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Original article

Impact of decreased ankle-brachial index on 30-day bleeding complications and long-term mortality in patients with acute coronary syndrome after percutaneous coronary intervention

Takuya Nakahashi MD[a,*], Hayato Tada MD[b], Kenji Sakata MD[b], Yohei Yakuta MD[c], Yoshihiro Tanaka MD[b], Tadatsugu Gamou MD[b], Akihiro Nomura MD[b], Hidenobu Terai MD[c], Yuki Horita MD, FJCC[c], Masatoshi Ikeda MD[c], Masanobu Namura MD[c], Masayuki Takamura MD[d], Kenshi Hayashi MD, FJCC[b], Masakazu Yamagishi MD, FJCC[b], Masa-aki Kawashiri MD, FJCC[b]

[a] *Department of Cardiology, Takaoka City Hospital, Takaoka, Japan*
[b] *Department of Cardiovascular and Internal Medicine, Kanazawa University Graduate School of Medicine, Kanazawa, Japan*
[c] *Department of Cardiology, Kanazawa Cardiovascular Hospital, Kanazawa, Japan*
[d] *Department of Disease Control and Homeostasis, Graduate School of Medical Science, Kanazawa University, Kanazawa, Japan*

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ABSTRACT

Background: Although concomitant peripheral artery disease in patients with acute coronary syndrome (ACS) has been considered as a high-risk subgroup with a greater incidence of bleeding after percutaneous coronary intervention (PCI), few data exist regarding the clinical utility of the ankle-brachial index (ABI) for predicting bleeding complications, which affects the subsequent outcome.
Methods: Eight hundred and twenty-four consecutive patients with ACS who underwent PCI and ABI examination were analyzed retrospectively. Decreased-ABI was defined as ABI <0.9. The primary outcome was bleeding complications within 30 days, which was defined according to the Bleeding Academic Research Consortium classification grade ≥ 3. The secondary endpoint was all-cause death during follow-up.
Results: Of the 824 patients with ACS, 137 (16.6%) exhibited decreased-ABI. The incidence of bleeding complications was significantly higher in patients with decreased-ABI, compared with the remaining patients (21.9% vs. 6.0%, $p < 0.001$). In multivariate analysis, anemia [odds ratio (OR) 2.14], estimated glomerular filtration rate < 60 mL/min/1.73 m^2 (OR 2.14), femoral access (OR 3.31), use of an intra-aortic balloon pump (OR 3.16), and decreased-ABI (OR 2.58) were independent predictors of 30-day bleeding complications. Assigning 1 point for each variable, we developed a new bleeding risk score (range, 0–5). The area under the receiver-operating characteristic curve for the probability of 30-day bleeding for the new risk score was significantly superior than that of the traditional one (0.82 vs. 0.76, $p < 0.05$). During the median 4-year follow-up, there were 98 incidents of all-cause death. Multivariate Cox-proportional hazard analysis revealed that decreased-ABI [hazard ratio (HR) 1.91, 95% confidence interval (CI) 1.15–3.13, $p < 0.05$] and 30-day bleeding (HR 3.00, 95% CI 1.76–4.97, $p < 0.001$) were associated with an increased risk of all-cause mortality.
Conclusions: Assessment of ABI provides useful information for predicting 30-day bleeding complications and long-term mortality in patients with ACS after PCI.

Introduction

The combination of adjunct pharmacologic therapies and percutaneous coronary intervention (PCI) in patients with acute coronary syndrome (ACS) frequently results in peri-procedural

* Corresponding author at: Department of Cardiology, Takaoka City Hospital, 4-1, Takara-machi, Takaoka, Toyama 933-8550, Japan.
E-mail address: nakataku_1104@med-takaoka.jp (T. Nakahashi).

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bleeding complications [1]. Furthermore, several studies have reported that in-hospital bleeding complications in patients undergoing PCI may also increase the short- and long-term mortality, suggesting a biological effect from hemodynamic compromise and blood transfusion [2–6]. Thus, identifying individuals at higher risk of bleeding complications and subsequently aggressively addressing modifiable risk factors among this population may further improve both the health and economic outcomes.

The presence of peripheral artery disease (PAD) in patients presenting with ACS has been associated with a more widespread atherosclerotic phenotype and higher risk of adverse cardiovascular events [7–10]. Recently, concomitant PAD in patients with ACS has also been considered as a high-risk subgroup with a greater incidence of in-hospital bleeding complications after PCI [9–12]. These associations may be due to the higher prevalence of advanced age, female sex, and renal dysfunction among patients with concomitant PAD, and many of these factors are known to be predisposed toward bleeding events [13,14]. Since the ankle-brachial index (ABI) is used in the simple, non-invasive diagnosis of lower-extremity PAD, we hypothesized that the combination of ABI and the classical bleeding risk factors would be useful in refining the predictive ability for the risk assessment of bleeding complications. However, there are no clinical data to corroborate this assumption.

Therefore, the aim of the present study was to investigate the incremental value of ABI for predicting in-hospital bleeding events in patients with ACS.

We also assessed the long-term prognostic value of the assessment of ABI and in-hospital bleeding events in patients with ACS under optimal medical therapies.

Materials and methods

Study population

The details of the study population have been described previously [15]. In brief, from November 2006 to October 2014, 1115 consecutive patients with ACS who underwent emergent coronary angiography were analyzed retrospectively. Among these, 5 patients without coronary revascularization and 41 patients who underwent emergent coronary artery bypass grafting were excluded from our analysis. Furthermore, 225 patients with ACS who did not undergo ABI examination, and 20 patients without follow-up information at 30 days were also excluded. Finally, 824 patients with ACS who underwent ABI examination were included in the current analysis (Fig. 1). The PCI strategies were determined by the operator for each case. All patients received intravenous heparin (8000 IU) before angiography and were treated with intravenous heparin (2000 IU) hourly throughout the procedure. Platelet glycoprotein IIb/IIIa receptor inhibitors were not used because these were, and continue to be, unavailable in Japan. Postprocedural administration of antiplatelet therapy has been described elsewhere [15]. All patient data, including the clinical records, laboratory results, and angiograms, were reviewed independently by two cardiologists.

This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Bioethical Committee on Medical Research, School of Medicine, Kanazawa University.

Outcome measurement and definitions

The primary outcome measure was the occurrence of bleeding complications within 30 days after PCI. Bleeding complications were assessed using the Bleeding Academic Research Consortium classification ≥3 [16]. Access and non-access site bleeding were also explored according to the previous report [17]. The secondary outcome was all-cause mortality during follow-up. Cardiovascular death was defined as presumed cardiovascular death, unexpected death, death from myocardial infarction, arrhythmia, congestive heart failure or stroke, and other cardiovascular diseases, including abdominal aortic aneurysm rupture and pulmonary embolism [18].

The study patients were divided into two groups based upon whether the ABI was decreased or preserved. Identification of PAD was determined by the ABI, as part of our standard practice. The ABI was measured using a validated automatic device (BP-203PRE

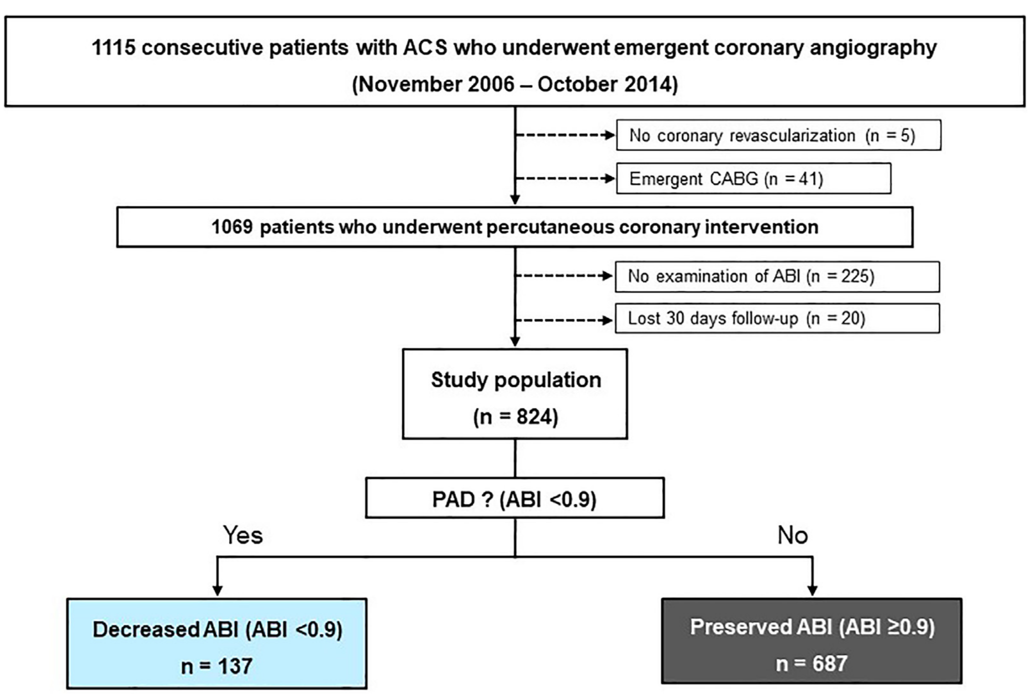

Fig. 1. Participant flow chart. ACS, acute coronary syndrome; ABI, ankle-brachial index; CABG, coronary artery bypass grafting; PAD, peripheral artery disease.

II; Omron-Colin, Tokyo, Japan). We selected the lowest ABI in cases of differences between the left and right ABI. Decreased ABI was defined as ABI <0.9 [8]. The median interval from the date of PCI to the examination of ABI was 7 days (interquartile range, 3–22 days). In addition, we collected the following indicators as history of PAD: prior lower extremity vascular bypass or intervention, and prior lower extremity amputation (nontraumatic).

All the variables required for calculating the bleeding risk score were obtained from clinical and procedural data. The Randomized Evaluation in PCI Linking Angiomax to reduced Clinical Events (REPLACE) bleeding score was calculated as described previously by Nikolsky et al. [19]. Calculation of REPLACE bleeding score included the following variables: age, sex, estimated glomerular filtration rate, anemia, administration of low-molecular-weight heparin within 48 h pre-PCI, use of glycoprotein IIb/IIIainhibitors, and intra-aortic balloon pump. Anemia was defined as admission hemoglobin <13 g/dL in men or <12 g/dL in women [15]. Full details on the calculation of the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association Guidelines (CRUSADE) bleeding score are reported elsewhere [11].

Statistical analysis

Continuous variables were expressed as the mean ± standard deviation and were compared using unpaired *t* test or Mann–Whitney

Table 1
Baseline clinical characteristics.

	All ($n = 824$)	Decreased ABI (ABI <0.9) ($n = 137$)	Preserved ABI (ABI ≥0.9) ($n = 687$)	*p*-Value
Age, years	68 ± 12	75 ± 10	66 ± 11	<0.001
Female gender	185 (22.5)	42 (30.7)	143 (20.8)	<0.05
Body mass index, kg/m^2	23.9 ± 3.5	22.9 ± 3.7	24.1 ± 3.4	<0.001
Clinical presentation				0.80
STEMI	395 (47.9)	64 (46.7)	331 (48.2)	
NSTEMI	124 (15.0)	19 (13.9)	105 (15.3)	
UAP	305 (37.0)	54 (39.4)	251 (36.5)	
Killip class ≥2	251 (30.5)	62 (45.3)	189 (27.5)	<0.001
Resuscitation before admission	42 (5.1)	5 (3.6)	37 (5.4)	0.38
Systolic blood pressure, mmHg	137 ± 32	137 ± 34	137 ± 31	0.85
Diastolic blood pressure, mmHg	78 ± 19	74 ± 19	79 ± 19	<0.05
Heart rate, beats/min	79 ± 20	81 ± 23	78 ± 19	0.11
Hypertension	559 (67.8)	93 (67.9)	466 (67.8)	0.99
Diabetes mellitus	328 (39.8)	76 (55.5)	252 (36.7)	<0.001
Dyslipidemia	411 (49.9)	71 (51.8)	340 (49.5)	0.62
Atrial fibrillation	71 (8.6)	20 (14.6)	51 (7.4)	<0.05
Current smoker	349 (42.4)	44 (32.1)	305 (44.4)	<0.05
Previous MI	74 (9.0)	17 (12.4)	57 (8.3)	0.14
Previous PCI	136 (16.5)	46 (33.6)	90 (13.1)	<0.001
Previous stroke	103 (12.5)	33 (24.1)	70 (10.2)	<0.001
History of PAD	43 (5.2)	30 (21.9)	13 (1.9)	<0.001
History of gastric ulcer	79 (9.6)	15 (10.9)	64 (9.3)	0.56
History of malignancy	85 (10.3)	17 (12.4)	68 (9.9)	0.39
Baseline hematocrit, %	40.2 ± 5.7	37.2 ± 6.5	40.8 ± 5.4	<0.001
Baseline hemoglobin, g/dL	13.7 ± 2.1	12.5 ± 2.3	13.9 ± 2.0	<0.001
Anemia	240 (29.1)	65 (47.4)	175 (25.5)	<0.001
Nadir hemoglobin, g/dL	11.7 ± 2.2	10.4 ± 2.3	11.9 ± 2.1	<0.001
Platelet count, ×10^9/L	211 ± 73	194 ± 75	215 ± 73	<0.05
Creatinine, mg/dL	1.2 ± 1.5	2.1 ± 2.4	1.0 ± 1.2	<0.001
Creatinine clearance, mL/min	78 ± 40	48 ± 35	84 ± 38	<0.001
eGFR, mL/min/1.73 m^2	70 ± 29	50 ± 32	74 ± 27	<0.001
ABI	1.03 ± 0.17	0.72 ± 0.14	1.09 ± 0.09	<0.001
Prehospital drug treatment				
Aspirin	214 (26.0)	61 (44.5)	153 (22.3)	<0.001
Thienopyridines	113 (13.7)	43 (31.4)	70 (10.2)	<0.001
Oral anticoagulant	28 (3.4)	7 (5.1)	21 (3.1)	0.25
Statins	167 (20.3)	36 (26.3)	131 (19.1)	0.06
ACE-I or ARB	196 (23.8)	47 (34.3)	149 (21.7)	<0.05
β-Blockers	47 (5.7)	10 (7.3)	37 (5.4)	0.39
H_2 blockers or PPI	165 (20.0)	46 (33.6)	119 (17.3)	<0.001
NSAIDs	15 (1.8)	2 (1.5)	13 (1.9)	0.72
Steroids	20 (2.4)	1 (0.7)	19 (2.8)	0.11
Medication at discharge				
Aspirin	813 (98.7)	130 (94.9)	683 (99.4)	<0.001
Thienopyridines	784 (95.1)	130 (94.9)	654 (95.2)	0.88
Oral anticoagulant	88 (10.7)	20 (14.6)	68 (9.9)	0.12
Statins	608 (73.8)	91 (66.4)	517 (75.3)	<0.05
ACE-I or ARB	577 (70.0)	94 (68.6)	483 (70.3)	0.69
β-Blockers	311 (37.7)	50 (36.5)	261 (38.0)	0.74
H_2 blockers or PPI	699 (84.8)	120 (87.6)	579 (84.3)	0.31
NSAIDs	10 (1.2)	1 (0.7)	9 (1.3)	0.55
Steroids	20 (2.4)	1 (0.7)	19 (2.8)	0.11

Variables are *n* (%), mean ± standard deviation.
ABI, ankle-brachial index; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; EF, ejection fraction; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; NSAIDs, Non-steroidal anti-inflammatory drugs; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PPI, proton pump inhibitors; STEMI, ST-segment elevated myocardial infarction; NSTEMI, Non ST-segment elevated myocardial infarction; UAP unstable angina pectoris.

U test. Frequency analysis was performed using χ^2 test. Multivariate logistic regression analysis was used to detect associations between the 30 days bleeding and risk factors. Multivariate analysis of independent predictors of all-cause mortality was performed using the Cox proportional hazard regression model. Age, gender, and variables with $p < 0.05$ on univariate analysis were selected into the multivariate analysis model in consideration of potential confounding variables. Continuous variables were dichotomized for the median or clinically relevant value in the univariate and multivariate models. Event-free survival analysis was performed using the Kaplan–Meier method with log-rank test for group comparisons. We performed receiver operating characteristic analysis and calculated the area under the receiver operator characteristic curve to estimate the predictive performance for 30-day bleeding complications. The area under the receiver operator characteristic curve was compared according to the method of DeLong et al. [20]. A probability value of $p < 0.05$ was considered statistically significant. Statistical analyses were performed using JMP pro Version 12 (SAS institute, Cary, NC, USA).

Results

Patient characteristics

Of the 824 patients with ACS, 137 (16.6%) exhibited decreased ABI (Table 1). Patients with decreased ABI were significantly older (75 ± 10 years vs. 66 ± 11 years, $p < 0.001$) and had a higher prevalence of female gender (30.7% vs. 20.8%, $p < 0.05$). Anemia was more common in patients with decreased ABI, compared with those with preserved ABI (47.4% vs. 25.5%, $p < 0.001$). There were significant differences in the use of aspirin (94.9% vs. 99.4%, $p < 0.001$) and statins (66.4% vs. 75.3%, $p < 0.05$) between patients with decreased ABI and those with preserved ABI with respect to medication at hospital discharge.

The angiographic and procedural characteristics are presented in Table 2. The prevalence of multivessel disease was significantly higher in patients with decreased ABI compared with those with preserved ABI (79.6% vs. 59.2%, $p < 0.001$). Of note, the femoral access was more commonly used in patients with decreased ABI compared with the preserved ABI group (40.9% vs. 32.0%, $p < 0.05$).

In-hospital bleeding complications

At 30 days, bleeding occurred in 30 patients (21.9%) with decreased ABI and 41 patients (6.0%) with preserved ABI ($p < 0.001$). The sources of the 30-day bleeding are presented in Table 3. The predominant bleeding complication occurred at the puncture site, followed by gastrointestinal bleeding.

On multivariate analysis of the 30-day bleeding complications (Table 4), anemia [odds ratio (OR), 2.14; 95% confidence interval (CI), 1.18–3.89; $p < 0.05$], estimated glomerular filtration rate < 60 mL/min/1.73 m^2 (OR, 2.14; 95% CI, 1.15–4.01; $p < 0.05$), decreased ABI (OR, 2.58; 95% CI, 1.34–4.92; $p < 0.05$), use of an intra-aortic balloon pump (OR, 3.16; 95% CI, 1.67–5.92; $p < 0.001$), and femoral access (OR, 3.31; 95% CI, 1.82–6.13; $p < 0.001$) were found to be independent factors. On the other hand, a history of PAD was no longer a significant factor for 30-day bleeding complications in multivariate analysis (OR, 0.82; 95% CI, 0.30–2.07; $p = 0.68$). Prehospital treatment with non-steroidal anti-inflammatory drugs and steroids did not affect the 30-day bleeding complications in the present study (data not shown).

In the present study, we developed a new scoring system using independent predictors that were identified here, including decreased **ABI**, estimated **G**lomerular filtration rate <60 mL/min/1.73 m^2, **A**nemia, **I**ntra-aortic balloon pump, and femora**L** access (thus, the **ABIGAIL** bleeding score). These variables each received 1 point (full score 5). The area under the curve for the probability of 30-day bleeding for the ABIGAIL score was much greater than the area under the curve for the REPLACE bleeding score (0.82 vs. 0.76, $p < 0.05$; Fig. 2). Although the area under the curve for the CRUSADE bleeding score was numerically greater than that of the ABIGAIL bleeding score, this was not statistically significant (Supplementary Table 1). ABIGAIL bleeding score ≥2 had 81.7% sensitivity and 70.4% specificity for predicting 30-day bleeding.

Clinical outcomes

The median follow-up duration was 4.4 years (interquartile range, 2.4–6.5 years). During follow-up, there were 98 incidents of all-cause death. Cardiovascular death occurred in 52 patients. Details of the death events are shown in Supplementary Table 2. On multivariate Cox proportional hazard regression analysis, age >70 years [hazard ratio (HR), 2.18; 95% CI, 1.40–3.48; $p < 0.001$], Killip class ≥2 (HR, 1.58; 95% CI, 1.03–2.43; $p < 0.05$), diabetes mellitus (HR, 1.84; 95% CI, 1.22–2.81; $p < 0.05$), anemia (HR, 1.97; 95% CI, 1.28–3.07; $p < 0.05$), decreased ABI (HR, 1.91; 95% CI, 1.15–3.13; $p < 0.05$), prescription of statins at discharge (HR, 0.53; 95% CI, 0.35–0.80; $p < 0.05$), and 30-day bleeding (HR, 3.00; 95% CI, 1.76–4.97; $p < 0.001$) were associated with all-cause death (Table 5).

Kaplan–Meier curve showed that patients with decreased ABI exhibited a higher rate of all-cause mortality compared with those

Table 2
Angiographic and procedural characteristics.

	All ($n = 824$)	Decreased ABI (ABI <0.9) ($n = 137$)	Preserved ABI (ABI ≥0.9) ($n = 687$)	*p*-Value
Culprit lesion location				
Left main	29 (3.5)	9 (6.6)	20 (2.9)	0.051
Left anterior descending	369 (44.8)	60 (43.8)	309 (45.0)	0.80
Left circumflex	146 (17.7)	27 (19.7)	119 (17.3)	0.51
Right	296 (35.9)	50 (36.5)	246 (35.8)	0.88
Multivessel disease	516 (62.6)	109 (79.6)	407 (59.2)	<0.001
Pre-PCI TIMI flow grade 0 or 1	432 (52.4)	65 (47.4)	367 (53.4)	0.20
Final post-PCI TIMI flow grade 3	786 (95.4)	131 (95.6)	655 (95.3)	0.89
Drug-eluting stent implantation	336 (40.8)	65 (47.4)	271 (39.4)	0.08
Use of aspiration catheter	503 (61.0)	72 (52.6)	431 (62.7)	<0.05
Use of distal protection device	261 (31.7)	38 (27.7)	223 (32.5)	0.27
Use of intravascular ultrasound	746 (90.5)	125 (91.2)	621 (90.4)	0.75
Insertion of IABP	102 (12.4)	22 (16.1)	80 (11.6)	0.16
Femoral approach	276 (33.5)	56 (40.9)	220 (32.0)	<0.05

Variables are *n* (%).
ABI, ankle-brachial index; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention; TIMI, Thrombosis In Myocardial Infarction.

Table 3
Source of 30-day bleeding complication.

	All ($n=824$)	Decreased ABI (ABI <0.9) ($n=137$)	Preserved ABI (ABI ≥0.9) ($n=687$)
Bleeding	71 (8.6)	30 (21.9)	41 (6.0)
Access site	30 (3.6)	9 (6.6)	21 (3.1)
Puncture site	26 (3.2)	8 (5.8)	18 (2.6)
Retroperitoneal	4 (0.5)	1 (0.7)	3 (0.4)
Non-access site	41 (5.0)	21 (15.3)	20 (2.9)
Gastrointestinal	10 (1.2)	6 (4.4)	4 (0.6)
Pericardial	6 (0.7)	2 (1.5)	4 (0.6)
Intracranial	3 (0.4)	1 (0.7)	2 (0.3)
Postoperative	2 (0.2)	0 (0.0)	2 (0.3)
Intraabdominal	1 (0.1)	1 (0.7)	0 (0.0)
Genitourinary	1 (0.1)	0 (0.0)	1 (0.1)
Hematologic disease	1 (0.1)	0 (0.0)	1 (0.1)
Unidentified	17 (2.1)	11 (8.0)	6 (0.9)

Variables are *n* (%).
ABI, ankle-brachial index.

Table 4
Univariate and multivariate analysis of 30-day bleeding complication.

	Univariate		Multivariate	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Age (>70 years)	2.26 (1.38–3.75)	<0.05	1.41 (0.78–2.56)	0.26
Female gender	2.31 (1.37–3.83)	<0.05	1.62 (0.89–2.92)	0.12
Anemia	4.06 (2.47–6.75)	<0.001	2.14 (1.18–3.89)	<0.05
eGFR <60 mL/min/1.73 m^2	4.81 (2.90–8.17)	<0.001	2.14 (1.15–4.01)	<0.05
Decreased ABI (ABI <0.9)	4.42 (2.63–7.36)	<0.001	2.58 (1.34–4.92)	<0.05
History of PAD	2.60 (1.08–5.60)	<0.05	0.82 (0.30–2.07)	0.68
Prehospital antiplatelet therapy	2.57 (1.56–4.22)	<0.001	1.28 (0.69–2.35)	0.42
Prehospital oral anticoagulant	3.81 (1.46–8.92)	<0.05	1.75 (0.58–4.84)	0.31
Prehospital H_2 blockers or PPI	2.06 (1.20–3.47)	<0.05	0.75 (0.39–1.42)	0.38
Use of IABP	5.15 (2.98–8.77)	<0.001	3.16 (1.67–5.92)	<0.001
Femoral access	5.16 (3.09–8.89)	<0.001	3.31 (1.82–6.13)	<0.001

ABI, ankle-brachial index; CI, confidence interval; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; OR, odds ratio; PAD, peripheral artery disease; PPI, proton pump inhibitors.

with preserved ABI (Fig. 3A). Similarly, patients who developed 30-day bleeding exhibited a higher rate of all-cause mortality compared with those without (Fig. 3B). Interestingly, a landmark survival analysis with the landmark set 30 days after PCI comparing with or without 30-day bleeding complications also revealed similar results (Fig. 3C).

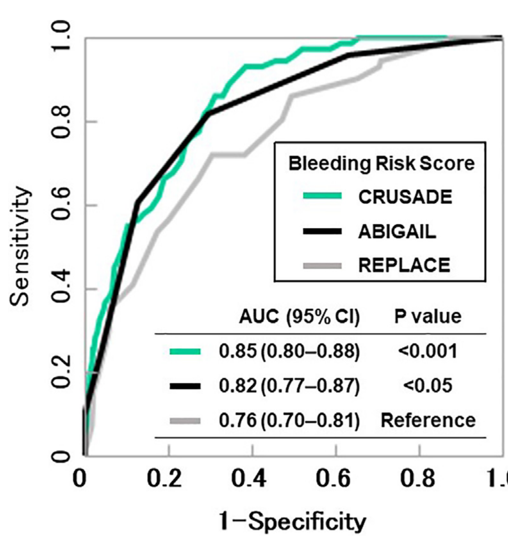

Fig. 2. The receiver-operator characteristic curve for 30-day bleeding according to the ABIGAIL and traditional bleeding risk scores. AUC, area under the curve; CI, confidence interval.

Discussion

The main findings of this study are as follows: (1) Decreased ABI, but not a history of PAD, was one of the major predictors of 30-day bleeding complications in patients with ACS after PCI. (2) Adding the ABI to the classical bleeding risk factors might improve the predictive ability for 30-day bleeding complications in these patients. (3) Patients with ACS who exhibited decreased ABI and 30-day bleeding complications had higher mortality after PCI. Our results are consistent with previous reports suggesting that the presence of PAD in patients with ACS leads to a higher risk profile of both in-hospital bleeding complications and future adverse cardiovascular events [9,10].

In addition, the incidence of bleeding complications was 8.6% in our study, which was consistent with previous data from ACS patients [1–3,11,12]. Of note, the present study demonstrated that decreased ABI was associated with 30-day bleeding complications after PCI, even after adjustment for advanced age and renal insufficiency, which are shared risk factors for bleeding complications. Although increased risk of bleeding in patients with PAD has been reported previously, the current study confirms this association with the assessment of ABI.

As compared with preserved ABI, vascular access in patients with decreased ABI may be more complicated due to the presence of atherosclerosis and calcification in the artery being punctured,

Table 5
Predictors of all-cause mortality.

	Univariate		Multivariate	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age (>70 years)	3.47 (2.29–5.37)	<0.001	2.18 (1.40–3.48)	<0.001
Female gender	1.47 (0.93–2.26)	0.10	0.89 (0.55–1.41)	0.64
Killip class ≥2	2.46 (1.65–3.66)	<0.001	1.58 (1.03–2.43)	<0.05
Diabetes mellitus	2.11 (1.42–3.16)	<0.001	1.84 (1.22–2.81)	<0.05
Anemia	3.96 (2.65–5.94)	<0.001	1.97 (1.28–3.07)	<0.05
eGFR <60 mL/min/1.73 m^2	3.27 (2.19–4.89)	<0.001	1.42 (0.90–2.24)	0.13
Decreased ABI (ABI <0.9)	4.39 (2.89–6.58)	<0.001	1.91 (1.15–3.13)	<0.05
History of PAD	2.77 (1.44–4.86)	<0.05	1.03 (0.51–1.94)	0.93
Multivessel disease	1.70 (1.10–2.70)	<0.05	1.09 (0.69–1.78)	0.71
Femoral access	2.01 (1.35–2.99)	<0.001	1.12 (0.72–1.74)	0.63
Prescription of statins at discharge	0.42 (0.28–0.63)	<0.001	0.53 (0.35–0.80)	<0.05
30-Day bleeding	5.83 (3.62–9.09)	<0.001	3.00 (1.76–4.97)	<0.001

ABI, ankle-brachial index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; PAD, peripheral artery disease.

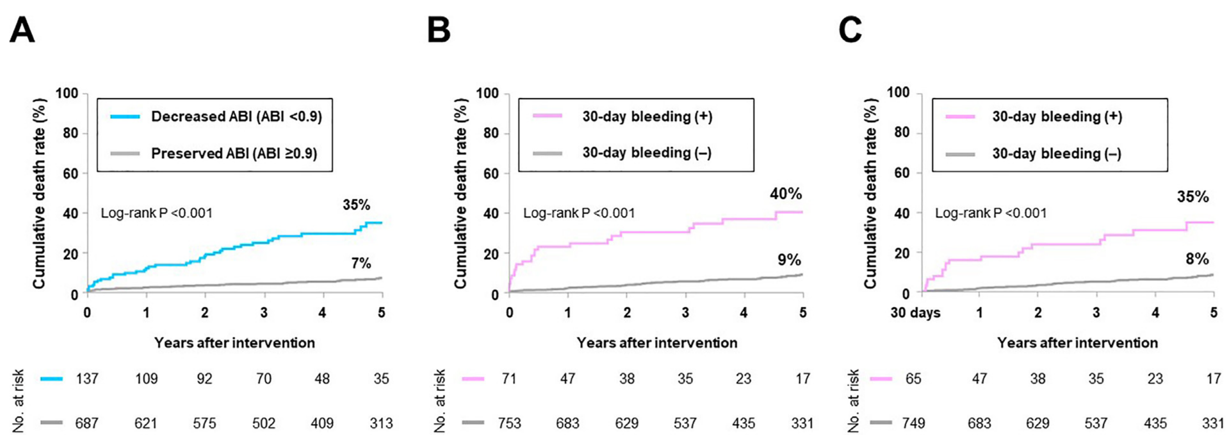

Fig. 3. Kaplan–Meier time-to-event curve stratified across the presence or absence of (A) decreased ABI, and (B) 30-day bleeding. (C) A landmark survival analysis with the landmark set 30 days after percutaneous coronary intervention comparing with or without 30-day bleeding complication is provided. The numbers of patients at risk at each time point are indicated below the graph. ABI, ankle-brachial index.

thus resulting in an increased incidence of periprocedural bleeding complications during PCI [21,22]. Nevertheless, the high frequency of non-access site bleeding in patients with decreased ABI in the present study is remarkable. A recent study reported that the presence of PAD is an important indicator in the development of acute mesenteric ischemia during cardiovascular surgery [23]. Furthermore, several studies have suggested that subjects with cardiovascular diseases have a higher risk of gastrointestinal malignancies through the mechanism of chronic inflammation [24,25]. Interestingly, compared with the patients affected by coronary artery disease alone, concomitant PAD patients tended to be strongly associated with increased inflammatory responses [26]. Although we did not perform a direct comparison of the findings obtained from gastrointestinal endoscopy, it is possible to speculate that the tolerance to intestinal ischemia and the difference in the inflammatory state may increase the risk of gastrointestinal bleeding complications, particularly in patients with PAD.

As mentioned above, the presence of PAD has been shown to be an important factor for bleeding complications during PCI [9–14,21,22]. However, interestingly, none of the previously mentioned existing bleeding risk scores have included the ABI. In registry studies, the definition of PAD has mainly been made based upon the clinical diagnosis alone, i.e. claudication, history of vascular bypass, amputation. Under these conditions, the prevalence of PAD might be underdiagnosed, thus contributing to differences in the performance for predicting bleeding complications and long-term prognosis compared with the assessment of ABI, as shown in the current study. Future investigations are needed to determine whether the assessment of ABI could help physicians to be able to estimate the bleeding risk before the PCI procedure and to implement the proper treatment strategy, including antithrombotic regimen.

There are several limitations to the present study. First, although patient management was relatively homogeneous this was a retrospective study. Despite the finding that the observed rate of bleeding in the present study was similar to recent PCI trials, there were still unidentified bleeding sources in several patients. Since the clinical scenario of subsequent bleeding events are complicated, a future study with more vigorous protocol to pursue bleeding after PCI is warranted. Second, we could not perform risk assessment of patients with borderline ABI (0.9–1.0), or high ABI (>1.4) compared with normal ABI as the reference group. Although the U-shaped relationship between ABI and future cardiovascular events has been well documented among both individuals with primary prevention and established atherosclerotic cardiovascular disease [27,28], there is no general consensus on the bleeding risk with each of the ABI levels, and more data are required to examine this issue. Third, we could not assess bleeding events using alternative definitions; however, recent studies have demonstrated that the Bleeding Academic Research Consortium definition, that was applied in the current study, was superior to the traditional bleeding definitions [29,30]. Fourth, although the proposed bleeding risk score in the current study showed adequate performance by comparison of previous risk models, future analysis including a development and validation cohort is desirable [31]. Finally, in the present study, antiplatelet therapy was mainly based on the use of aspirin and clopidogrel administration. A recent study showed the efficacy and safety of the newer thienopyridine antiplatelet agent in patients with ACS, irrespective of genetic polymorphisms [32]. Therefore, whether the new P2Y12 receptor inhibitors may further improve clinical outcomes in patients with PAD should be investigated in a future study.

Conclusions

To our knowledge, this is the first study to demonstrate the clinical utility of ABI for predicting 30-day bleeding complications in patients with ACS. Furthermore, ABI also provides useful information for predicting long-term mortality in these patients. The combination of the classical bleeding risk factors and the ABI assessment may improve risk stratification of ACS patients undergoing PCI.

Conflict of interests

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2019.01.008.

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