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.
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 \(\leq 0.9\)), (3) same patient multiple occurrences (i.e.,, \(\geq 2\) 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 \(\geq 0.9\)) 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 \(\geq 140\) mmHg, diastolic blood pressure \(> 90\) mmHg, or medical treatment for hypertension\(^{19}\). Diabetes mellitus was defined as hemoglobin A1c \(\geq 6.5\%\) or treatment for diabetes mellitus\(^{19}\). Dyslipidemia was defined as total cholesterol \(\geq 220\) mg/dL, low-density lipoprotein (LDL) cholesterol \(\geq 140\) 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 = \(194 \times \text{Cr}^{-1.094} \times \text{age}^{-0.287}\) (male), or eGFR = \(194 \times \text{Cr}^{-1.094} \times \text{age}^{-0.287} \times 0.739\) (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 \(\pm\) 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 \(p < 0.01\)
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 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.

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

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).
### 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/m²)**    | 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  |
| **Laboratory data**            |               |                      |                         |         |
| Hemoglobin levels, g/dL        | 13.5 ± 2.1    | 12.3 ± 2.1           | 13.6 ± 2.0              | <0.001  |
| Platelets, × 10⁹/L             | 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 ± 1.5              | <0.001  |
| eGFR, mL/min/1.73 m²           | 65.7 ± 27.7   | 45.6 ± 28.6          | 68.1 ± 26.6             | <0.001  |
| Hemoglobin A1c, %              | 6.65 ± 1.42 (n=840) | 6.75 ± 1.78 (n=86) | 6.54 ± 1.37 (n=754) | 0.308   |
| C-reactive protein, mg/dL      | 2.16 ± 5.11   | 1.11 ± 3.77          | 1.16 ± 3.8              | <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 creatinine kinase, U/L** | 155.8 ± 69.1 | 884.1 ± 129.7 | 1635.3 ± 75.2 | <0.001 |
| Peak creatinine 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  |
| Thienopryridine, 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 (22.7) (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=726) | 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   |
| Thienopryridine, 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)              | 0.107   |
| Calcium channel blocker, n (%) | 790 (92.9)    | 80 (88.9)            | 710 (93.4)              | 0.125   |
| 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.
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 creatinine 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
**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 |
| Re-admission 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 asymptomatic 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)\(^31\), 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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