels, use of potent P2Y12 inhibitors, non-radial artery puncture (femoral or brachial artery puncture), and use of mechanical circulatory support devices.

Discussion

The major findings from this analysis of nationwide prospective AMI registries in Japan and South Korea are as follows: (1) bleeding events defined by the BARC system were significantly associated with an elevated risk of all-cause mortality; (2) the mortality risk was higher in patients with BARC type 3 bleeding than in those with BARC type 2 bleeding; and (3) after adjusting for potential confounders, BARC type 2 or 3 bleeding remained independently associated with an increased risk of mortality. This association was consistently observed when BARC type 2 and 3 bleeding events were analyzed separately. (4) Even when restricted to late-phase bleeding events (> 30 days after AMI admission), BARC-defined bleeding remained significantly associated with increased mortality. (5) BARC-defined bleeding events were associated with an increased risk of mortality not only in the acute phase (< 30 days

Table 5 Multivariate analysis of BARC type 2 or 3 bleeding events

	OR	95% CI		p-value
Age	1.008	0.998	1.019	0.127
Female	1.173	0.909	1.515	0.221
BMI	0.959	0.927	0.993	0.017
STEMI	0.968	0.775	1.211	0.779
Killip class II	1.166	0.914	1.486	0.217
Use of oral anticoagulants	1.392	0.903	2.145	0.135
Previous cerebrovascular disease	1.382	0.967	1.975	0.076
eGFR	0.997	0.992	1.002	0.204
Haemoglobin level	0.909	0.856	0.966	0.002
Higher peak CK (>509 IU/L)	1.279	1.032	1.584	0.024
Use of potent P2Y12 inhibitor	1.642	1.304	2.068	<0.0001
LMT culprit lesion	1.051	0.608	1.815	0.859
Non-radial artery puncture	2.315	1.853	2.891	<0.0001
Use of IABP or V-A ECMO	3.249	2.169	4.867	<0.0001
Use of glycoprotein IIb/IIIa	1.218	0.906	1.637	0.192

Abbreviations: BARC, Bleeding Academic Research Consortium; BMI, body mass index; CI, confidence interval; CK, creatinine kinase; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IABP, intra-aortic balloon pumping; LMT, left main coronary artery; STEMI, ST-elevation myocardial infarction; V-A ECMO, venoarterial extracorporeal membrane oxygenation.

after the bleeding event) but also in the chronic phase (≥ 90 days post-bleeding).

Prognostic Impact of BARC-defined Bleeding in East Asian versus Non-East Asian Populations

Previous studies conducted primarily in non-East Asian populations highlighted the prognostic implications of BARC-defined bleeding events. For instance, a pooled analysis of 12,459 patients from six randomized trials involving PCI demonstrated that BARC grade ≥ 2 was associated with a substantial increase in 1-year mortality (adjusted HR 2.72, 95% CI 2.03–3.63).⁹ Similarly, Vranckx et al found that BARC-defined bleeding independently predicted long-term mortality in patients with acute coronary syndrome (ACS), with mortality risk increasing progressively with higher BARC grades.⁸ Notably, this association was independent of the timing of the bleeding event (in-hospital or post-discharge). Another randomized trial, which included patients undergoing PCI with or without ACS, confirmed the mortality risk associated with BARC type 2, 3, and 5 bleeding. Importantly, BARC type 3 or 5 bleeding conferred a comparable mortality risk to bleeding events defined by Thrombolysis In Myocardial Infarction (TIMI) minor/major (HR 7.64, 95% CI 4.53–12.87) or Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) moderate/severe classifications (HR 7.36, 95% CI 4.38–12.34).¹⁰ Additionally, Hara et al demonstrated a significant association between BARC type 2, 3, or 5 bleeding and increased mortality in an all-comer PCI cohort (adjusted HR 5.97, 95% CI 4.76–7.49, $p < 0.001$).²¹

However, few studies have explored the prognostic effect of BARC-defined bleeding in East Asian populations. A nationwide cohort study using Taiwan's National Health Insurance Research Database found that BARC type 2, 3, or 5 bleeding events were

associated with increased all-cause mortality in patients with ACS and chronic coronary syndrome than in those without (HR 1.28, 95% CI 1.11–2.63, $p = 0.002$).²² However, this retrospective study had notable limitations, including its focus on a single country and the exclusion of patients not on dual antiplatelet therapy, those with prior bleeding events, and those receiving anticoagulant therapy. Furthermore, the study did not analyze the specific mortality risk of each BARC-defined bleeding type.

Clinical Relevance of BARC-defined Bleeding in East Asian AMI Patients

To our knowledge, this is among the largest prospective East Asian AMI cohorts evaluating BARC-defined bleeding, combining data from nationwide registries in Japan and South Korea. Using this large-scale dataset, the present study demonstrated that BARC-defined bleeding represents a significant clinical event associated with an increased mortality risk in East Asian populations. Importantly, this study also revealed that BARC-defined bleeding was an independent predictor of mortality, and the association remained consistent when each BARC type (2 or 3) was analyzed individually.

Mortality risk was higher in patients with BARC type 3 bleeding than in those with BARC type 2 bleeding. Considering that BARC type 5 bleeding is fatal, BARC-defined bleeding demonstrates a progressive increase in mortality risk with higher BARC grades (type 5 > type 3 > type 2). This observation aligns with those of previous studies conducted predominantly in non-East Asian populations,^{8,10,21} underscoring the utility of the BARC classification as a bleeding endpoint in clinical research. A particularly noteworthy result of this study is that BARC type 2 bleeding, often considered a relatively mild event, was independently associated with an increased mortality risk (adjusted HR 1.6, 95% CI 1.2–2.3). Similar associations between BARC type 2 bleeding and mortality

have been previously reported.^{8,21} These findings suggest that including BARC type 2 bleeding, in addition to types 3 and 5, as an endpoint in clinical trials may provide a more comprehensive assessment of patient risk.

In addition, our study extends previous evidence by providing temporal insights into the prognostic impact of bleeding. Even when restricted to late-phase bleeding events (>30 days after AMI admission), BARC-defined bleeding continued to show a strong association with subsequent mortality. This highlights that bleeding complications occurring well beyond the acute hospitalization phase still carry important prognostic implications. Furthermore, we demonstrated that the excess mortality risk associated with BARC-defined bleeding was not limited in the acute phase (<30 days after the bleeding event) but persistent into the chronic phase (≥90 days post-bleeding). This underscores the importance of continued careful monitoring and proactive secondary prevention strategies long after index AMI admission, particularly in East Asian patients who are inherently at higher bleeding risk.

Given the strong association between BARC-defined bleeding and increased mortality, identifying patients at high risk of bleeding is critical. This study identified several determinants of BARC type 2 or 3 bleeding, including lower BMI, lower haemoglobin levels, higher peak CK levels, use of potent P2Y12 inhibitors, non-radial artery puncture, and use of mechanical circulatory support devices. These findings were consistent with those of previous studies.^{23–26} For patients with these high bleeding risk characteristics, implementing strategies to minimize bleeding risk is particularly important in East Asian populations, who may have a greater susceptibility to bleeding events during antithrombotic therapy.¹⁵ These strategies may include individualized antithrombotic regimens, optimal procedural techniques to reduce access-site complications, and close monitoring of bleeding parameters.

Limitations

This study had some limitations. First, this study did not include data based on bleeding criteria other than the BARC, preventing direct comparison of the impact on mortality with other criteria, such as the TIMI bleeding criteria. Second, the associations between mortality and BARC type 1 (bleeding that is not actionable) and BARC type 4 bleeding (CABG-related bleeding) were not analyzed, as these data were not available in this study. Therefore, further studies are warranted to clarify the relationship between bleeding events and mortality rates in East Asian populations. Third, although multivariate analyses were performed to assess the association between BARC-defined bleeding events and mortality, the possibility of residual or unmeasured confounding factors could not be excluded. Fourth, in the analysis of predictors for BARC type 2 or 3 bleeding, the variable ‘non-radial approach’ yielded inconsistent results between the unadjusted and multivariate models. In the unadjusted analysis, the non-radial approach was less common in patients with bleeding events than in those without. However, after adjusting for the patient characteristics, it emerged as an independent predictor of bleeding. This apparent contradiction may reflect a clinical tendency to preferentially select the radial approach for patients considered to have a higher bleeding risk in an effort to minimize bleeding complications. Fifth, although our study utilized large-scale nationwide registries from Japan and

South Korea, it did not allow a direct comparison with Western cohorts. Further studies are needed to address this gap. Sixth, in this analysis, Cox regression was used to assess the association between BARC-defined bleeding and all-cause mortality. However, this approach may not fully account for competing risks, such as non-bleeding deaths or other cardiovascular events. Future studies incorporating multi-state modeling could provide more comprehensive insights into the complex relationships among bleeding, competing events, and mortality. Finally, as this study was conducted using registry data from patients with AMI, further validation is necessary to determine the generalizability of these findings to patients with stable coronary artery disease.

Conclusion

In East Asian patients with AMI, bleeding events defined by the BARC system are significantly associated with an increased risk of subsequent mortality. These findings underscore the relevance of incorporating the BARC classification into clinical trials targeting AMI populations in East Asia to enhance the evaluation of bleeding-related outcomes.

What is known about this topic?

- The Bleeding Academic Research Consortium (BARC) classification was proposed by consensus to standardize bleeding endpoint definitions.
- However, its prognostic value has not been fully validated in East Asian patients with acute myocardial infarction (AMI).

What does this paper add?

- In an analysis of nationwide prospective AMI registries from Japan and South Korea, BARC type 2 or 3 bleeding was independently associated with an increased risk of mortality, even after adjustment for potential confounders.
 - This association remained consistent when BARC type 2 and 3 bleeding events were analyzed separately.
 - Even when restricted to late-phase bleeding events (>30 days after AMI admission), BARC-defined bleeding remained significantly associated with increased mortality.
 - BARC-defined bleeding events were associated with an increased risk of mortality not only in the acute phase (<30 days after the bleeding event) but also in the chronic phase (≥90 days post-bleeding).
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Statements and Additional Information

Conflict of Interest S.Y. reports remuneration for lectures from Takeda, Daiichi Sankyo, and Bristol-Myers Squibb, and trust research/joint research funds from Takeda and Daiichi Sankyo. M.T. reports lecture fees from Daiichi Sankyo. H.O. reports lecture fees and research grants from Abbot Medical Japan, Bayer, Daiichi Sankyo, Eisai, Kowa, Takeda Pharmaceutical, and Teijin. K.H.C. reports lecture fees from Amgen, Sanofi Aventis, and Viatrix. The authors declare no conflicts of interest.

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