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Association of Asymptomatic Low Ankle–Brachial Index with Long-Term Clinical Outcomes in Patients after Acute Myocardial Infarction

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Aims: Peripheral arterial disease (PAD) is the well-known risk factor for cardiovascular events. Although low ankle–brachial index (ABI) is recognized as a risk factor in general population, low ABI without any symptoms of PAD has not been established as a prognostic marker in patients with acute myocardial infarction (AMI) yet. The purpose of this retrospective study was to examine whether asymptomatic low ABI was associated with long-term clinical outcomes in AMI patients without treatment history of PAD.

Methods: We included 850 AMI patients without a history of PAD and divided them into the preserved ABI (ABI ≥ 0.9) group (n=760) and the reduced ABI (ABI <0.9) group (n=90) on the basis of the ABI measurement during the hospitalization. The primary endpoint was the major adverse cardiovascular events (MACE) defined as the composite of all-cause death, non-fatal myocardial infarction, and hospitalization for heart failure.

Results: During the median follow-up duration of 497 days (Q1: 219 days to Q3: 929 days), a total of 152 MACE were observed. The Kaplan–Meier curves showed that MACE were more frequently observed in the reduced ABI group than in the preserved ABI group (p<0.001). The multivariate COX hazard analysis revealed that reduced ABI was significantly associated with MACE (hazard ratio 2.046, 95% confidence interval 1.344–3.144, p=0.001) after controlling confounding factors.

Conclusions: Reduced ABI was significantly associated with long-term adverse events in AMI patients without a history of PAD. Our results suggest the usefulness of ABI as a prognostic marker in AMI patients irrespective of symptomatic PAD.

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Key words: Acute myocardial infarction, Ankle–brachial index, Peripheral artery disease

Introduction

Acute myocardial infarction (AMI) is the most important cause of sudden cardiac death[1]. Primary percutaneous coronary intervention (PCI) as well as intensive coronary care unit (CCU) management significantly reduced the in-hospital mortality of patients with AMI[2]. However, some patients with AMI would suffer from cardiovascular events even after the hospital discharge[3]. It is not surprising that AMI patients with symptomatic ischemia or exercise-induced ischemia would have long-term adverse events[4, 5]. Moreover, AMI patients with left ventricular dysfunction would definitely have poor clinical outcomes[6]. Therefore, AMI patients with residual ischemia or left ventricular dysfunction should be closely followed up by cardiologists. However, since AMI patients with unrecognized risk factors may miss the opportunity to be closely followed up, it would be clinically important to find those unrecognized risk factors to improve long-term clinical outcomes in AMI patients.

Peripheral arterial disease (PAD), especially symptomatic PAD, is the well-known risk factor for

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cardiovascular events[7-9]. Although low ankle–brachial index (ABI) is recognized as a risk factor in general population[10] and patients with coronary artery disease[11, 12], low ABI without any symptoms or treatment history of PAD has not been established as a risk factor in patients after AMI yet. This retrospective study was aimed to examine whether asymptomatic low ABI was associated with long-term clinical outcomes in AMI patients without a treatment history of PAD.

Methods

Study Design

We reviewed all AMI patients treated at our institution (Saitama Medical Center, Jichi Medical University) between January 2015 and December 2019. The inclusion criteria were (1) patients with AMI and (2) patients who underwent ABI measurement during the index AMI hospitalization. The exclusion criteria were (1) patients with a history of endovascular, surgical, or medical treatment for PAD, (2) patients with symptomatic reduced ABI (ABI < 0.9), (3) same patient multiple occurrences (i.e.,., ≥ 2 AMI) during the study period, (4) patients who did not undergo PCI, (5) patients who underwent CABG, (6) patients who died in the index hospitalization, and (7) patients without any follow-up after the hospital discharge.

We adopted ABI 0.90 as a cutoff value because several clinical guidelines have used 0.9 as a cutoff for abnormal ABI[13-15]. The final study population was divided into a preserved ABI group (ABI ≥ 0.9) and a reduced ABI group (ABI < 0.9) according to the ABI values during the index hospitalization. The primary endpoint was major cardiovascular events (MACE) defined as the composite of all-cause death, non-fatal myocardial infarction, and readmission for heart failure. Information regarding the above clinical outcomes was acquired from hospital records. The day of the index hospital discharge was defined as the index day (day 1). The study patients were followed until meeting MACE or until the study end date (November 30, 2020). This study was approved by the institutional review board of the Saitama Medical Center, Jichi Medical University (S20-181), and written informed consent was waived because of the retrospective study design. The data collection and storage were performed anonymously, according to the Japan Ministry of Health, Labor and Welfare guidelines.

Definitions

AMI was defined according to the universal definition[16, 17]. Diagnostic ST elevation was defined as new ST elevation at the J point in at least two contiguous leads of 2 mm (0.2 mV), and the AMI patients with ST elevation were diagnosed as STEMI[18]. Hypertension was defined as systolic blood pressure of > 140 mmHg, diastolic blood pressure > 90 mmHg, or medical treatment for hypertension[19]. Diabetes mellitus was defined as hemoglobin A1c ≥ 6.5% or treatment for diabetes mellitus[19]. Dyslipidemia was defined as total cholesterol ≥ 220 mg/dL, low-density lipoprotein (LDL) cholesterol ≥ 140 mg/dL, or treatment for dyslipidemia[20]. We used the laboratory data at admission. Since we could not measure some laboratory data such as HbA1c or LDL cholesterol levels at off-hours (night or holidays), we substituted the earliest HbA1c or LDL cholesterol levels since admission for the laboratory data at admission[20]. Left ventricular ejection fraction (LVEF) was measured by transthoracic echocardiography during the index hospitalization. LVEF was calculated through either a modified Simpson method, Teichholz method, or eyeball estimation. The Teichholz method was adopted only when a modified Simpson method was not available. An eyeball estimation was adopted only when both the modified Simpson method and the Teichholz method were not available. We also calculated the estimated glomerular filtration rate (eGFR) using serum creatinine (Cr), age, weight, and gender according to the following formula: $eGFR = 194 \times Cr^{-1.094} \times age^{-0.287}$ (male), or $eGFR = 194 \times Cr^{-1.094} \times age^{-0.287} \times 0.739$ (female)[21]. The initial thrombolysis in myocardial infarction (TIMI) flow grade and final TIMI flow grade were recorded from coronary angiography[22].

Statistical Analysis

Data were expressed as mean ± SD or percentage. Categorical variables were presented as numbers (percentage) and were compared using the Chi-square test. For continuous variables, the Shapiro–Wilk test was performed to determine whether the continuous variables were normally distributed or not. Normally distributed continuous variables were compared using a student *t* test. Otherwise, continuous variables were compared using a Mann–Whitney *U* test. Event-free survival curves were constructed using the Kaplan–Meier method, and statistical differences between curves were assessed using the log-lank test. We also performed a multivariate COX hazard analysis to investigate the association between reduced ABI and MACE after controlling confounding factors. Variables that were significantly different ($p < 0.01$) between the reduced and preserved groups were considered as confounding factors. We used $p < 0.01$

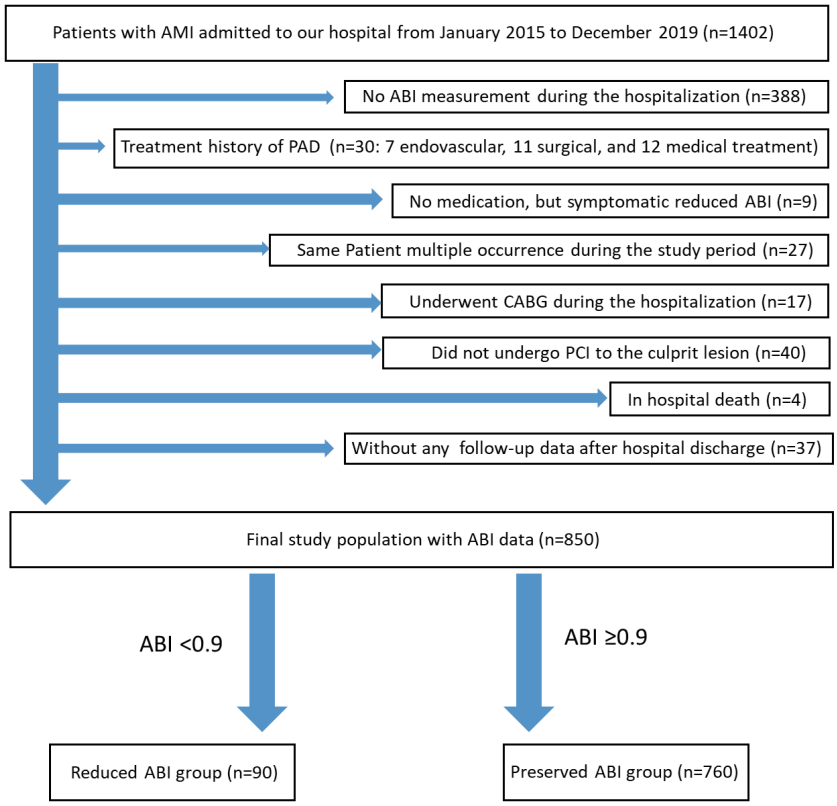

Fig. 1. Study flowchart

Abbreviations: AMI = acute myocardial infarction, ABI = ankle–brachial index, PAD = peripheral arterial disease, CABG = coronary artery bypass graft surgery.

rather than $p < 0.05$ for selecting confounding factors in the multivariate model to avoid overfitting of the model. Variables with missing values were not included in the model. Moreover, similar variables were not entered into the model simultaneously to avoid multicollinearity. Hazard ratios and the 95% confidence intervals (CIs) were calculated; a p value of < 0.05 was considered statistically significant. All analyses were performed using statistical software, SPSS 25/Windows (SPSS, Chicago, IL, USA).

Results

From January 2015 to December 2019, a total of 1402 AMI patients were admitted to our medical center. After excluding 552 patients who were compatible with the exclusion criteria, the final study population consisted of 850 AMI patients, which were divided into the preserved ABI group ($n = 760$) and the reduced ABI group ($n = 90$) **(Fig. 1)**.

Table 1 shows the comparison of patient's characteristics between the two groups. Age was significantly younger in the preserved ABI group than in the reduced ABI group. Estimated GFR was significantly greater in the preserved ABI group than in the reduced ABI group. The prevalence of STEMI was significantly greater in the preserved ABI group than in the reduced ABI group. Peak creatinine kinase (CK) and peak CK-myocardial band were significantly greater in the preserved ABI group than in the reduced ABI group.

Table 2 shows the comparison of angiographic and procedural findings between the two groups. The prevalence of single-vessel disease was significantly greater in the preserved ABI group than in the reduced ABI group. The prevalence of chronic total occlusion (CTO) in non-culprit arteries was significantly greater in the reduced ABI group than in the preserved ABI group.

Fig. 2 shows the Kaplan–Meier curves for MACE between the two groups. The median follow-up duration was 497 days (Q1: 219 days to Q3: 929 days). The incidence of MACE was significantly greater in the reduced ABI group than in the preserved ABI group. **Table 3** shows the comparison of clinical outcomes between the two groups. The prevalence of MACE, all-cause death, cardiac death, non-fatal MI, and readmission of heart failure was significantly

Table 1. The comparison of patient clinical characteristic between the reduced ABI and preserved ABI groups

	All ($n=850$)	Reduced ABI ($n=90$)	Preserved ABI ($n=760$)	P value
Age, years	68.9 ± 12.4	75.1 ± 11.0	68.2 ± 12.3	< 0.001
Male, *n* (%)	657 (77.3)	62 (68.9)	595 (78.3)	0.061
Body mass index (kg/m^2)	24.0 ± 3.6	22.9 ± 3.3	24.1 ± 3.6	0.004
Comorbidities				
Hypertension, *n* (%)	698 (82.1)	81 (90.0)	617 (81.2)	0.041
Hyperlipidemia, *n* (%)	502 (59.1)	52 (57.8)	450 (59.2)	0.821
Diabetes mellitus, *n* (%)	358 (42.1)	50 (55.6)	308 (40.5)	0.007
Current smoker, *n* (%)	292 (34.8) ($n=839$)	24 (27.0) ($n=89$)	268 (35.7) ($n=750$)	0.126
Chronic renal failure on hemodialysis, *n* (%)	48 (5.6)	17 (18.9)	31 (4.1)	< 0.001
History of previous PCI, *n* (%)	138 (16.2)	22 (24.4)	116 (15.3)	0.033
History of previous CABG, *n* (%)	21 (2.5)	3 (3.3)	18 (2.4)	0.48
History of previous myocardial infarction, *n* (%)	93 (10.9)	12 (13.3)	81 (10.7)	0.474
History of stroke, *n* (%)	105 (12.4)	23 (25.6)	82 (10.8)	< 0.001
Type of acute myocardial infarction				
STEMI, *n* (%)	528 (62.1)	34 (37.8)	494 (65.0)	< 0.001
NSTEMI, *n* (%)	322 (37.9)	56 (62.2)	266 (35.0)	< 0.001
Cardiopulmonary arrest out of hospital, *n* (%)	28 (3.3)	4 (4.4)	24 (3.2)	0.527
Shock at admission, *n* (%)	64 (7.5)	8 (8.9)	56 (7.4)	0.532
Killip 1 or 2, *n* (%)	720 (84.7)	68 (75.6)	652 (90.6)	0.019
Killip 3 or 4, *n* (%)	131 (15.4)	22 (24.4)	109 (14.3)	0.019
Vital signs				
Systolic blood pressure at admission, mmHg	143.4 ± 30.2	143.8 ± 33.7	143.3 ± 29.8	0.896
Diastolic blood pressure at admission, mmHg	83.2 ± 19.9	79.8 ± 23.2	83.7 ± 19.5	0.045
Heart rate at admission, bpm	81.4 ± 22.0	89.1 ± 27.1	80.5 ± 21.1	0.002
Laboratory data				
Hemoglobin levels, g/dL	13.5 ± 2.1	12.3 ± 2.1	13.6 ± 2.0	< 0.001
Platelets, × 10^3/uL	23.1 ± 8.5	23.1 ± 8.4	23.1 ± 8.5	0.922
Serum creatinine, mg/dL	1.31 ± 1.77	2.37 ± 2.89	1.18 ± 1.54	< 0.001
eGFR, mL/min/1.73 m^2	65.7 ± 27.7	45.6 ± 28.6	68.1 ± 26.6	< 0.001
Hemoglobin A1c, %	6.56 ± 1.42 ($n=840$)	6.75 ± 1.78 ($n=86$)	6.54 ± 1.37 ($n=754$)	0.308
C-reactive protein, mg/dL	1.26 ± 3.11	2.11 ± 3.77	1.16 ± 3.0	< 0.001
Brain natriuretic peptide, pg/ml	341.4 ± 21.0 ($n=835$)	827.0 ± 94.8 ($n=90$)	282.7 ± 19.6 ($n=745$)	< 0.001
Peak creatine kinase, U/L	1555.8 ± 69.1	884.1 ± 129.7	1635.3 ± 75.2	< 0.001
Peak creatine kinase-myocardial band, U/L	146.5 ± 6.6 ($n=849$)	77.2 ± 11.7 ($n=90$)	154.7 ± 7.2 ($n=759$)	< 0.001
Left ventricular ejection fraction, %	53.1 ± 13.7	47.4 ± 14.7	53.7 ± 13.4	< 0.001
Medication at admission				
Aspirin, *n* (%)	218 (26.8) ($n=813$)	38 (43.7) ($n=87$)	180 (24.8) ($n=726$)	< 0.001
Thienopyridine, *n* (%)	109 (11.8) ($n=813$)	23 (26.4) ($n=87$)	86 (11.8) ($n=726$)	< 0.001
Statin, *n* (%)	256 (31.5) ($n=823$)	34 (39.1) ($n=87$)	222 (30.6) ($n=726$)	0.113
ACE inhibitors or ARBs, *n* (%)	306 (37.6) ($n=813$)	47 (54.0) ($n=87$)	259 (35.4) ($n=726$)	0.001
Beta-blockers, *n* (%)	157 (19.3) ($n=813$)	20 (12.7) ($n=87$)	137 (18.9) ($n=726$)	0.388
Calcium channel blocker, *n* (%)	306 (37.6) ($n=813$)	44 (50.6) ($n=87$)	262 (36.1) ($n=726$)	0.01
Diuretics, *n* (%)	100 (12.3) ($n=813$)	18 (20.7) ($n=87$)	82 (11.3) ($n=726$)	< 0.001
Oral antidiabetic, *n* (%)	210 (25.8) ($n=813$)	32 (36.8) ($n=87$)	178 (24.5) ($n=726$)	0.019
Insulin, *n* (%)	54 (6.6) ($n=813$)	12 (13.8) ($n=87$)	42 (5.8) ($n=76$)	0.01
Direct oral anticoagulants., *n* (%)	10 (1.2) ($n=813$)	0 (0) ($n=87$)	10 (1.4) ($n=726$)	0.611
Warfarin, *n* (%)	19 (2.3) ($n=813$)	0 (0) ($n=87$)	19 (2.6) ($n=726$)	0.25
Medication at discharge				
Aspirin, *n* (%)	840 (98.8)	90 (100)	750 (98.7)	0.611
Thienopyridine, *n* (%)	820 (96.5)	86 (95.6)	734 (96.6)	0.548
Statin, *n* (%)	838 (98.6)	88 (97.8)	750 (98.7)	0.368
ACE inhibitors or ARBs, *n* (%)	817 (96.1)	82 (91.1)	735 (96.7)	0.017
Beta-blocker s, *n* (%)	790 (92.9)	80 (88.9)	710 (93.4)	0.125
Calcium channel blocker, *n* (%)	161 (18.9)	21 (23.3)	140 (18.4)	0.257
Diuretics, *n* (%)	260 (30.6)	45 (50.0)	215 (28.3)	< 0.001
Oral antidiabetic, *n* (%)	277 (32.6)	39 (43.3)	238 (31.3)	0.024
Insulin, *n* (%)	68 (8.0)	16 (17.8)	52 (6.8)	0.001
Direct oral anticoagulants., *n* (%)	57 (6.7)	6 (6.7)	51 (6.7)	1.0
Warfarin, *n* (%)	35 (4.1)	1 (1.1)	34 (4.5)	0.164

Data were expressed as mean ± SD or numbers (percentages). A Student's t test was used for normally distributed continuous variables and Mann–Whitney U test was used for abnormally distributed continuous variables. A Chi-square test was used for categorical variables. Abbreviations: ABI = ankle brachial index, PCI = percutaneous coronary intervention, CABG = coronary artery-bypass grafting, STEMI = ST-segment elevation myocardial infarction, NSTEMI = non-ST-segment elevation myocardial infarction, eGFR = estimated glomerular filtration rate, ACE inhibitors = angiotensin-converting enzyme inhibitor, ARBs = angiotensin receptor blockers.

Table 2. The comparison of lesion and procedural characteristic between the reduced ABI and preserved ABI groups

	All (n=850)	Reduced ABI (n=90)	Preserved ABI (n=760)	P value
Number of narrowed coronary arteries				0.001
Single, *n* (%)	368 (43.3%)	23 (25.6%)	345 (45.4%)	
Double, *n* (%)	286 (33.6%)	37 (41.1%)	249 (32.8%)	
Triple, *n* (%)	196 (23.1%)	30 (33.3%)	166 (21.8%)	
Infarct-related artery				0.289
Left main-left anterior descending artery, *n* (%)	425 (50.0%)	43 (47.8%)	382 (50.3%)	
Right coronary artery, *n* (%)	290 (34.1%)	28 (31.1%)	262 (34.5%)	
Left circumflex artery, *n* (%)	123 (14.5%)	16 (17.8%)	107 (14.1%)	
Not determined, *n* (%)	12 (1.4%)	3 (3.3%)	9 (1.2%)	
50% ≥ stenosis at left main, *n* (%)	79 (9.3%)	10 (11.1%)	69 (9.1%)	0.563
First TIMI flow (0, 1, 2, 3)				<0.001
0, *n* (%)	331 (38.9%)	25 (27.8%)	306 (40.3%)	
1, *n* (%)	69 (8.1%)	1 (1.4%)	68 (8.9%)	
2, *n* (%)	142 (16.7%)	14 (15.6%)	128 (16.8%)	
3, *n* (%)	308 (36.2%)	50 (55.6%)	258 (33.9%)	
Final TIMI flow (0, 1, 2, 3)				0.706
0, *n* (%)	4 (0.5%)	1 (1.1%)	3 (0.4%)	
1, *n* (%)	7 (0.8%)	1 (1.1%)	6 (0.8%)	
2, *n* (%)	29 (3.4%)	2 (2.2%)	27 (3.6%)	
3, *n* (%)	810 (95.3%)	86 (95.6%)	724 (89.4%)	
CTO in non-culprit arteries, *n* (%)	106 (12.5%)	21 (23.3%)	85 (11.2%)	0.002
Use of aspiration catheter, *n* (%)	142 (16.7%)	5 (5.6%)	137 (18.0%)	0.002
Final PCI Procedure				0.045
POBA only, *n* (%)	30 (3.5%)	6 (6.7%)	24 (3.2%)	
Drug coated balloon, *n* (%)	29 (3.4%)	4 (4.4%)	25 (3.3%)	
Bare metal stent, *n* (%)	14 (1.6%)	3 (3.3%)	11 (1.4%)	
Drug eluting stent, *n* (%)	765 (90.0%)	75 (83.3%)	690 (90.8%)	
POBA and aspiration, *n* (%)	4 (0.5%)	0 (0%)	4 (0.5%)	
Aspiration only, *n* (%)	4 (0.5%)	0 (0%)	4 (0.5%)	
Wire did not cross the lesion, *n* (%)	4 (0.5%)	2 (2.2%)	2 (0.3%)	
Approach site				<0.001
Radial, *n* (%)	587 (69.1%)	47 (52.2%)	540 (71.1%)	
Brachial, *n* (%)	11 (1.3%)	5 (5.6%)	6 (0.8%)	
Femoral, *n* (%)	252 (29.6%)	38 (42.2%)	214 (28.2%)	
Guide-Catheter size (Fr)				0.003
6Fr, *n* (%)	577 (67.9%)	47 (52.2%)	530 (69.7%)	
7Fr, *n* (%)	266 (31.3%)	42 (46.7%)	224 (29.5%)	
8Fr, *n* (%)	7 (0.8%)	1 (1.1%)	6 (0.8%)	

Data were expressed as mean ± SD or numbers (percentages). A Student's t test was used for normally distributed continuous variables, and Mann–Whitney U test was used for abnormally distributed continuous variables. A Chi-square test was used for categorical variables. Abbreviations: TIMI = thrombolysis in myocardial infarction, CTO = Chronic total occlusion, POBA = Plain old balloon angioplasty.

greater in the reduced ABI group than in the preserved ABI group.

The multivariate COX hazard analysis was performed in Table 4. Reduced ABI was significantly associated with MACE (HR 2.046, 95% CI 1.344–3.144, p=0.001) after controlling multiple confounding factors including age, body mass index, diabetes mellitus, chronic renal failure on hemodialysis, history of stroke, STEMI, heart rate at admission, hemoglobin, C-reactive protein, peak creatine kinase levels, LVEF, insulin at discharge, diuretics at discharge, number of narrowed coronary arteries, CTO in non-culprit arteries, use of aspiration catheter, and approach site.

Discussion

We included 850 AMI patients without a history

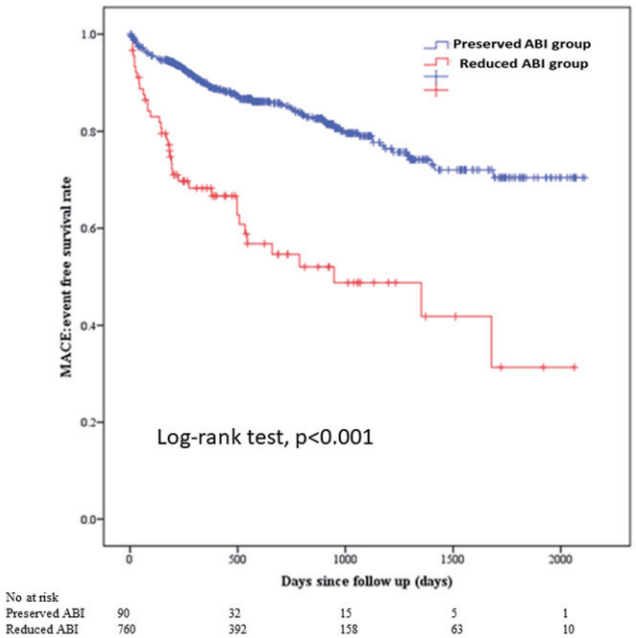

Fig. 2. Kaplan–Meier curves for MACE-free survival between the reduced ABI group and the preserved ABI group
A log-rank test was used.

Table 3. Comparison of Clinical Outcomes Between the reduced ABI and preserved ABI groups

	all (n=850)	Reduced ABI (n=90)	Preserved ABI (n=760)	p value
MACE, n (%)	152 (17.9)	38 (42.2)	114 (15.0)	<0.001
All-cause death, n (%)	50 (5.9)	12 (13.3)	38 (5.0)	0.004
Cardiac death, n (%)	19 (2.2)	6 (6.7)	13 (1.7)	0.01
Non-fatal myocardial infarction, n (%)	60 (7.1)	12 (13.3)	48 (6.3)	0.026
Re-admission for heart failure, n (%)	75 (8.8)	23 (25.6)	52 (6.8)	<0.001

Data were expressed as numbers (percentages). A Chi-square test was used for categorical variables. Abbreviations: MACE = major cardiovascular events.

Table 4. Multivariate COX Hazard Model to Predict MACE

Composite endpoint	Hazard ratios	95% confidence interval	P value
MACE			
Preserved ABI (≥ 0.9)	Reference		
Unadjusted reduced ABI (<0.9)	3.489	2.416-5.040	<0.001
Adjusted reduced ABI (<0.9)	2.046	1.344-3.144	0.001
Component endpoints	**Hazard ratios**	**95% confidence interval**	**P value**
All cause death			
Preserved ABI (≥ 0.9)	Reference		
Unadjusted reduced ABI (<0.9)	2.977	1.555-5.700	0.001
Adjusted reduced ABI (<0.9)	1.358	0.664-2.777	0.401
Non-fatal myocardial infarction			
Preserved ABI (≥ 0.9)	Reference		
Unadjusted reduced ABI (<0.9)	2.433	1.291-4.583	0.006
Adjusted reduced ABI (<0.9)	1.144	0.548-2.388	0.721
Readmission for heart failure			
Preserved ABI (≥ 0.9)	Reference		
Unadjusted reduced ABI (<0.9)	4.353	2.663-7.114	<0.001
Adjusted reduced ABI (<0.9)	2.660	1.526-4.637	0.001

In the adjusted model, Reduced ABI (vs. preserved ABI) was adjusted for age, body mass index, diabetes mellitus, chronic renal failure on hemodialysis, history of stroke, STEMI, heart rate at admission, hemoglobin, C-reactive protein, peak creatine kinase levels, left ventricular ejection fraction, insulin at discharge, diuretics at discharge, number of narrowed coronary arteries, CTO in non-culprit arteries, use of aspiration catheter, and approach site.

or symptom of PAD and divided those into the preserved ABI group (n=760) and the reduced ABI group (n=90). Patients in the reduced ABI group did not have a history of PAD or a symptom of PAD. We followed up those patients with a median duration of 497 days. MACE were more frequently observed in the reduced ABI group than in the preserved ABI group. The multivariate COX hazard analysis revealed that reduced ABI was significantly associated with MACE (HR 2.046, 95% CI 1.344–3.144, p=0.001) after controlling multiple confounding factors. Our results support the routine ABI measurement to identify the high-risk group among AMI patients.

First, we should elucidate the difference between the present study and earlier studies. Attar *et al.* reported that PAD was significantly associated with long-term adverse events using a national registry data of Sweden[23]. Although their study included a large number of patients (n=110,976), only 3.8% were diagnosed with PAD, which probably missed many asymptomatic patients[23]. Inglis *et al.* also reported the strong association between PAD and long-term adverse events using an individual-patient meta-analysis of 28,771 patients after AMI[24]. Thus, the association between symptomatic PAD and long-term poor outcomes is well established in patients with AMI. Ostman *et al.* investigated the impact of subclinical extracoronary artery disease, which included asymptomatic abnormal ABI, abnormal carotid artery disease, and abdominal artery disease, in patients after AMI[25]. In their study, in comparison with patients without extracoronary artery disease, long-term clinical outcomes were worse in patients with symptomatic extracoronary artery disease but were comparable in patients with asymptomatic extracoronary artery disease[25]. Although their study design was relatively similar to our study, we focused on asymptomatic abnormal ABI, which is a simpler and more objective than ultrasonographic examinations of the carotid arteries or abdominal aorta.

We should discuss why asymptomatic reduced ABI was associated with long-term MACE in patients with AMI. One explanation is that asymptomatic reduced ABI might develop to critical limb ischemia. Although the incidence of the development of critical limb ischemia among asymptomatic abnormal ABI is unknown, Yoshikawa *et al.* reported that critical limb ischemia occurred in 18% of asymptomatic abnormal ABI (<1.0) patients with hemodialysis over a mean follow-up period of 3.2±1.2 years[26]. Because the 2 year mortality including noncardiovascular causes is more than 40% in patients with critical limb ischemia[27], the development of critical limb ischemia might be associated with poor clinical outcomes. Another explanation is that reduced ABI was a strong risk marker of systemic atherosclerotic diseases. A meta-analysis including 16 cohort studies revealed that low ABI (≤ 0.9) was associated with approximately twice the 10 year total mortality, cardiovascular mortality, and major coronary event rate compared with the overall rate in each Framingham risk score category during 480,325 person-years of follow-up[10]. Our results could confirm low ABI as a strong risk marker in the category of patients with AMI.

Clinical implications of the present study should be noted. Since asymptomatic reduced ABI was associated with long-term adverse outcomes, our results support the routine measurement of ABI for patients with AMI irrespective of clinical symptoms of PAD. If ABI was low in patients with AMI, those high-risk patients should be carefully followed up by cardiologists or generalists who are familiar with cardiovascular disease. In comparison with other risk markers such as carotid intima-media thickness or computed tomography coronary calcium[28, 29], ABI would be a simpler and less invasive marker. It is not difficult for patients with AMI to measure ABI during their hospitalization. Although imaging studies such as angiography, computed tomography angiography, or magnetic resonance angiography are not recommended for patients with asymptomatic low ABI in the clinical guidelines for PAD (class III)[14], patients with asymptomatic low ABI also should be closely followed up to notice any initial signs of PAD to prevent critical limb ischemia[30].

Several limitations associated with the present study warrant mention. Since this study was a single-center, retrospective study, there was a potential selection bias. The ABI measurement was performed in the physiological laboratory, which was apart from CCU/intensive care unit. The most severe patients who could not move to the physiological laboratory did not undergo the ABI measurement, which is also a selection bias. The ABI values during the AMI hospitalization may not represent the patient's real ABI values because approximately 30% of study patients underwent transfemoral PCI, which might affect ABI. Although we entered more than 15 variables in the multivariate COX hazard model, the clinical characteristics were widely different between the reduced ABI and preserved ABI groups, which poses a fact that our multivariate model could not adjust all confounding factors.

Conclusions

Reduced ABI was significantly associated with long-term adverse events in AMI patients without a

history of PAD. Our results suggest the usefulness of ABI as a prognostic marker in AMI patients irrespective of symptomatic PAD.

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Conflict of Interest

Dr. Sakakura has received speaking honoraria from Abbott Vascular, Boston Scientific, Medtronic Cardiovascular, Terumo, OrbusNeich, Japan Lifeline, Kaneka, and NIPRO. Dr. Jinnouchi has received speaking honoraria from Abbott Vascular. Prof. Fujita has served as a consultant for Mehergen Group Holdings, Inc.

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