

Practical Assessment of the Tradeoff between Fatal Bleeding and Coronary Thrombotic Risks using the Academic Research Consortium for High Bleeding Risk Criteria

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Aims: We aimed to establish a practical method for the assessment of tradeoff between thrombotic and bleeding risks.

Methods: We aimed to investigate the balance between bleeding risk and coronary thrombotic risk according to the number of the Academic Research Consortium for high bleeding risk (ARC-HBR) criteria in the multicenter prospective ST/non-ST elevation myocardial infarction (STEMI/NSTEMI) registry (N=12,093). Patients were divided as follows by the number of ARC-HBR criteria fulfilled: group 0, 0 major with ≤ 1 minor (N=6,792); group 1, 1 major with 0 minor (N=1,705); group 2, 0 major with ≥ 2 minors (N=790); group 3, 1 major with ≥ 1 minor (N=1,709); group 4, 2 majors with ≥ 0 minors (N=861); and group 5, ≥ 3 majors with ≥ 0 minor (N=236). We assessed the acute-phase absolute risk differences between bleeding and coronary thrombotic events in each group.

Results: At 7-day follow-up, all patients (groups 0–5) had a higher risk of major bleeding than that of any myocardial infarction (MI). Patients at ARC-HBR (groups 1–5) had a balanced risk between fatal MI and fatal bleeding, whereas patients at non-ARC-HBR (group 0) had a higher risk of fatal MI than that of fatal bleeding.

Conclusions: All STEMI/NSTEMI patients have a relatively high risk of major bleeding as compared with the risk of any MI in the acute phase. The ARC-HBR criteria would be a practical tool for assessing the tradeoff between fatal bleeding and fatal MI risks. This practical assessment would be helpful for the optimal decision-making of appropriate treatment strategy considering the balance between bleeding and coronary thrombotic risks.

Clinical Trial Registration UMIN000004575

Key words: Academic Research Consortium, High bleeding risk, Myocardial infarction, Thrombotic risk, Tradeoff

Introduction

The Academic Research Consortium (ARC)

recently proposed the new practical definition of patients at a high bleeding risk (HBR)¹. This ARC-HBR criteria has been validated in Japan, Europe, and

the USA²⁻⁷). The ARC-HBR patients accounted for 43.8% in the Japanese prospective ST/non-ST elevation myocardial infarction (STEMI/NSTEMI) registry⁷). The risk of fatal bleeding event significantly increased as the number of the ARC-HBR criteria increased. It is likely that the same goes for thrombotic events, as similar factors are associated with both thrombotic and bleeding events⁸). Although bleeding risk is currently discussed intensively in the interventional field, thrombotic events remain to be an important concern of interventional cardiologists. In our daily clinical practice, a treatment strategy should be developed based on the balance between thrombotic and bleeding risks in each case. However, few studies focused on the tradeoff between them. Non-HBR patients may have a higher ischemic risk rather than bleeding risk, whereas patients with multiple HBR criteria would have a higher bleeding risk rather than ischemic risk. The border line between a high-thrombotic-risk subset and a high-bleeding-risk subset should exist in the in-between stratification. Precise assessment of the balance between thrombotic and bleeding risks is of paramount importance, and a practical assessment methodology should be established.

Aim

We aimed to investigate the tradeoff between bleeding risk and coronary thrombotic risk according to the number of ARC-HBR criteria fulfilled in the large-scale STEMI/NSTEMI registry.

Methods

Study Population

We applied the ARC-HBR criteria to the Osaka Acute Coronary Insufficiency Study (OACIS) database (N = 12,093). The OACIS is a prospective, multicenter observational study designed to collect and analyze demographic, procedural, and outcome data from patients with STEMI/NSTEMI at 25 collaborating hospitals with cardiac emergency units. Written informed consent was obtained from each patient. Myocardial infarction (MI) was diagnosed based on the World Health Organization's criteria, which requires at least two of the following three criteria to be met: (1) clinical history of central chest pressure, pain, or tightness lasting >30 min, (2) ST segment

elevation >0.1 mV in at least one standard lead, and (3) a rise in serum creatinine phosphokinase concentration to more than twice the normal laboratory value. All collaborating hospitals were encouraged to enroll consecutive patients with STEMI/NSTEMI. We prospectively collected data obtained by research cardiologists and trained research nurses using a specific reporting form. The OACIS enrolled patients from 1998 to 2014 and followed them up until 2019. The study was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) in Japan (ID: UMIN000004575). The study protocol complied with the Declaration of Helsinki and was approved by the Ethical Review Board of Osaka University Hospital (reference number: 14360) as well as the institutional ethics committee of each participating institution. Details of the study design and data collection are described elsewhere⁷).

The ARC-HBR Criteria

The ARC-HBR criteria have been reported elsewhere¹). In the original definition, patients are categorized to be at HBR if at least one major or two minor criteria are met. Since we retrospectively applied the recently proposed criteria to the registry data, data of several major and minor criteria were not available⁷). The following variables were not collected in the OACIS registry: 1) prior bleeding and transfusion, 2) chronic bleeding diathesis, 3) planned major noncardiac surgery following PCI, 4) PCI after recent major surgery or trauma, and 5) long-term use of oral nonsteroidal anti-inflammatory drugs or steroids. In addition, definitions of the following criteria were not exactly the same as the original ones: 1) "liver cirrhosis with portal hypertension" was replaced by a history of liver disease, 2) "active malignancy within the past 12 months" was replaced by a history of cancer, and 3) "previous ischemic stroke or intracerebral hemorrhage" was substituted by a history of cerebrovascular disease as a major criterion. In this study, we divided all patients, based on the patients' data on hospital admission, into six groups according to the number of the ARC-HBR major and minor criteria fulfilled (**Fig. 1**): group 0, 0 major with ≤ 1 minor; group 1, 1 major with 0 minor; group 2, 0 major with ≥ 2 minors; group 3, 1 major with ≥ 1 minor; group 4, 2 majors with ≥ 0 minors; and group 5, ≥ 3 majors with ≥ 0 minor.

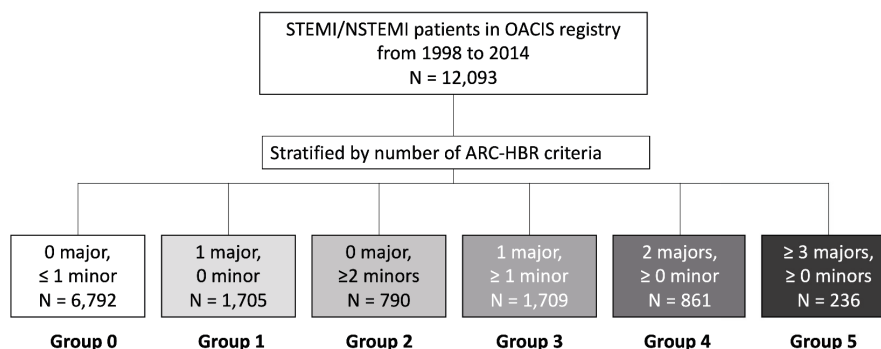


Fig. 1. Patient flowchart

Abbreviations: ARC-HBR, Academic Research Consortium for High Bleeding Risk.

Study Endpoints

The bleeding endpoints of the present study are major bleeding and fatal bleeding. Major bleeding in the OACIS registry is defined as bleeding event fulfilling at least one of the following: 1) hemoglobin drop ≥ 4 g/dL, 2) intracranial hemorrhage, 3) requirement of surgical treatment, or 4) requirement of any transfusion. Fatal bleeding is defined as probable fatal bleeding or definite fatal bleeding (overt or autopsy or imaging confirmation)⁹⁾. The coronary thrombotic endpoints are any MI and fatal MI. Any MI is defined as recurrence of MI regardless of lesion derived from the first culprit site¹⁰⁾. The criteria for diagnosis of the recurrent MI are identical to those used at the time of registration. Fatal MI is defined as recurrent MI that occurred after index hospitalization and resulted in death.

The collection of major bleeding data was started from 2003. Note that major bleeding data was collected only at 7 days follow-up but not thereafter. Clinical data on the bleeding event after hospital discharge was not specifically collected in this registry. However, data on the cause of death was prospectively collected, which enabled the analysis of fatal bleeding in the chronic phase (data on the cause of death was accessible in 1,453 deaths (86%) out of 1,923 all-cause deaths). The MI data was collected during the entire study period (1998–2019). Information on clinical events was collected by local investigators when visiting outpatient clinics or through verbal or written contact with patients or family members.

The primary analysis involved the comparison of bleeding events and coronary thrombotic events at 7 days (acute phase). We compared major bleeding vs. any MI and fatal bleeding vs. fatal MI in this acute phase. The secondary analysis involved the comparison after hospital discharge up to 5 years. In this chronic phase, we compared fatal bleeding vs. any MI/fatal MI.

PCI Procedure and Post-PCI Medication

PCI treatment strategies, including thrombectomy, pre-dilatation, atherectomy, post-dilatation, use of intracoronary imaging, and use of cardiocirculatory support devices, were decided at the operators' discretion. The operators followed the basic instructions for use in terms of pre-dilatation, device sizing and implantation, post-dilatation, and other PCI procedures. Post PCI medications were prescribed at the discretion of the attending physicians. The physicians were encouraged to follow the standard guideline for the treatment of MI¹¹⁾.

Statistical Analysis

All analyses were conducted using the SPSS 26.0 software (IBM Corporation, Armonk, NY) or the R software (version 4.0.5; R Foundation for Statistical Computing, Vienna, Austria). A *P*-value of <0.05 was considered statistically significant. Data are presented with list-wise deletion. Categorical variables are expressed as counts (percentages) and compared using the chi-squared test. Continuous variables are expressed as median (interquartile range) and compared using analysis of variance and Kruskal–Wallis test as appropriate. Pre- and in-hospital patient information and clinical outcomes were compared according to the groups. A trend test was conducted using the Cochran–Armitage trend test. As a primary analysis, we computed the absolute risk differences between major bleeding vs. any MI and those between fatal bleeding vs. fatal MI at 7 days in each group. As a secondary analysis, post-discharge clinical outcomes of fatal bleeding, any MI, and fatal MI were evaluated using cumulative incidence function approach and compared using Gray's test, considering all-cause death as a competing risk. The annual absolute risk differences after discharge were computed up to 5 years follow-up.

Results

Study Subjects

A total of 12,093 patients (66 ± 12 years, 9,096 males) were enrolled between 1998 and 2014 from 25 institutions. ARC-HBR patients accounted for 43.8% ($N=5,301$) of the whole population. The prevalence of the individual components of the HBR criteria is summarized in **Supplemental Fig. 1**⁷⁾. Oral anticoagulation was the most frequent major criterion in the ARC-HBR criteria. The patients were divided into six groups according to the number of ARC-HBR criteria fulfilled: group 0 ($N=6,792$), group 1 ($N=1,705$), group 2 ($N=790$), group 3 ($N=1,709$), group 4 ($N=861$), and group 5 ($N=236$) (**Fig. 1**).

Patient Characteristics

The baseline characteristics of the patients stratified by the groups are presented in **Table 1**. The patients in group 5 (the highest risk group) were older, more likely to be female, and had a higher prevalence of chronic kidney disease, peripheral vascular disease, and cancer as well as a lower frequency of ST elevation and abnormal Q wave on electrocardiogram than the other groups. Patients with single criterion (groups 0 and 1) were significantly younger than those with multiple criteria (groups 2–5). The procedural characteristics are presented in **Table 2**. Primary PCI within 24 h of hospital admission was less frequently performed in group 5. A circulatory assist device (percutaneous cardiopulmonary support or intra-aortic balloon pumping) was more frequently used in group 5. As to the medication at hospital discharge (**Supplemental Table 1**), ACEi (angiotensin-converting enzyme inhibitors) or ARB (angiotensin II receptor blockers), statins, and antiplatelets were less frequently prescribed, and beta blockers were more frequently used in group 5 than in the other groups.

Clinical Outcomes

The median follow-up duration was 4.84 [interquartile range: 1.35, 5.01] years. The clinical outcomes in the acute phase (7 days and in-hospital) and chronic phase (after hospital discharge) are summarized in **Table 3**. Major bleeding and any MI occurred at 7 days in 382 of 7,821 patients (4.9%) and 239 of 12,093 (2.0%) patients, respectively. Fatal bleeding and fatal MI occurred at 7 days in 35 of 12,093 patients (0.3%) and 55 of 12,093 patients (0.5%), respectively. Majority of the bleeding events occurred in the acute phase. Intracranial bleeding (29%) was found to be the most frequent (**Supplemental Fig. 2**). The bleeding event rates increased as the bleeding criteria increased (P -value for

trend < 0.05), whereas the rates of any MI did not. The fatal MI rate after hospital discharge increased as the HBR criteria increased. The absolute risk differences are presented in **Fig. 2** and **Fig. 3**. Patients in all groups had a higher risk of major bleeding than of any MI (**Fig. 2**). Non-ARC-HBR (group 0) patients had a higher risk of fatal MI than of fatal bleeding (**Fig. 3**). ARC-HBR patients had a balanced risk between fatal bleeding and fatal MI.

As to the outcomes after hospital discharge ($N=11,081$; patients who survived to discharge), fatal bleeding occurred in 41 patients (0.4%) during the entire follow-up period. Any MI and fatal MI occurred in 511 patients (4.6%) and 61 patients (0.6%), respectively. Cumulative incidence of the study endpoints after hospital discharge stratified by the groups is presented in **Fig. 4**. The incidence of any MI did not differ by the groups (Gray's test $P=0.993$), whereas the rates of fatal MI were different by the groups (Gray's test $P=0.003$). Fatal bleeding was clearly stratified by the groups (P for trend=0.0011) (**Fig. 4**). Temporal changes in the absolute risk differences between fatal bleeding and any MI and those between fatal bleeding and fatal MI up to 5 years are summarized in **Supplemental Fig. 3** and **Supplemental Fig. 4**, respectively. When comparing fatal bleeding with any MI (**Supplemental Fig. 3**), any MI risk generally exceeded fatal bleeding risk in all groups both at short-term (1 year) and long-term (5 years) follow-ups. When comparing fatal bleeding with fatal MI (**Supplemental Fig. 4**), both risks were generally counterbalanced up to 5 years in all groups.

Discussion

The present real-world prospective STEMI/NSTEMI data provided the following findings: 1) In the acute phase, the patients in all groups had a higher risk of major bleeding than of any MI at 7 days; non-ARC-HBR (group 0) patients had a higher risk of fatal MI than of fatal bleeding, whereas ARC-HBR patients had a balanced risk between fatal bleeding and fatal MI. 2) In the chronic phase, when fatal bleeding was compared with any MI, any MI risk generally exceeded fatal bleeding risk in all groups up to 5 years follow-up; when fatal bleeding was compared with fatal MI, both risks were generally counterbalanced up to 5 years in all groups.

The ARC-HBR consensus paper, numerous randomized controlled trials assessing the safety of the ultra-short dual antiplatelet therapy (DAPT) strategy, and clinical data of the new technology of drug-coated stent have led many physicians to pay more careful attention to the risk assessment of bleeding events

Table 1. Patient characteristics

	Group 0	Group 1	Group 2	Group 3	Group 4	Group 5	P value	Data missing (%)
	0 major, ≤ 1 minor	1 major, 0 minor	0 major, ≥ 2 minors	1 major, ≥ 1 minor	2 majors, ≥ 0 minor	≥ 3 majors, ≥ 0 minors		
Patient number	6792	1705	790	1709	861	236		
Number of ARC-HBR major criteria								
0	6792 (100.0)	0 (0.0)	790 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)		
1	0 (0.0)	1705 (100.0)	0 (0.0)	1709 (100.0)	0 (0.0)	0 (0.0)		
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	861 (100.0)	0 (0.0)		
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	196 (83.1)		
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	38 (16.1)		
5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)		
Number of ARC-HBR minor criteria								
0	4613 (67.9)	1705 (100.0)	0 (0.0)	0 (0.0)	312 (36.2)	72 (30.5)		
1	2179 (32.1)	0 (0.0)	0 (0.0)	1126 (65.9)	364 (42.3)	120 (50.8)		
2	0 (0.0)	0 (0.0)	675 (85.4)	502 (29.4)	162 (18.8)	38 (16.1)		
3	0 (0.0)	0 (0.0)	115 (14.6)	81 (4.7)	23 (2.7)	6 (2.5)		
Age (years)	63.0 [56.0, 71.0]	63.0 [56.0, 69.0]	79.0 [76.0, 84.0]	77.0 [70.0, 82.0]	74.0 [67.0, 80.0]	77.0 [69.0, 82.0]	<0.001	0
Male sex	5369 (79.1)	1388 (81.4)	507 (64.2)	1108 (64.8)	570 (66.2)	154 (65.3)	<0.001	0
Body mass index (kg/m ²)	23.78 [21.72, 26.02]	23.63 [21.79, 25.92]	22.64 [20.31, 24.77]	22.83 [20.54, 24.97]	22.82 [20.58, 24.81]	22.22 [19.92, 24.51]	<0.001	6.4
Diabetes mellitus	2169 (33.0)	594 (35.9)	217 (29.1)	555 (33.7)	370 (44.5)	104 (44.4)	<0.001	3.3
Hypertension	3690 (56.5)	928 (56.1)	512 (68.2)	1179 (71.8)	646 (77.6)	187 (80.6)	<0.001	3.7
Dyslipidemia	3040 (47.1)	724 (44.4)	277 (37.5)	593 (36.8)	304 (37.1)	79 (34.8)	<0.001	5.1
Smoking	4600 (69.3)	1166 (69.7)	338 (45.4)	776 (48.3)	399 (48.6)	93 (42.9)	<0.001	3.3
Chronic kidney disease	282 (4.3)	132 (7.9)	31 (4.3)	184 (11.1)	180 (21.2)	97 (41.3)	<0.001	3.6
Prior myocardial infarction	674 (10.2)	223 (13.5)	117 (15.3)	226 (13.6)	130 (15.4)	30 (13.0)	<0.001	2.8
Peripheral vascular disease	96 (1.5)	42 (2.5)	27 (3.7)	76 (4.6)	38 (4.5)	25 (10.6)	<0.001	3.6
Cancer	0 (0.0)	161 (9.6)	0 (0.0)	229 (13.8)	198 (23.3)	109 (46.4)	<0.001	3.6
Cerebrovascular disease	0 (0.0)	270 (16.2)	0 (0.0)	380 (22.9)	354 (41.6)	136 (57.9)	<0.001	3.6
Status on admission								
ST elevation on ECG	5738 (86.1)	1427 (85.3)	647 (83.5)	1374 (82.5)	686 (82.4)	178 (77.4)	<0.001	2.1
Abnormal Q wave on ECG	2975 (45.9)	831 (50.4)	363 (47.0)	788 (48.0)	383 (45.9)	94 (40.9)	0.009	4
SBP on admission (mmHg)	138.0 [119.0, 158.0]	140.0 [120.0, 160.0]	130.0 [110.0, 152.0]	130.0 [110.0, 150.0]	132.0 [110.0, 152.0]	122.0 [105.50, 146.0]	<0.001	33
DBP on admission (mmHg)	81.0 [70.0, 95.0]	82.0 [70.0, 97.0]	75.0 [62.0, 87.0]	76.0 [62.0, 88.0]	76.0 [60.0, 89.0]	70.0 [58.0, 82.0]	<0.001	34.7
HR on admission (beats per minute)	78.0 [65.0, 90.0]	79.0 [66.0, 92.0]	78.0 [63.0, 91.0]	78.0 [64.0, 95.50]	82.0 [66.0, 98.0]	80.0 [64.0, 101.25]	<0.001	33
Time from symptom onset to coronary angiography (h)	4.00 [2.00, 11.97]	4.50 [2.33, 12.00]	4.00 [2.00, 11.00]	4.50 [2.20, 12.00]	5.00 [2.20, 12.50]	4.50 [2.50, 11.38]	0.105	19.7
Killip class III or IV	516 (7.6)	146 (8.6)	150 (19.0)	342 (20.0)	195 (22.6)	67 (28.4)	<0.001	0
Hemoglobin (g/dL)	14.60 [13.60, 15.70]	14.50 [13.50, 15.60]	12.50 [11.70, 13.40]	12.50 [11.20, 14.00]	11.20 [9.90, 13.60]	10.10 [9.15, 10.90]	<0.001	52
Creatinine (mg/dL)	0.80 [0.70, 0.97]	0.79 [0.66, 0.90]	1.01 [0.89, 1.20]	1.09 [0.82, 1.32]	1.20 [0.85, 2.05]	1.80 [1.11, 3.09]	<0.001	30.4
Enrolment period (year)							<0.001	0
1998–2003	3385 (49.8)	994 (58.3)	142 (18.0)	473 (27.7)	212 (24.6)	18 (7.6)		
2004–2009	2134 (31.4)	502 (29.4)	396 (50.1)	786 (46.0)	375 (43.6)	121 (51.3)		
2010–2014	1273 (18.7)	209 (12.3)	252 (31.9)	450 (26.3)	274 (31.8)	97 (41.1)		
Follow-up duration (day)	1808.0 [802.0, 1831.0]	1809.0 [1008.0, 1829.0]	1093.5 [104.5, 1822.0]	1089.0 [114.0, 1821.0]	901.0 [93.0, 1816.0]	433.0 [70.0, 1544.75]	<0.001	0

Data with list-wise deletion are expressed as median

[interquartile range] or number (percentage). Abbreviations: ECG, electrocardiogram; CAG, coronary angiography; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TIMI, thrombolysis in myocardial infarction; PCI, percutaneous coronary intervention; PCPS, percutaneous cardiopulmonary support; IABP, intra-aortic balloon pumping; CK, creatine kinase; CK-MB, creatine kinase myocardial band; ACEi, Angiotensin-converting-enzyme inhibitors; ARB, Angiotensin II receptor blockers.

Table 2. Procedural characteristics

	Group 0	Group 1	Group 2	Group 3	Group 4	Group 5	P value	Data missing (%)
	0 major, ≤ 1 minor	1 major, 0 minor	0 major, ≥ 2 minors	1 major, ≥ 1 minor	2 majors, ≥ 0 minor	≥ 3 majors, ≥ 0 minors		
Number	6792	1705	790	1709	861	236		
Primary PCI performed within 24 h of hospital admission	5835 (85.9)	1375 (80.6)	666 (84.3)	1388 (81.2)	641 (74.4)	174 (73.7)	<0.001	0
Target vessel								
Left anterior descending artery	2992 (47.8)	834 (53.3)	292 (42.0)	701 (45.7)	341 (45.5)	95 (45.7)	<0.001	8.9
Left circumflex artery	975 (15.6)	230 (14.7)	111 (15.9)	250 (16.3)	120 (16.0)	48 (23.1)	0.067	8.9
Right coronary artery	2212 (35.3)	501 (32.0)	272 (39.1)	568 (37.1)	277 (36.9)	74 (35.6)	0.012	8.9
Left main trunk	129 (2.1)	34 (2.2)	36 (5.2)	68 (4.4)	39 (5.2)	10 (4.8)	<0.001	8.9
Collateral blood flow (+)	2163 (34.1)	537 (34.2)	219 (30.6)	433 (28.2)	212 (28.2)	62 (31.2)	<0.001	8.1
Stenting performed	4125 (60.7)	803 (47.1)	574 (72.7)	1091 (63.8)	484 (56.2)	137 (58.1)	<0.001	0
PCPS use	232 (3.4)	38 (2.2)	60 (7.6)	105 (6.1)	66 (7.7)	19 (8.1)	<0.001	0
IABP use	1153 (17.0)	367 (21.5)	197 (24.9)	463 (27.1)	239 (27.8)	80 (33.9)	<0.001	0
Peak CK	1956.50 [919.0, 3826.25]	2115.0 [958.0, 4213.0]	1917.50 [958.50, 3740.0]	1978.0 [901.0, 3766.0]	1528.0 [702.0, 3383.0]	1427.0 [727.0, 3064.50]	<0.001	6
Peak CK-MB	173.0 [80.0, 332.75]	180.0 [84.0, 356.48]	172.0 [84.0, 353.65]	176.0 [81.0, 363.0]	150.0 [64.0, 318.0]	138.35 [75.0, 292.25]	0.001	14
TIMI grade 3 post PCI	4575 (91.7)	931 (88.2)	620 (90.4)	1174 (88.7)	523 (86.0)	154 (89.5)	<0.001	27
TIMI grade 0/1 post PCI	141 (2.8)	44 (4.2)	23 (3.4)	57 (4.3)	26 (4.3)	7 (4.1)	0.036	27

Data with list-wise deletion are expressed as median [interquartile range] or number (percentage). Abbreviations: PCI, percutaneous coronary intervention; PCPS, percutaneous cardiopulmonary support; IABP, intra-aortic balloon pumping; CK, creatine kinase; CK-MB, creatine kinase myocardial band; TIMI, thrombolysis in myocardial infarction.

Table 3. Clinical outcomes

	Group 0	Group 1	Group 2	Group 3	Group 4	Group 5	P value [§]	P-value for trend [†]
	0 major, ≤ 1 minor	1 major, 0 minor	0 major, ≥ 2 minors	1 major, ≥ 1 minor	2 majors, ≥ 0 minor	≥ 3 majors, ≥ 0 minors		
Patient number	6792	1705	790	1709	861	236		
Outcomes at 7 days								
Any myocardial infarction	140 (2.1)	31 (1.8)	13 (1.7)	33 (1.9)	18 (2.1)	4 (1.7)	0.953	0.667
Fatal myocardial infarction	34 (0.5)	2 (0.1)	6 (0.8)	7 (0.4)	5 (0.6)	1 (0.4)	0.251	0.948
Major bleeding*	103/3935 (1.5)	34/842 (2.0)	59/727 (7.5)	108/1403 (6.3)	63/690 (7.3)	27/224 (11.4)	<0.001	<0.001
Fatal bleeding	16 (0.2)	1 (0.1)	4 (0.5)	9 (0.5)	3 (0.3)	2 (0.8)	0.049	0.019
In-hospital outcomes								
Any myocardial infarction	164 (2.4)	49 (2.9)	18 (2.3)	40 (2.3)	28 (3.3)	8 (3.4)	0.529	0.303
Fatal myocardial infarction	42 (0.6)	7 (0.4)	7 (0.9)	9 (0.5)	7 (0.8)	2 (0.8)	0.683	0.619
Fatal bleeding	36 (0.5)	8 (0.5)	10 (1.3)	18 (1.1)	9 (1.0)	4 (1.7)	0.008	<0.001
Outcomes after discharge up to 5 years								
Any myocardial infarction	299 (4.4)	85 (5.0)	27 (3.4)	63 (3.7)	30 (3.5)	7 (3.0)	0.183	0.036
Fatal myocardial infarction	25 (0.4)	8 (0.5)	4 (0.5)	13 (0.8)	9 (1.0)	2 (0.8)	0.066	0.002
Fatal bleeding	9 (0.1)	8 (0.5)	2 (0.3)	12 (0.8)	7 (1.0)	3 (1.5)	<0.001	<0.001
5-year mortality								
All-cause death	737 (10.9)	192 (11.3)	199 (25.2)	455 (26.6)	254 (29.5)	86 (36.4)	<0.001	<0.001
Cardiac death	419 (6.2)	81 (4.8)	101 (12.8)	206 (12.1)	110 (12.8)	35 (14.8)	<0.001	<0.001
Non-cardiac death	230 (3.4)	77 (4.5)	68 (8.6)	183 (10.7)	104 (12.1)	39 (16.5)	<0.001	<0.001
Death from unknown cause	88 (1.3)	34 (2.0)	30 (3.8)	66 (3.9)	40 (4.6)	12 (5.1)	<0.001	<0.001

Data are expressed as number (percentage). *Major bleeding data was available only at 7-day follow-up in the OACIS registry. The data is collected only in patients who were enrolled between 2003 to 2014 (N=7,821). [§]P value for Chi square test. [†]P value for Cochran-Armitage trend test.

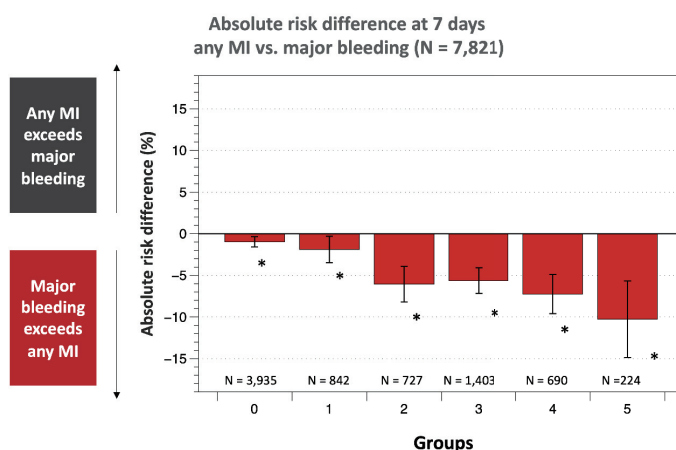


Fig. 2. Absolute risk difference between major bleeding and any myocardial infarction at 7 days

The absolute risk differences between major bleeding and any MI in each group at 7 days are presented as bar graphs. The availability of major bleeding data was limited to the cohort enrolled from 2003 to 2014 (N=7,821). Patients in all groups had a higher risk of major bleeding than of any MI. The error bar shows 95% confidence interval. *indicates statistically significant absolute risk difference. Abbreviations: MI, myocardial infarction.

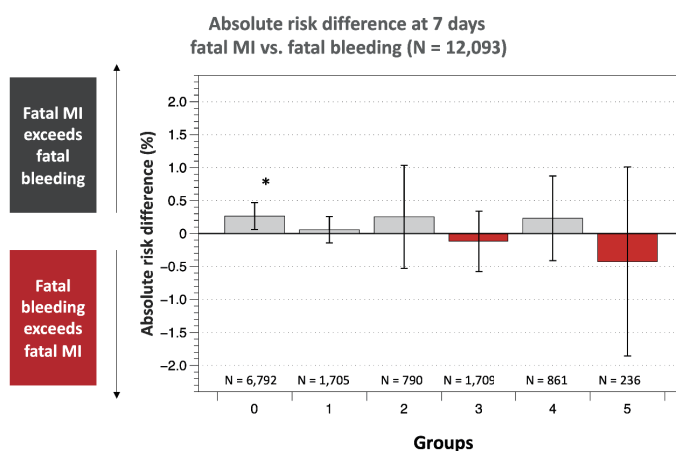


Fig. 3. Absolute risk difference between fatal bleeding and fatal myocardial infarction at 7 days

The absolute risk differences between fatal bleeding and fatal MI in each group at 7 days are presented as bar graphs. Non-ARC-HBR (group 0) patients had a higher risk of fatal MI than of fatal bleeding. ARC-HBR (group 1–5) patients had a balanced risk between fatal bleeding and fatal MI. Error bar shows 95% confidence interval. *indicates statistically significant absolute risk difference. Abbreviations: MI, myocardial infarction.

than they used to^{1, 12-14}). Nevertheless, we must keep in mind the enhanced thrombogenic property of MI lesions. Accurate assessment of individual bleeding and thrombotic risks before PCI is a prerequisite for an appropriate decision-making for the treatment strategy. In this study, we evaluated the absolute risk difference between bleeding and coronary thrombotic events. Although we attempted to investigate the borderline between subsets with high thrombotic risk vs. high bleeding risk, the present study demonstrated that all groups had a relatively high risk of major bleeding compared with the risk of any MI at 7 days (Fig. 5). When fatal MI was compared with fatal

bleeding, the ARC-HBR criteria successfully stratified patients with high thrombotic risk vs. high bleeding risk. Non-ARC-HBR patients had a higher risk of fatal MI than of fatal bleeding, whereas ARC-HBR patients had a balanced risk between fatal bleeding and fatal MI (Fig. 5). The balance between bleeding and thrombotic events can vary in different time phases¹⁵). Coronary thrombotic events kept occurring during the long-term follow-up due to the natural progression of systemic atherosclerosis, whereas bleeding events mainly occurred within 7 days of the procedure¹⁶). Therefore, the relative weight of coronary thrombotic events in comparison with

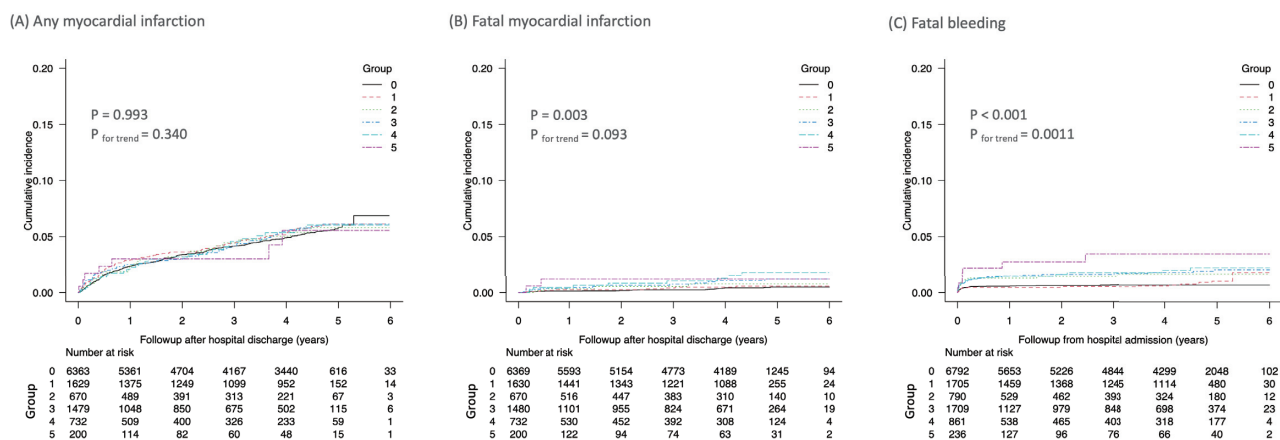


Fig. 4. Cumulative incidence curves

Cumulative incidence curves stratified by the number of ARC-HBR criteria for (A) any myocardial infarction, (B) fatal myocardial infarction, and (C) fatal bleeding after hospital discharge are illustrated. Abbreviations: ARC-HBR, Academic Research Consortium for High Bleeding Risk.

bleeding increases over time. In this regard, a strategy oriented toward bleeding risk should be prioritized, especially in the acute phase. Current short-DAPT and non-DAPT trials will further provide more profound insights into the optimal approach^{13,17}.

We compared any MI vs. major bleeding and fatal MI vs. fatal bleeding. The appropriateness of these comparisons might be a matter of debate. Valgimigli *et al.* reported a tradeoff of any MI vs. bleeding types on mortality after acute coronary syndrome from the TRACER trial¹⁸. Both MI and bleeding significantly impacted mortality with a similar time-dependency. Although Bleeding Academic Research consortium (BARC) 2 and 3a bleeding were less prognostic for death than MI, the risk of mortality was equivalent between BARC 3b bleeding and MI and was higher following BARC 3c bleeding⁹. In this regard, comparison of \geq BARC 3b with reference to any MI would be desirable, although the detailed BARC 3 bleeding classification data was unavailable in our dataset. This approach should be implemented in future studies.

The precise risk assessment model has been recently proposed by Urban *et al.*¹⁹. Prior MI, medical treatment of diabetes, STEMI/NSTEMI, and use of bare-metal stents were predictors for MI and/or stent thrombosis, whereas age \geq 65 years, chronic obstructive pulmonary disease, cancer, severe liver disease, planned surgery, and planned oral anticoagulation were predictors for BARC type 3–5 bleeding events⁹. Anemia, kidney insufficiency, current smoking, and complex PCI procedure were associated with both ischemic and bleeding events. An easy assessment tool on a smartphone will be available in the near future. Although such application tools

would be useful, the present study suggested that the simple use of the ARC-HBR criteria would be helpful for the quick assessment of the tradeoff between fatal bleeding and fatal MI in our daily clinical practice. When major bleeding was compared with any MI, all patients were found to be at a higher risk of major bleeding than of any MI. The PCI approach site and stent selection, periprocedural anticoagulation, indication of cardiopulmonary support device, and duration and type of DAPT may be decided based on this quick assessment. Further prospective investigation is warranted to assess its clinical utility and validity in the up-to-date clinical practice.

Several limitations should be acknowledged. First, due to the *post hoc* nature of the present analysis, data on several ARC-HBR criteria was not available, and the definitions of some ARC-HBR criteria were not exactly matched, which might have resulted in the underestimation or overestimation of the prevalence of some ARC-HBR criteria. Moreover, although some ARC-HBR criteria are thought to be also related to thrombotic events, some are not. Considering practical utility, we just counted the number of the ARC-HBR criteria. However, appropriate criteria selection and weighting of each criterion would provide more precise estimation than the current method. This approach will be a topic of the future study. Second, the long enrollment period of 1998–2014 is of potential concern since pharmacologic practice and interventional technologies have significantly evolved in this period. We had access to data on medication prescribed only at the time of discharge but not during the long-term follow-up. Some medications may have changed during the follow-up period. The duration of DAPT could not

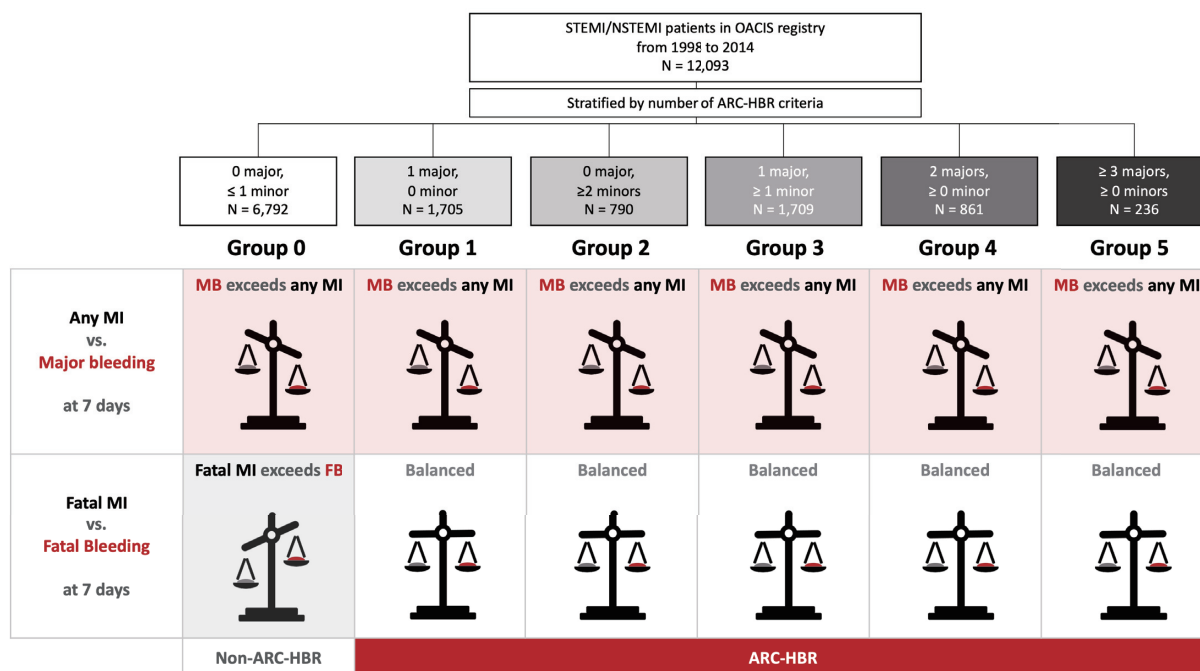


Fig. 5. Tradeoff between fatal bleeding and coronary thrombosis in the acute phase

In the acute phase, all patients (groups 0–5) had a higher risk of MB than of any MI (upper row). ARC-HBR (group 1–5) patients have a balanced risk between fatal MI and FB, whereas non-ARC-HBR (group 0) patients have a higher risk of fatal MI than of FB (bottom row). Abbreviations: MI, myocardial infarction; MB, major bleeding; FB, fatal bleeding.

be assessed, although we can assume based on the standard clinical practice in the period that most of the patients had 1 year or longer DAPT. The radial approach as compared with femoral approach has reduced the risk of bleeding, whereas the current DES has also reduced the risk of stent thrombosis. Recent advancement of these PCI procedure and device technologies possibly leads to different results²⁰⁻²⁷. Third, the definition of major bleeding in the present study is slightly different from that of BARC 3 or 5. The availability of major bleeding data was limited to the short-term follow-up (only at 7 days) and to the cohort enrolled from 2003 to 2014. Lastly, the present study is the East Asian registry, which would limit the generalizability of the current findings to other races.

Conclusion

All STEMI/NSTEMI patients have a relatively high risk of major bleeding as compared with the risk of any MI in the acute phase. The ARC-HBR criteria would be a practical tool for assessing the tradeoff between fatal bleeding and fatal MI. This practical assessment would be helpful for the optimal decision-making for an appropriate treatment strategy considering the balance between bleeding and coronary thrombotic risks.

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Conflict of Interest

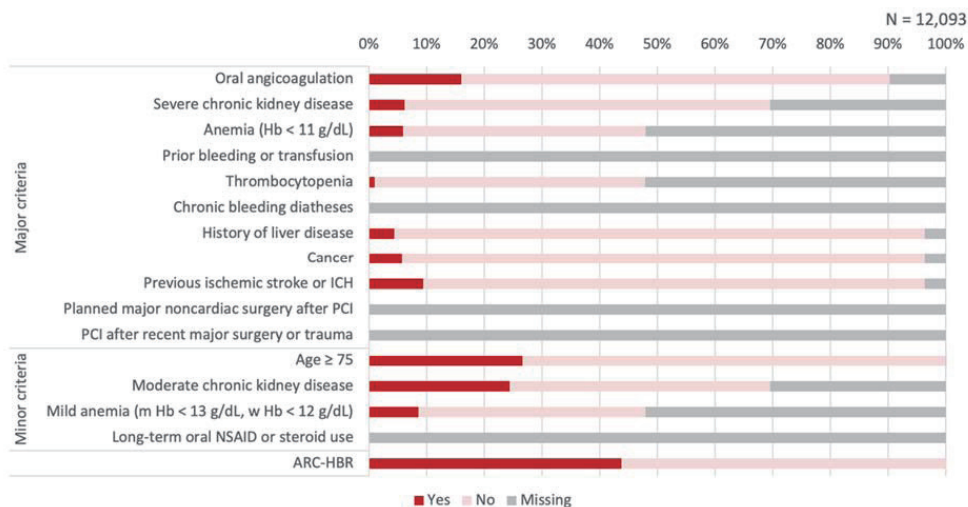
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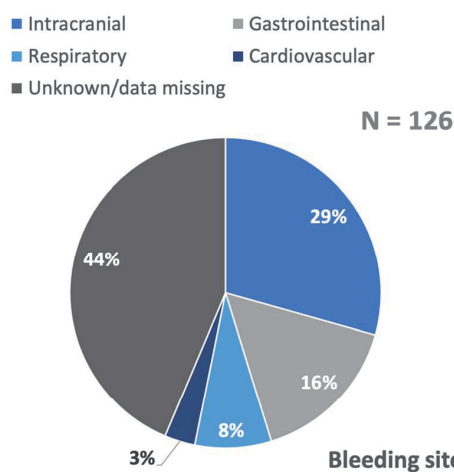
Supplemental Fig. 1. Prevalence of the individual components of the HBR criteria

Prevalence of the individual components of the HBR criteria is summarized in bar graphs. Abbreviations: ICH, intracranial hemorrhage; PCI percutaneous coronary intervention, NSAID Non-steroidal anti-inflammatory drug, ARC academic research consortium, HBR high bleeding risk. Reproduced with permission from Springer Nature 2021 (Prevalence of the Japanese high bleeding risk criteria and its prognostic significance for fatal bleeding in patients with acute myocardial infarction. Heart Vessels. 2021).

Supplemental Table 1. Medication at hospital discharge

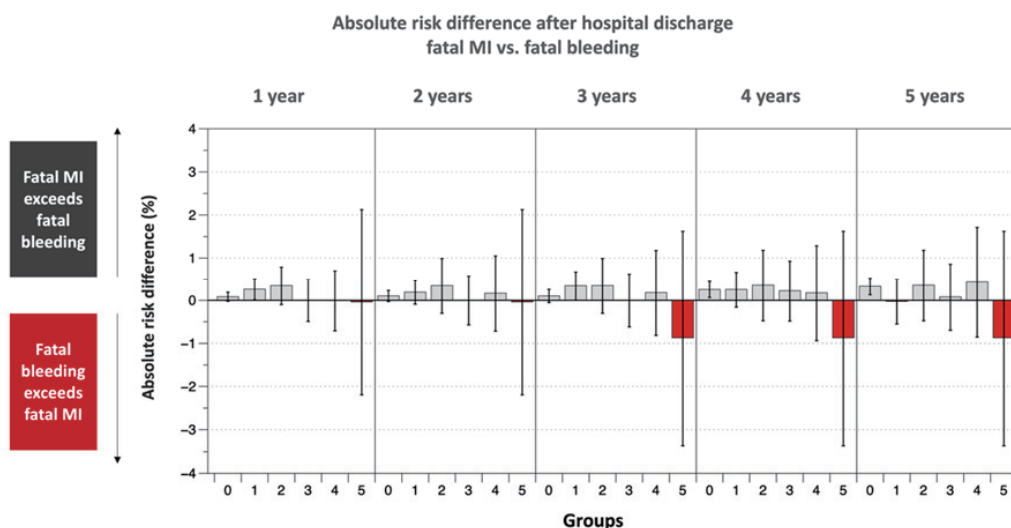
	Group 0	Group 1	Group 2	Group 3	Group 4	Group 5	P value	Data missing (%)
	0 major, ≤ 1 minor	1 major, 0 minor	0 major, ≥ 2 minors	1 major, ≥ 1 minor	2 majors, ≥ 0 minor	≥ 3 majors, ≥ 0 minors		
Number	6792	1705	790	1709	861	236		
ACEi	3387 (54.0)	838 (51.7)	280 (42.9)	623 (42.7)	262 (36.3)	56 (28.3)	<0.001	9.7
ARB	1588 (25.3)	353 (21.8)	240 (36.8)	469 (32.2)	228 (31.6)	62 (31.3)	<0.001	9.7
ACEi or ARB	4873 (77.8)	1164 (71.9)	500 (76.6)	1056 (72.4)	474 (65.7)	115 (58.1)	<0.001	9.7
Beta blockers	3276 (52.3)	832 (51.4)	393 (60.2)	858 (58.8)	428 (59.4)	129 (65.2)	<0.001	9.7
Statins	3204 (51.1)	705 (43.5)	334 (51.1)	685 (47.0)	327 (45.4)	81 (40.9)	<0.001	9.7
Antiplatelets	6165 (98.4)	1578 (97.4)	640 (98.0)	1396 (95.7)	687 (95.3)	186 (93.9)	<0.001	9.7
Anticoagulants	0 (0.0)	901 (55.6)	0 (0.0)	522 (35.8)	411 (57.0)	102 (51.5)	<0.001	9.7

Data with list-wise deletion are expressed as number (percentage). Abbreviations: ACEi, Angiotensin-converting-enzyme inhibitors; ARB, Angiotensin II receptor blockers.



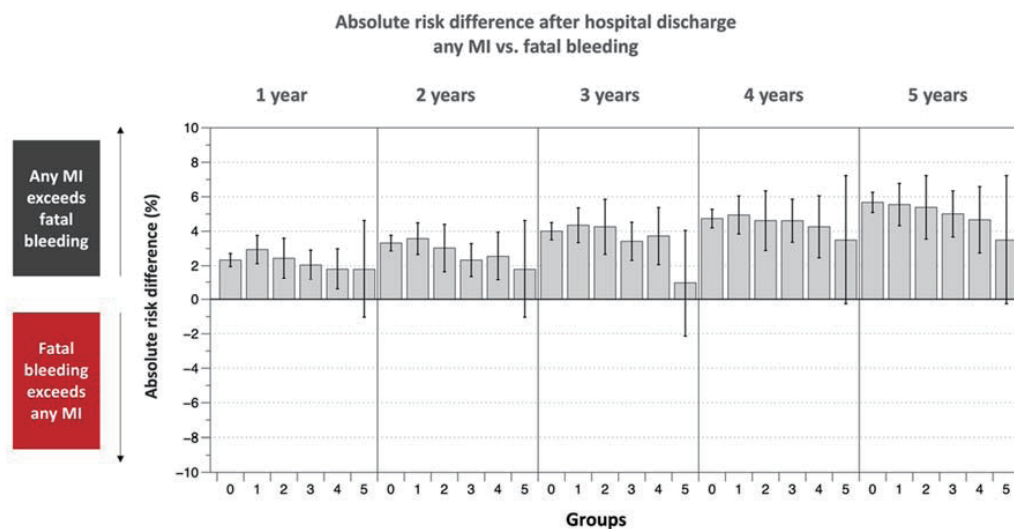
Supplemental Fig. 2. Fatal bleeding site

Fatal bleeding occurred in 126 patients in the entire follow-up period. Bleeding site is summarized in a pie chart. Intracranial bleeding was the most frequent cause of fatal bleeding. Reproduced with permission from Springer Nature 2021 (Prevalence of the Japanese high bleeding risk criteria and its prognostic significance for fatal bleeding in patients with acute myocardial infarction. Heart Vessels. 2021).



Supplemental Fig. 3. Absolute risk difference between fatal bleeding and fatal myocardial infarction

Absolute risk differences between fatal bleeding and fatal MI in each group after discharge up to 5 years are presented as bar graphs. Error bar shows 95% confidence interval. Abbreviations: MI, myocardial infarction.



Supplemental Fig. 4. Absolute risk difference between fatal bleeding and any myocardial infarction

Absolute risk differences between fatal bleeding and any MI in each group after discharge up to 5 years are presented as bar graphs. Error bar shows 95% confidence interval. Abbreviations: MI, myocardial infarction.