

# **Prevalence of the Academic Research Consortium High Bleeding Risk Criteria in Patients Undergoing Endovascular Therapy for Peripheral Artery Disease in Lower Extremities**

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**Short title:** Prevalence of HBR in Patients Undergoing EVT

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## Abstract

The Academic Research Consortium (ARC) has recently published a definition of patients at high bleeding risk (HBR) undergoing percutaneous coronary intervention. However, the prevalence of the ARC-HBR criteria in patients undergoing endovascular therapy (EVT) for peripheral artery disease in lower extremities has not been thoroughly investigated. This study sought to investigate the prevalence and impact of the ARC-HBR criteria in patients undergoing EVT. We analyzed 277 consecutive patients who underwent their first EVT from July 2011 to September 2019. We applied the full ARC-HBR criteria to the study population. The primary end point was a composite outcome of all-cause mortality, Bleeding Academic Research Consortium 3 or 5 bleeding, and lower limb amputation within 12 months of EVT. Among the 277 patients, 193 (69.7%) met the ARC-HBR criteria. HBR patients had worse clinical outcomes than non-HBR patients at 12 months after EVT, including the composite primary outcome (19.2% vs. 3.6%,  $p<0.001$ ) and all-cause death (7.8% vs. 0%,  $p=0.007$ ). In multivariate Cox proportional-hazards regression analysis, presence of the ARC-HBR criteria (hazard ratio [HR]: 4.15, 95% confidence interval [CI]: 1.25–13.80,  $p=0.020$ ), body mass index (HR: 1.13, 95% CI: 1.01–1.27,  $p=0.042$ ), diabetes mellitus (OR: 2.70, 95% CI: 1.28–5.69,  $p=0.009$ ), hyperlipidemia (OR: 0.41, 95% CI: 0.21–0.80,  $p=0.009$ ), and infrapopliteal lesion (OR 3.51, 95% CI 1.63–7.56,  $p=0.001$ ) were independent predictors of primary composite outcome. Approximately 70%

of Japanese patients undergoing EVT met the ARC-HBR criteria, and its presence was strongly associated with adverse outcomes within 12 months of EVT.

**Keywords**

high bleeding risk, peripheral artery disease, endovascular therapy, percutaneous coronary intervention

## Introduction

Bleeding events are strongly associated with worse clinical outcomes, such as death or myocardial infarction, after percutaneous coronary intervention (PCI) [1–4]. Recently, the definition of high bleeding risk (HBR) from the Academic Research Consortium (ARC) in patients undergoing PCI has attracted widespread interest [5]. In the ARC-HBR definition, HBR is defined as a Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding risk of  $\geq 4\%$ , or a risk of an intracranial hemorrhage of  $\geq 1\%$  at 1 year after PCI [5,6].

Previous studies from all-comers registries demonstrated that more than 40% of patients undergoing PCI met the ARC-HBR definition in real-world settings [7–10]. In addition, HBR patients undergoing PCI had worse clinical outcomes than non-HBR patients, including not only bleeding events but also death or myocardial infarction [1,7–9,11,12]. Therefore, risk stratification according to the ARC-HBR criteria is essential and useful for clinical decision making prior to PCI.

Currently, owing to the aging societies in advanced nations, patients with peripheral artery disease in lower extremities who undergo endovascular therapy (EVT) have been increasing [13–15]. In general, patients undergoing EVT tend to have higher-risk profiles and more comorbidities than those undergoing PCI, including older age, higher prevalence of hypertension and chronic kidney disease (CKD), despite the common cause of atherosclerosis [14,16]. In addition, because the standard

EVT access site is by the transfemoral approach, which is associated with a higher risk of bleeding complications than the transradial approach in patients undergoing PCI [17], bleeding risk assessment is essential in patients undergoing EVT. However, the prevalence and impact of the ARC-HBR criteria in patients undergoing EVT for peripheral artery disease in lower extremities has never been thoroughly investigated. In this study, we sought to apply the ARC-HBR criteria to a Japanese database of unselected and consecutive patients undergoing their first EVT, with the aim to evaluate whether the ARC-HBR criteria could stratify a high-risk patient group in the study population.

## **Methods**

This study was conducted as a single-center, retrospective cohort study designed to collect clinical backgrounds and outcomes in patients undergoing EVT for intermittent limb claudication or critical limb ischemia. We analyzed data from 277 consecutive patients who underwent their first EVT for peripheral artery disease in lower extremities in the Japanese Red Cross Ashikaga Hospital from July 2011 to September 2019 (Figure 1). Patients who underwent second or subsequent EVT were excluded to avoid re-inclusion of the same patients in this study. Patients were divided into two groups; HBR and non-HBR, according to the ARC-HBR criteria [5]. We applied the full ARC-HBR 11 major and 6 minor criteria to the study patients, and those who met at least 1 major or 2 minor criteria were stratified

in the HBR group. All other patients were included in the non-HBR group. Differences in baseline clinical characteristics, procedural data, and clinical outcomes were assessed between the two groups. The primary end point of this study was a composite of all-cause mortality, bleeding complications, and lower limb amputation within 12 months of EVT. Bleeding complications in this study were further defined as the BARC 3 or 5 bleeding according to the ARC-HBR definition [5,6].

All patients underwent EVT by transfemoral and/or retrograde transpopliteal approach. The devices used in EVT and post-procedural management including antithrombotic therapy, such as antiplatelets and/or anticoagulants, were at the discretion of the treating physicians. In brief, the recommended antiplatelet therapy was long-term aspirin (100 mg/day) with clopidogrel (75 mg/day) and/or cilostazol (100 or 200 mg/day) [18]. Dual antiplatelet therapy was continued for at least 1 month after bare-metal stent implantation or balloon angioplasty using a drug-coated balloon, and at least 2 months after drug-eluting stent implantation. This study complied with the principles contained within the Declaration of Helsinki and was approved by the institutional ethical committee of the Japanese Red Cross Ashikaga Hospital. Written informed consent was waived because of the retrospective enrollment and observational study design.

For statistical analyses, clinical variables were compared between the HBR and non-HBR groups. Continuous variables are expressed as mean  $\pm$  standard deviation. Categorical variables are

expressed as frequency and percentage. Continuous variables were compared using Student's t-test, and the differences between categorical variables were examined using the chi-square test or Fisher's exact test. Kaplan-Meier cumulative event curves were constructed for the primary composite outcome, all-cause mortality, BARC 3 or 5 bleeding, and lower limb amputation and differences between the HBR and non-HBR groups were assessed with the log-rank test. In addition, univariate and multivariate Cox proportional-hazards regression analyses were performed to determine the hazard ratios (HR) with upper and lower 95% confidence intervals (CI) for the primary composite outcome. Variables in the multivariate analysis were selected based on univariate p-values of  $<0.05$  and overall clinical significance. Specifically, presence of HBR, body mass index (BMI), diabetes mellitus, hyperlipidemia, and infrapopliteal lesion were entered into the multivariate analysis. All statistical calculations and analyses were performed using JMP version 15.0 (SAS Institute, Cary, NC, USA). P-values of  $<0.05$  were considered statistically significant.

## **Results**

Of the 277 patients who underwent their first EVT and included in this study, 193 patients (69.7%) met the ARC-HBR criteria (Figure 1). The prevalence of each ARC-HBR major and minor criterion is shown in Figure 2. Among the 11 major criteria, moderate or severe anemia, oral anticoagulants, and

severe or end-stage CKD were common, whereas advanced age ( $\geq 75$  years), moderate CKD, and mild anemia were common among the 6 minor criteria. Of note, there were no patients who met the following three major criteria; chronic bleeding diathesis, liver cirrhosis with portal hypertension, and recent major surgery or trauma.

The baseline clinical characteristics and procedural data of the patients in the total cohort, HBR group, and non-HBR group are shown in Table 1. HBR patients were older, and had a higher incidence of CKD, history of heart failure, ischemic stroke, intracranial hemorrhage, and atrial fibrillation than non-HBR patients. They also had lower baseline hemoglobin, worse renal function such as estimated glomerular filtration rate and creatinine clearance, and higher prevalence of infrapopliteal lesions and critical limb ischemia than non-HBR patients. Procedural data including devices, amount of contrast agent, and fluoroscopic time were comparable between the two groups, except bare metal stents were used more frequently in non-HBR patients than HBR patients. HBR patients took oral anticoagulants such as warfarin or direct oral anticoagulants,  $\beta$ -blockers, and calcium channel blockers more frequently than non-HBR patients, whereas statins were more often prescribed in the non-HBR group.

The clinical outcomes of the study patients 12 months after EVT are shown in Table 2. Overall, the primary composite outcome, defined as the composite of all-cause death, BARC 3 or 5



bleeding, and lower limb amputation, was observed in 40 patients (14.4%). Notably, HBR patients had worse clinical outcomes than non-HBR patients with significant differences in composite primary outcome (19.2% vs. 3.6%,  $p<0.001$ ) and all cause death (7.8% vs. 0%,  $p=0.007$ ). In addition, HBR patients had numerically higher incidence of BARC 3 or 5 bleeding (5.7% vs. 1.2%,  $p=0.114$ ) and lower limb amputation (8.8% vs. 2.4%,  $p=0.068$ ) compared with non-HBR patients but these did not reach statistical significance. In addition, Kaplan-Meier cumulative event curves demonstrated that HBR patients had significantly higher incidence of primary composite outcome ( $p=0.001$ ), all-cause mortality ( $p=0.009$ ), and lower limb amputation ( $p=0.045$ ) at 1-year after EVT (Figure 3).

The results of the univariate and multivariate Cox proportional-hazards regression analyses for the primary composite outcome are shown in Table 3. In the multivariate analysis, presence of the ARC-HBR criteria (OR: 4.15, 95% CI: 1.25–13.80,  $p=0.020$ ), BMI (HR: 1.13, 95% CI: 1.01–1.27,  $p=0.042$ ), diabetes mellitus (OR: 2.70, 95% CI: 1.28–5.69,  $p=0.009$ ), hyperlipidemia (OR: 0.41, 95% CI: 0.21–0.80,  $p=0.009$ ), and infrapopliteal lesion (OR 3.51, 95% CI 1.63–7.56,  $p=0.001$ ) were independent predictors of primary composite outcome.

## **Discussion**

This is the first study to investigate the prevalence and impact of the ARC-HBR criteria in unselected

and consecutive patients undergoing EVT for peripheral artery disease in lower extremities. The major findings from this study show that approximately 70% of the patients undergoing EVT met the ARC-HBR definition and patients defined as HBR had an increased risk of adverse clinical outcomes including all-cause death, bleeding, and lower limb amputation after EVT.

Previous all-comer registry studies demonstrated that more than 40% of patients undergoing PCI met the ARC-HBR definition in real-world settings [7-10]. With regard to the prevalence of the ARC-HBR criteria, our study suggests that patients undergoing EVT are more frequently at HBR compared with those undergoing PCI, despite the common cause of atherosclerosis. From a Japanese nationwide database, Takahara et al. [14] reported that patients undergoing EVT tend to have higher-risk profiles than those undergoing PCI, including older age and higher prevalence of hypertension and CKD. Because older age and CKD are included in the ARC-HBR criteria, this finding is consistent with our current study. In addition, the latest updated guideline from the Japanese Circulation Society includes the presence of peripheral artery disease as a major criterion of the Japanese version of HBR criteria [19]. In general, peripheral artery disease is one of the most important clinical presentations of advanced systemic atherosclerosis and is associated with both thrombotic and bleeding events [8,10,16,19,20]. The high prevalence of the ARC-HBR criteria in patients undergoing EVT for peripheral artery disease in this study supports this updated Japanese HBR guideline.

The rate of BARC 3 or 5 bleeding events within 1 year of EVT was 5.7% in the HBR group in this study. This is higher than the 4% cut-off value for bleeding events within 1 year defined by the ARC-HBR criteria [5]. Therefore, our study results indicate that the ARC-HBR criteria successfully stratifies HBR patients from an unselected patient cohort undergoing EVT. Additionally, consistent with previous studies, HBR patients had an increased risk of not only bleeding events, but also other adverse clinical events including all-cause death and lower limb amputation. These findings suggest that HBR patients represent a high-risk patient group [1,7–9,11,12]. There are some important risk prediction models and risk scores for post-PCI adverse events [20–22]. However, because precise risk models and scores that predict adverse events such as death or bleeding after EVT are lacking [18,23], the risk stratification according to the ARC-HBR criteria in patients undergoing EVT may be useful.

Consistent with the previous real-world data regarding the prevalence of the ARC-HBR in patients undergoing PCI [7–10], moderate or severe anemia was the most frequent major criterion, and advanced age ( $\geq 75$  years) was the most common minor criterion in this study. In addition, various stages of CKD and prescription of oral anticoagulants were also common in these patients [1]. Because populations are aging, especially in advanced nations including Japan [24], increasing numbers of old patients with multiple comorbidities such as anemia and CKD are undergoing EVT for peripheral artery disease [13–15]. Therefore, efforts to reduce procedure-related complications are crucial in this

high-risk patient group. For such HBR patients with multiple comorbidities, transradial EVT for peripheral artery disease in lower extremities [25,26], if technically feasible, may be associated with a lower risk of bleeding complications than conventional transfemoral EVT, as well as PCI [17,27].

In the multivariate analysis, in addition to presence of the ARC-HBR criteria, BMI, diabetes mellitus, hyperlipidemia, and infrapopliteal lesion were independently associated with post-procedural adverse outcomes in this study. Precise mechanism between higher BMI and primary composite outcome in this study remains unclear but is thought to be multifactorial. Previous studies reported that obesity is an important risk factor for advanced cardiovascular disease, and cardiac structural changes in obese patients are associated with fatal ventricular arrhythmias and/or sudden cardiac death [28–30]. In addition, it is well-known that diabetes mellitus is an important risk factor for the advancement of atherosclerosis and lower limb amputation due to critical limb ischemia [14,16,31,32]. Conversely, hyperlipidemia was inversely associated with primary composite outcome in this study. This finding is consistent with previous studies regarding post-EVT or post-PCI outcomes [18,33], and aggressive medical therapy in patients with hyperlipidemia such as statins might be a potential explanation of this result. Because EVT for infrapopliteal lesions is performed for patients presenting with critical limb ischemia, these patients tend to have more advanced systemic atherosclerosis and higher risk profiles than those with aorto-iliac or femoro-popliteal lesions [18,23]. In addition, we

previously reported that the presence of infrapopliteal lesions is associated with a high prevalence of coronary artery disease [34]. These are the potential explanations of an increased risk of adverse outcomes in patients undergoing EVT for infrapopliteal lesions. Finally, given the small number of study patients and low event rates, findings from the multivariate analysis should be cautiously interpreted.

Risk stratification prior to the interventional procedures is essential to improve the quality of medical care, particularly in the current EVT era. Physicians should be aware that the prevalence of HBR in patients undergoing EVT is much higher than those undergoing PCI, and patients defined as HBR are at greater risk of adverse clinical outcomes after EVT.

### **Study limitations**

This study had several important limitations. First, this was a single center observational study. Because we only included patients undergoing their first EVT to avoid re-enrolling the same patients, the number of patients was small despite the inclusion of unselected and consecutive patients. Therefore, the generalizability of this study may be limited. Conversely, a single center study enabled us to achieve sufficient data collection including complete validation of the ARC-HBR criteria. Second, this study did not include patients who underwent surgical revascularization for peripheral artery

disease in lower extremities. Third, although we performed univariate and multivariate Cox proportional-hazards regression analyses to adjust confounding variables, residual unmeasured or uncaptured factors such as frailty, cognitive function, and socioeconomic status might affect the primary composite outcomes. Fourth, the wide range of study period was an important limitation, because devices and medications had changed dramatically. Finally, although our institution has a dialysis center, the number of patients who underwent EVT for infrapopliteal lesions was relatively small (approximately 6%) in this study, and there were no such patients in the non-HBR group. Despite these limitations, we believe that our study provides novel and important clinical implications regarding HBR in patients with peripheral artery disease undergoing EVT. Further studies with larger cohorts are warranted to validate the current findings, and to investigate more precise prognostic impact of the ARC-HBR criteria in patients undergoing EVT.

## **Conclusions**

The ARC-HBR criteria successfully stratified a high-risk patient group in patients undergoing EVT for peripheral artery disease in lower extremities. Approximately 70% of Japanese patients undergoing EVT were classified as HBR, and its presence was strongly associated with adverse outcomes.

## **Conflict of Interest**

The authors declare that they have no conflict of interest.

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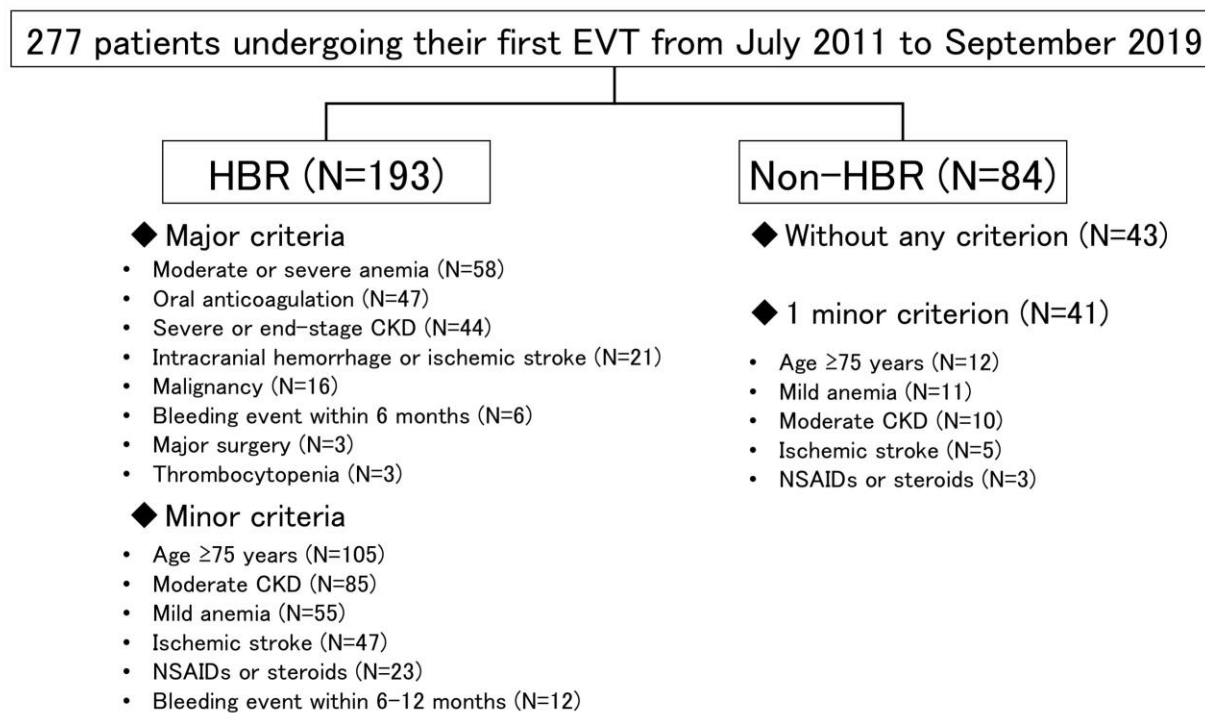
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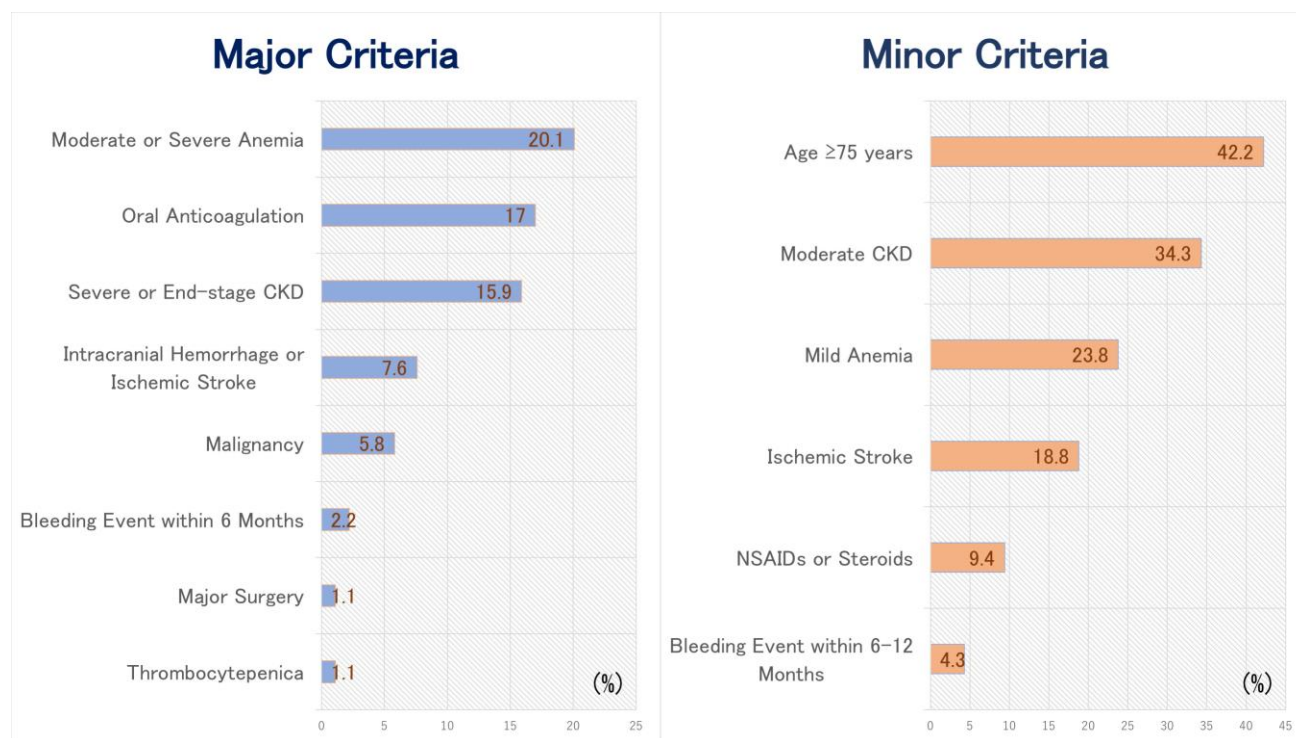
## Figure legends

Figure 1. Study flow chart



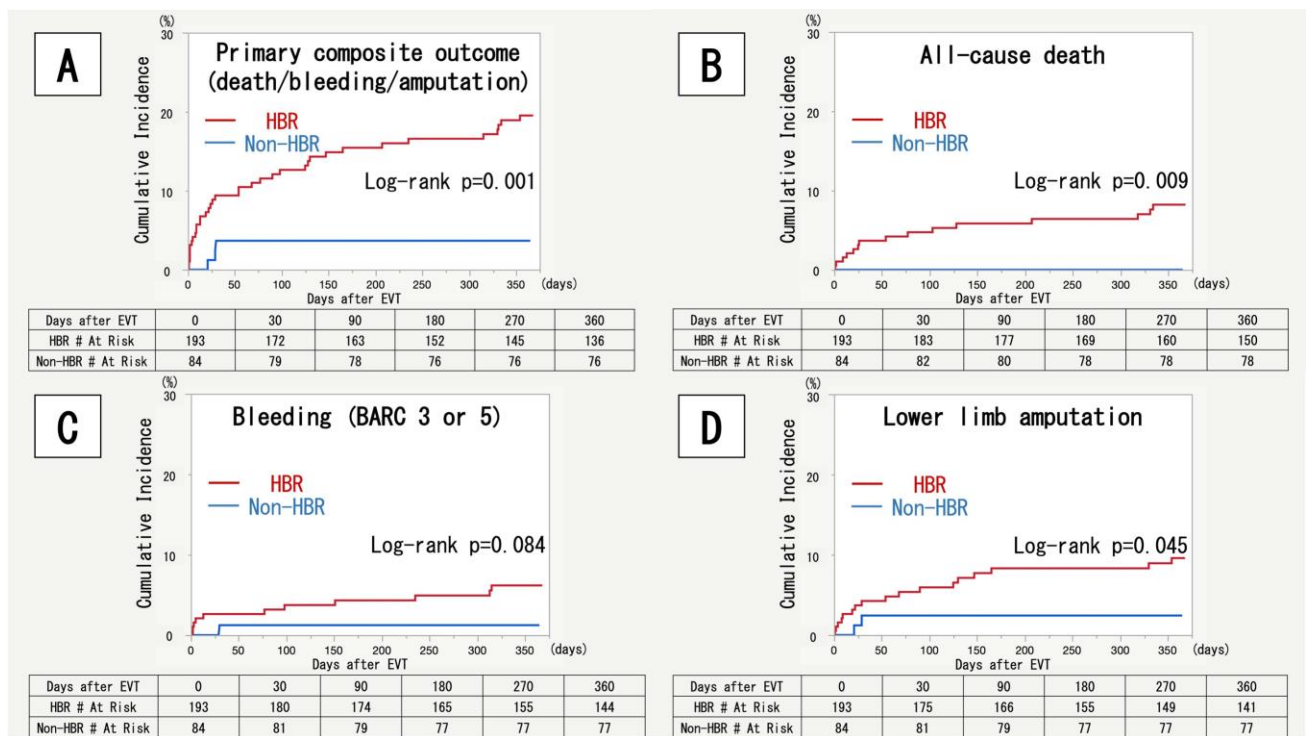
EVT: endovascular therapy, HBR: high bleeding risk, CKD: chronic kidney disease, NSAIDs: non-steroidal anti-inflammatory drugs

Figure 2. Prevalence of the major and minor ARC-HBR criteria in the whole study population



CKD: chronic kidney disease, NSAIDs: non-steroidal anti-inflammatory drugs

Figure 3. Kaplan-Meier curves of clinical outcomes 12 months after EVT, stratified by the ARC-HBR criteria



A: primary composite outcome, B: all-cause death, C: BARC 3 or 5 bleeding, D: lower limb amputation

HBR: high bleeding risk, EVT: endovascular therapy, BARC: Bleeding Academic Research Consortium

Table 1. Baseline Clinical Characteristics

	Total cohort (n=277)	HBR (n=193)	Non-HBR (n=84)	p-value (HBR vs. Non-HBR)
Age (years)	72.4±9.3	74.6±8.4	67.4±9.5	<0.001
Male	206 (74.4)	140 (72.5)	66 (78.6)	0.369
Height (cm)	159.3±8.9	158.4±9.0	161.3±8.4	0.013
Body weight (kg)	57.4±10.7	56.2±10.0	60.1±11.8	0.005
Body mass index	22.6±3.5	22.4±3.4	23.0±3.5	0.179
Hypertension	233 (84.1)	164 (85.0)	69 (82.1)	0.593
Hyperlipidemia	174 (62.8)	122 (63.2)	52 (61.9)	0.893
Diabetes mellitus	149 (53.8)	108 (56.0)	41 (48.8)	0.296
Current smoker	168 (60.7)	111 (57.5)	57 (67.9)	0.111
Chronic kidney disease	65 (23.4)	63 (32.6)	2 (2.4)	<0.001
Dialysis	36 (13.0)	36 (18.7)	0 (0)	<0.001
Chronic obstructive pulmonary disease	7 (2.5)	5 (2.6)	2 (2.4)	1.000
History of percutaneous coronary intervention	76 (27.4)	51 (26.4)	25 (29.8)	0.562
History of coronary artery bypass grafting	12 (4.3)	8 (4.2)	4 (4.8)	0.759
History of myocardial infarction	40 (14.4)	30 (15.5)	10 (11.9)	0.464
History of heart failure	38 (13.7)	33 (17.1)	5 (6.0)	0.013
History of ischemic stroke	52 (18.8)	47 (24.4)	5 (6.0)	<0.001
History of intracranial hemorrhage	11 (4.0)	11 (5.7)	0 (0)	0.038
Atrial fibrillation	38 (13.7)	37 (19.2)	1 (1.2)	<0.001
Ejection fraction (%)	57.4±12.1	56.7±12.8	59.3±10.0	0.143
Hemoglobin (g/dL)	12.8±2.0	12.2±1.9	14.0±1.4	<0.001
Platelet (×10 <sup>4</sup> /μL)	22.6±9.5	22.5±10.3	22.9±7.4	0.730
Serum Creatinine (mg/dL)	1.8±2.4	2.3±2.8	0.8±0.2	<0.001
eGFR (ml/min)	56.1±28.0	47.2±27.0	76.4±17.7	<0.001
CrCl (ml/min)	54.4±29.7	43.5±24.3	79.4±25.6	<0.001
Presentation				

Intermittent limb claudication	210 (75.8)	137 (71.0)	73 (86.9)	0.004
Critical limb ischemia	67 (24.2)	56 (29.0)	11 (13.1)	0.004
Target artery				
Aorto-iliac lesion	136 (49.1)	84 (43.5)	52 (61.9)	0.006
Femoro-popliteal lesion	142 (51.3)	106 (54.9)	36 (42.9)	0.069
Infrapopliteal lesion	16 (5.8)	16 (8.3)	0 (0)	0.004
Devices				
Balloon angioplasty	266 (96.0)	184 (95.3)	82 (97.6)	0.513
Bare metal stent	162 (58.4)	103 (53.4)	59 (70.2)	0.012
Drug eluting stent	34 (12.2)	26 (13.5)	8 (9.5)	0.430
Drug coated balloon	19 (6.9)	15 (7.8)	4 (4.8)	0.446
Contrast agent (ml)	128.6±50.9	125.7±51.6	135.1±48.7	0.161
Fluoroscopic time (min)	28.4±22.1	28.4±21.8	28.4±23.1	0.981
Radiation dose (mGy)	431.8±533.0	401.1±545.8	502.2±498.3	0.147
Medications				
Aspirin	243 (87.7)	165 (85.5)	78 (92.9)	0.111
Clopidogrel	197 (71.1)	133 (68.9)	64 (76.2)	0.250
Cilostazol	51 (18.4)	38 (19.7)	13 (15.5)	0.501
Prasugrel	5 (1.8)	3 (1.6)	2 (2.4)	0.641
Ticlopidine	9 (3.2)	6 (3.1)	3 (3.6)	1.000
Direct oral anticoagulant	20 (7.2)	20 (10.4)	0 (0)	<0.001
Warfarin	27 (9.7)	27 (14.0)	0 (0)	<0.001
Statins	175 (63.2)	113 (58.6)	62 (73.8)	0.021
ACE-I / ARB	186 (67.1)	134 (69.4)	52 (61.9)	0.266
β-blockers	122 (44.0)	94 (48.7)	28 (33.3)	0.018
Calcium channel blockers	155 (56.0)	119 (61.7)	36 (42.9)	0.006
Insulin	37 (13.4)	29 (15.0)	8 (9.5)	0.253

HBR: high bleeding risk, eGFR: estimated glomerular filtration rate, CrCl: creatinine clearance, ACE-I: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker

Table 2. Clinical Outcomes within 1 year

	Total cohort (n=277)	HBR (n=193)	Non-HBR (n=84)	p-value (HBR vs. Non-HBR)
Primary composite outcome (death, bleeding, and amputation)	40 (14.4)	37 (19.2)	3 (3.6)	<0.001
All-cause death	15 (5.4)	15 (7.8)	0 (0)	0.007
Cardiovascular death	8 (2.9)	8 (4.2)	0 (0)	0.111
Non-cardiovascular death	7 (2.5)	7 (3.6)	0 (0)	0.106
Bleeding (BARC 3 or 5)	12 (4.3)	11 (5.7)	1 (1.2)	0.114
Access site bleeding	4 (1.4)	4 (2.1)	0 (0)	0.318
Intracranial bleeding	3 (1.1)	2 (1.0)	1 (1.2)	1.000
Gastrointestinal bleeding	0 (0)	0 (0)	0 (0)	-
Genitourinary bleeding	1 (0.4)	1 (0.5)	0 (0)	1.000
Other bleeding	3 (1.1)	3 (1.6)	0 (0)	0.556
Lower limb amputation	19 (6.9)	17 (8.8)	2 (2.4)	0.068
Target vessel revascularization	13 (4.7)	7 (3.6)	6 (7.1)	0.223

HBR: high bleeding risk, BARC: Bleeding Academic Research Consortium

Table 3. Univariate and multivariate Cox proportional-hazards regression analyses for the primary composite outcome

	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
HBR	5.71	1.76-18.54	0.004	4.15	1.25-13.80	0.020
Body mass index	1.16	1.05-1.28	0.003	1.13	1.01-1.27	0.042
Diabetes mellitus	2.31	1.15-4.64	0.019	2.70	1.28-5.69	0.009
Hyperlipidemia	0.38	0.20-0.71	0.003	0.41	0.21-0.80	0.009
Infrapopliteal lesion	8.02	3.89-16.54	<0.001	3.51	1.63-7.56	0.001

HR: hazard ratio, CI: confidence interval, HBR: high bleeding risk