Ankle-Brachial Index as a Prognostic Indicator in Patients with Atrial Fibrillation-A Subanalysis of the IMPACT-ABI Study

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Background：The CHADS$_2$ score is a well-established predictor for outcomes in patients with atrial fibrillation (AF). The ankle-brachial index (ABI) is a known tool for diagnosing peripheral artery disease and a predictor for cardiovascular diseases；however, it is unclear whether it can predict cardiovascular death, myocardial infarction [MI], and stroke (major adverse cardiovascular event (MACE)) in patients with AF. The aim of this study was to investigate whether ABI could predict the prognosis in AF patients.

Methods：We measured ABI in 3131 consecutive patients who visited our cardiovascular center from 2005 to 2015, of which 401 had AF, and they were enrolled in this study. Three patients were excluded because their ABI was inadequate or higher than 1.5. The mean age was 68.0 ± 11.3 years old, and mean observation period was 4.6 ± 2.7 years. We examined the relationship between ABI and MACE.

Results：Of 398 patients, 52 (13.1 %) had MACE. Patients with ABI < 0.92 had an increased incidence of MACE over those with ABI > 0.92 (17 of 66 vs. 35 of 332, HR 2.2, 95 % CI 1.3 to 3.6, p = 0.0056). Patients with CHADS$_2$ score > 2 had a statistically insignificant increase in MACE over those with CHADS$_2 < 1$ (HR 1.6, 95 % CI 0.92 to 2.73, p = 0.12). Further, a CHA$_2$DS$_2$-VASc score > 2 showed a significant difference from that < 1 (HR 3.0, 95 % CI 1.2 to 7.4, p = 0.0079).

Conclusions：The ABI could predict the prognosis of patients with AF comparable to the CHADS$_2$ or CHA$_2$DS$_2$-VASc scores. *Shinshu Med J 67 : 197—204, 2019*

Abbreviations：ABI, ankle brachial index；MACE, major adverse cardiovascular event；BMI, body mass index；CAD, coronary artery disease；CHF, congestive heart failure；HT, hypertension；DM, diabetes mellitus；SAS, sleep apnea syndrome；AF, atrial fibrillation；MI, myocardial infarction；ACE-I, angiotensin-converting enzyme inhibitor；ARB, angiotensin receptor blocker；CCB, calcium channel blocker；Hb, hemoglobin；Cr, creatinine；eGFR, estimated glomerular filtration rate；T-Cho, total cholesterol；HDL-Cho, high-density lipoprotein cholesterol；LDL-Cho, low-density lipoprotein cholesterol；HbA1c, hemoglobin A1c；CRP, C-reactive protein；BNP, B-type-natriuretic peptide；LVDd, left ventricular end diastolic diameter；LVDs, left ventricular end systolic diameter；LVEF, left ventricular ejection fraction；LADs, left atrial diameter of systole；LV, left ventricular；NYHA, New York Heart Association；RA, right atrial

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I　Introduction

The CHADS$_2$ (congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke [doubled]) score and CHA$_2$DS$_2$-VASc (congestive heart failure, hypertension, age ≥ 75 years [doubled], diabetes, stroke

[doubled], vascular disease, sex category [if female, counted]) score are well-established predictors of stroke in patients with atrial fibrillation (AF)[1]. Moreover, they are known to be predictors of adverse cardiovascular events[2)-4)]. On the other hand, the ankle-brachial index (ABI) is known as a tool for detecting peripheral artery disease (PAD) with high specificity (low ABI (ABI≤0.9, a strong predictor of future cardiovascular events and mortality[5)-7)], and as a predictor for cardiovascular diseases and all-cause mortality[8)9)]. However, the influence of the ABI in predicting the disease outcome of AF patients has not been well researched. We think that ABI measurement in AF patients has two clinical meanings. First, we wanted to evaluate their prognosis using only ABI, which is simple and non-invasive. Also, no other study has clarified this hitherto. The aim of the study was to investigate whether the ABI could predict the prognosis in AF patients.

II Methods

A Study design and patient population

This study was a sub-analysis of the impressive predictive value of ABI for clinical long-term outcome in patients with cardiovascular disease examined by the ABI (IMPACT-ABI) study. The IMPACT-ABI study was a retrospective, single-center, observational study. We retrospectively identified 4619 consecutive patients admitted to Shinshu University for any cardiovascular disease between January 2005 and December 2012. All patients had their ABI measured upon admission. Of 4619 patients, 1488 were excluded because of missing data on ABI, and the remaining 3131 patients were enrolled for our study. We obtained the clinical, demographic, and laboratory data from the electronic medical records. The follow-up data were collected from the medical records or by contacting the patients. This study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of Shinshu University School of Medicine. As this study was performed retrospectively without written informed consent, the data were analyzed anonymously. This study was registered with the University Hospital

Medical Information Network Clinical Trials Registry (UMIN-CTR), as accepted by the International Committee of Medical Journal Editors (UMIN-ID; 000020276). Of the initial 3,131 patients, 2730 were excluded because of the presence of sinus rhythm on admission, 2 subjects owing to ABI>1.5, and 1 with inadequate ABI data. Thus, we evaluated 398 patients who presented with atrial fibrillation on admission. We divided the study cohort into 2 groups based on the ABI : a low ABI group (ABI<0.92, n＝66), and high ABI group (ABI≥0.92, n＝332). We also analyzed the relation between ABI and prognosis **(Fig. 1)** and analyzed between $CHADS_2/CHA_2DS_2$-VASc score and prognosis. The mean observation period was 4.6±2.7 years.

B Definitions

Body mass index (BMI) was calculated as weight (kg) divided by height squared (m²). Smoking habit was defined as previous/current smoking status, as obtained by an interview. Coronary artery disease was defined as a history of angina and/or previous MI. Hypertension was defined as systolic blood pressure≥140 mmHg, diastolic blood pressure≤90 mmHg, or the current use of anti-hypertensive agents. Dyslipidemia was defined as serum total cholesterol levels ≥220 mg/dL, low-density lipoprotein cholesterol levels ≥140 mg/dL, high-density lipoprotein cholesterol levels≤40 mg/dL, triglyceride levels≥150 mg/dL, or the use of lipid lowering agents. Diabetes mellitus (DM) was defined as fasting blood glucose levels≥ 126 mg/dL, casual plasma glucose levels≥200 mg/ dL, HbA1c≥6.5 %, or the use of insulin or oral hypoglycemic agents. Stroke was defined as ischemic stroke that persisted for≥24 hours or evidence of infarction on magnetic resonance imaging in accordance with the statement from the American Heart Association/American Stroke Association[10]. Previous heart failure was defined as a prior diagnosis of heart failure according to the Framingham criteria[11] or current treatment for heart failure. Sleep apnea syndrome was defined as apnea hypopnea index (AHI)≥15 with or without symptoms[12]. The echocardiographic parameters included the left ventricular end diastolic diameter (LVDd), left ventricular

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│        Hospitalization for cardiovascular disease, n = 3131       │
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                              │    │ Exclusion criteria, n = 2733               │
                              ▼    │ 1.  Inadequate ABI data, n = 1             │
                                   │ 2.  ABI > 1.5, n = 2                        │
                                   │ 3.  Sinus rhythm on admission, n = 2730    │
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│                  Enrolled in this study, n = 398                  │
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│             Divided into two groups, based on ABI                 │
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           │                                        │
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┌──────────────────────────┐          ┌──────────────────────────┐
│  High ABI group (≥ 0.92) │          │  Low ABI group (< 0.92)  │
│        N = 332           │          │        N = 66            │
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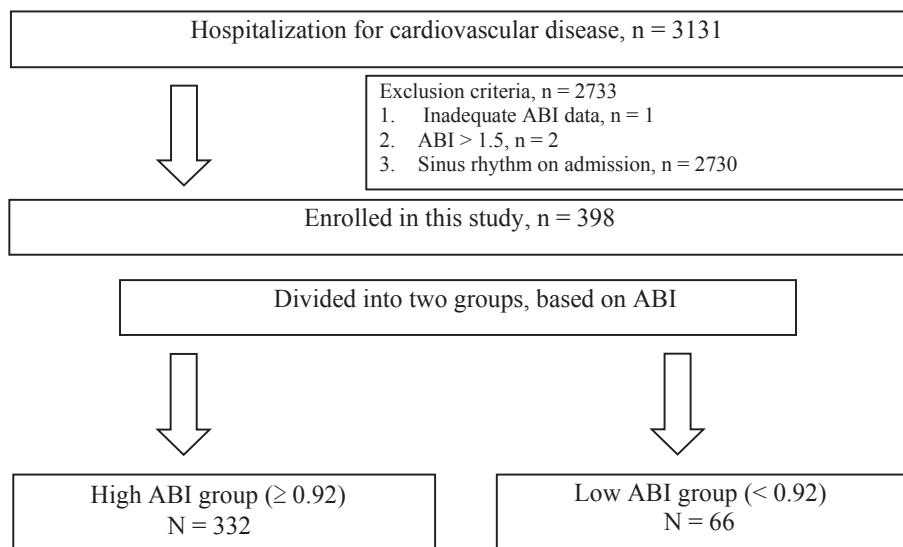
Fig. 1   Study design
Study flow diagram illustrating the inclusion process and exclusion criteria. Patients
were stratified into two groups based on their ankle-brachial index (ABI) values.

end systolic diameter (LVDs), and left ventricular ejection fraction (LVEF), as estimated using the Teichholz method. The estimated glomerular filtration rate (eGFR) was calculuated using the Japanese equation to estimate kidney function as follows: eGFR (ml/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ for male patients, and the same formula multiplied by 0.739 for female patients[13]. The all-cause death was defined as any death recorded during the follow-up period. Cardiovascular death was defined as death resulting from acute myocardial infarction (MI), significant cardiac arrhythmia, congestive heart failure (HF), stroke, or other cardiovascular causes[14]. MI was defined as a 2-fold rise in serum troponin I or creatine kinase-MB isoenzyme to at least twice the upper normal limits with acute onset of prolonged typical ischemic chest pain, ST-segment elevation of at least 1 mm in 2 contiguous electrocardiogram leads, or ST-segment depression of at least 0.5 mm in 2 contiguous leads[14].

C   ABI measurements

The ABI was determined with the patient at rest in the supine position for at least 10 minutes using the form pulse wave velocity (PWV)/ABI (Omron Colin, Tokyo, Japan), which is an automated oscillometric device with four cuffs that can measure the blood pressure in both upper and lower extremities simultaneously. The ABI was obtained as a ratio of the systolic blood pressure measured in the lower extremity divided by the higher of the two systolic blood pressures measured in the upper extremities. The lower of the two results was used as the patient ABI for all analyses.

D   Endpoint

The primary endpoint of this study was the composite of major adverse cardiovascular events (MACE), including cardiovascular death, myocardial infarction, and stroke. The secondary endpoint was all-cause death and cardiovascular death.

E   Statistical analysis

Statistical analyses were performed using JMP 13.0 (SAS Institute, Cary, NC, USA). Continuous variables were summarized as mean ± standard deviation if normally distributed and as median and interquartile range if not normally distributed. Normal data distribution was assessed using the Shapiro-Wilk test. Categorical variables were reported as numbers and percentages and were compared using the Chi-square test and the Mann-Whitney U test for continuous variables. Kaplan-Meier plots were calculated from baseline to the time of occurrence of cardiac event and were compared using the log-rank test. Adjusted odd ratios (OR) and 95 % confidence interval (CI) for high ABI were obtained by

multiple logistic regression analysis. Univariate Cox proportional hazard analyses were performed to identify the independent predictors of MACE. The optimal Receiver-Operating-Characteristic (ROC) curve cutoff value for prediction of MACE was considered as the value maximizing sensitivity plus specificity. The proportional hazards assumption was verified with log (time) vs. log [-log (survival)] plots. The variables that exhibited a P-value of<0.05 in the univariate analysis were included in the multivariate model. The magnitude of the relationship between the variables and MACE was expressed as the hazard ratio (HR) and 95 % CI. P-values of< 0.05 were considered statistically significant.

III　Results

A　Baseline characteristics

Baseline characteristics are summarized in **Table 1**. This study enrolled 398 patients, with a median age of 68.0 ± 11.3 years ; the majority of patients were male (76.9 %). The causes of admission among participants included acute myocardial infarction (1.5 %), unstable angina pectoris (0.5 %), stable angina pectoris (17.3 %), other atherosclerotic diseases (14.1 %), arrythmia (38.2 %), heart failure (8.8 %), and others (19.3 %). On the basis of the ABI, all patients were divided into two groups : 66 patients (16.6 %) had low ABI, 332 patients (83.4 %) had high ABI. No significant differences were found in BMI, coronary artery disease, hypertension, dyslipidemia, stroke, and sleep apnea syndrome between each group. However, low ABI values were significantly associated with higher smoking status and higher $CHADS_2$ and CHA_2DS_2-VASc scores. An increased number of patients exhibited diabetes mellitus and congestive heart failure in the low ABI group. In the echocardiographic findings, there were no significant differences in median LVDd, LVDs, and LADs ; however, patients with high ABI showed significantly higher LVEF than those with low ABI. A lower ABI was significantly associated with greater levels of creatinine and B-type natriuretic peptide (BNP) and lower levels of hemoglobin, estimated GFR, and HDL-Cho. At discharge, the prescription rates of drugs such as statins, angio-

tensin converting enzyme inhibitors (ACEIs), and/or angiotensin receptor blockers (ARBs), and amiodarone showed no difference ; however, the use of calcium channel blockers was significantly higher in patients with low ABI.

B　Outcomes

During the follow-up period (mean 4.6 years), a total of 52 cases (13.1 %) of MACE were recorded, including 37 of cardiovascular death, 4 of MI, and 11 of stroke. Between the two groups, the low ABI group exhibited significantly higher values of MACE, with significant differences in MI ; however, no significant differences in cardiovascular death and stroke were observed.

C　Predictors of MACE

The univariate Cox proportional hazards analysis showed that low ABI as well as higher CHA_2DS_2-VASc score (≥ 2) were independent predictors of MACE. Multivariate Cox proportional hazards analysis shows that adjusted for low ABI (<0.92), CHA_2DS_2-VASc score ≥ 2, LVEF, diabetes mellitus, congestive heart failure, and prescription of ACEIs, low ABI independently predicted a poorer prognosis (OR, 2.21 ; 95 % CI, 1.03-4.66 ; P = 0.039). **(Table 2)**. The Kaplan-Meier analysis showed that the cumulative event-free survival rate of MACE was markedly lower in patients with a low ABI **(Fig. 2)**.

IV　Discussion

To the best of our knowledge, this is the first report demonstrating the predictive power of low ABI on the prognosis of patients with AF. The major finding of this study was that low ABI could predict cardiovascular events as well as a high (≥ 2) $CHADS_2$ or CHA_2DS_2-VASc score. In patients with AF, higher $CHADS_2$ or CHA_2DS_2-VASc score (≥ 2) is known to be a predictor of stroke[1]. On the other hand, the prognosis of AF patients with heart failure is poor[15], and it is known that their risk for stroke, hospitalization for heart failure, and death is high[16)-19]. In such patients, higher $CHADS_2$ or CHA_2DS_2-VASc score (≥ 2) is also known to be a predictor of hospitalization for worsening of heart failure and mortality[3]. Ostergren and Sleight[20]. demonstrated that low ABI predicted

Table 1 Baseline Characteristics

Variables	Overall Population	ABI≥0.92	ABI<0.92	P-value
	(n = 398)	(n = 332)	(n = 66)	
Mean age (years)	68 ± 11	67 ± 11	72 ± 11	0.0031
Male gender, n (%)	308 (77)	254 (77)	54 (82)	0.420
Smoking, n (%)	161 (38)	126 (38)	35 (53)	0.0283
Body mass index (kg/m^2)	23 ± 4	23 ± 4	23 ± 4	0.161
CHADS$_2$ score	1.6 ± 1.2	1.5 ± 1.2	2.2 ± 0.2	<0.0001
CHA$_2$DS$_2$-VASc score	2.7 ± 1.7	2.5 ± 1.6	3.8 ± 0.2	<0.0001
Comorbidities				
Hypertension, n (%)	229 (58)	184 (55)	45 (68)	0.058
Diabetes mellitus, n (%)	98 (25)	70 (21)	28 (42)	0.0005
Coronary artery disease, n (%)	130 (33)	103 (31)	27 (41)	0.150
Dyslipidemia, n (%)	131 (33)	114 (34)	17 (26)	0.198
Stroke, n (%)	51 (13)	41 (12)	10 (15)	0.546
Congestive heart failure, n (%)	82 (21)	62 (19)	20 (30)	0.045
Sleep apnea syndrome, n (%)	12 (3)	10 (4)	2 (4)	1.00
Medications				
ACEIs, n (%)	80 (20)	64 (20)	16 (24)	0.408
ARBs, n (%)	143 (36)	117 (36)	26 (39)	0.679
β-blockers, n (%)	155 (39)	124 (38)	31 (47)	0.215
CCB, n (%)	116 (29)	87 (27)	29 (44)	0.0079
Statin, n (%)	113 (28)	91 (28)	22 (33)	0.457
Amiodarone, n (%)	22 (6)	19 (6)	3 (5)	1.00
Echocardiographic data				
LVEF (%)	61 ± 16	62 ± 16	58 ± 16	0.044
LV end-diastolic dimension (cm)	5.0 ± 0.8	5.0 ± 0.8	5.1 ± 1.0	0.110
LV end-systolic dimension (cm)	3.4 ± 1.4	3.3 ± 1.5	3.4 ± 1.1	0.549
LA end-systolic dimension (cm)	4.7 ± 1.0	4.7 ± 1.1	4.7 ± 1.0	0.704
Laboratory data				
Hemoglobin (g/dL)	14.1 ± 2.0	14.2 ± 2.3	13.5 ± 2.3	0.0129
eGFR (mL/min/1.73 m^2)	56 ± 23	58 ± 22	45 ± 24	0.0016
Total cholesterol (mg/dL)	187 ± 41	187 ± 40	186 ± 44	0.963
HDL-cholesterol (mg/dL)	51 ± 15	52 ± 14	45 ± 15	0.0007
LDL-cholesterol (mg/dL)	107 ± 30	106 ± 30	112 ± 34	0.185
Hemoglobin A$_{1c}$ (%)	6.27 ± 0.9	6.2 ± 1.0	6.3 ± 0.8	0.317
BNP (pg/mL)	253 ± 352	232 ± 317	357 ± 479	0.0088

CHADS$_2$, congestive heart failure/hypertension/age≥75 years old/diabetes/stroke [doubled]; CHA$_2$DS$_2$-VASc, congestive heart failure/hypertension/age ≥75 years old [doubled]/diabetes/stroke [doubled]/vascular disease/sex category [if female, counted]; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BNP, B-type-natriuretic peptide; LA, left atrial.

cardiovascular mortality and development of future heart failure.

We showed that low ABI was associated with increased incidence of MACE and all-cause mortality as well as higher CHADS$_2$ or CHA$_2$DS$_2$-VASc score (≥2) in patients with AF. AF and atherosclerosis are known to be a chronic inflammatory disease and in-flammation is a triggering factor of atherosclerotic plaque rupture. AF is also associated with the in-flammatory state such as obesity, diabetes mellitus, hypertension, heart failure, metabolic syndrome and sedentary lifestyle[21]. In this regard, ABI serves as a measure of atherosclerosis, and thus, lower ABI can indicate vascular abnormalities causing adverse car-

Table 2　Cox Regression Analysis for MACE

Variables	Unadjusted HR (95 % CI)	P	Adjusted HR (95 % CI)	P
Male	0.58 (0.30–1.15)	0.117		
Age (years)	1.03 (1.00–1.07)	0.026		
BMI (kg/m^2)	1.00 (0.93–1.08)	0.999		
Smoking	1.05 (0.63–1.73)	0.858		
ABI＜0.92	2.76 (1.37–5.38)	0.0054	2.21 (1.03–4.66)	0.039
CHADS$_2$≥2	1.69 (0.92–3.16)	0.094		
CHA$_2$DS$_2$-VASc≥2	3.35 (1.41–9.90)	0.0047	1.91 (0.78–5.41)	0.184
Coronary artery disease	0.62 (0.34–1.08)	0.090		
Hypertension	0.98 (0.59–1.63)	0.938		
Dyslipidemia	0.61 (0.34–1.06)	0.081		
Diabetes mellitus	1.76 (1.02–3.01)	0.043	0.94 (0.43–1.98)	0.883
Stroke	1.34 (0.64–2.62)	0.428		
Congestive heart failure	1.89 (1.06–3.30)	0.031	1.04 (0.46–2.23)	0.923
Echocardiographic data				
LVEF (%)	0.97 (0.96–0.99)	0.0048	0.97 (0.95–1.00)	0.015
LVDd (cm)	1.00 (0.99–1.01)	0.889		
LVDs (cm)	1.01 (0.99–1.03)	0.292		
Medication				
Statin	1.12 (0.56–2.15)	0.747		
ACEIs	2.41 (1.22–4.66)	0.0126	1.76 (0.81–3.70)	0.140
ARBs	0.94 (0.48–1.78)	0.858		
Beta-blockers	1.01 (0.53–1.89)	0.982		
CCB	1.50 (0.77–2.83)	0.228		
Amiodarone	1.22 (0.28–3.78)	0.760		
Laboratory data				
Hemoglobin (g/dL)	0.89 (0.77–1.03)	0.124		
eGFR (mL/min/1.73 m^2)	0.99 (0.97–1.01)	0.397		
Total cholesterol (mg/dL)	1.00 (0.99–1.01)	0.630		
LDL-cholesterol (mg/dL)	1.00 (0.98–1.02)	0.512		
Hemoglobin A$_{1c}$ (%)	1.05 (0.75–1.43)	0.771		
BNP (pg/mL)	1.00 (0.99–1.00)	0.098		

BMI, body mass index ; CHADS$_2$, congestive heart failure/hypertension/age≥75 years old/diabetes/stroke [doubled] ; CHA$_2$DS$_2$-VASc, congestive heart failure/hypertension/age≥75 years old [doubled]/diabetes/stroke [doubled]/vascular disease/sex category [if female, counted] ; ACEIs, angiotensin-converting enzyme inhibitor ; ARBs, angiotensin receptor blocker ; CCB, calcium channel blocker ; LVEF, left ventricular ejection fraction ; LVDd, left ventricular end diastolic diameter ; LVDs, left ventricular end systolic diameter ; LA, left atrial ; eGFR, estimated glomerular filtration rate ; HDL, high-density lipoprotein ; LDL, low-density lipoprotein ; BNP, B-type-natriuretic peptide.

diovascular events and heart failure in the future. Thus, we should be cautious in AF patients with low ABI, because this patient population is more likely to experience cardiovascular events in the future than those with higher ABI. There is a possibility that early intervention in AF patients with low ABI can help in preventing the progression of the cardiovascular disease.

A　Limitations

While our study included data from a large sample to detect a sufficient number of cardiovascular events, this study has several potential limitations. First, it was a single center, retrospective analysis and involved patients who were hospitalized for cardiovascular disease. Thus, our study population may not be representative of the general population. Second, the patients who were enrolled in this registry had heterogeneous baseline cardiovascular diseases, so sample bias might have affected the results of the study. Third, we measured ABI only once at the

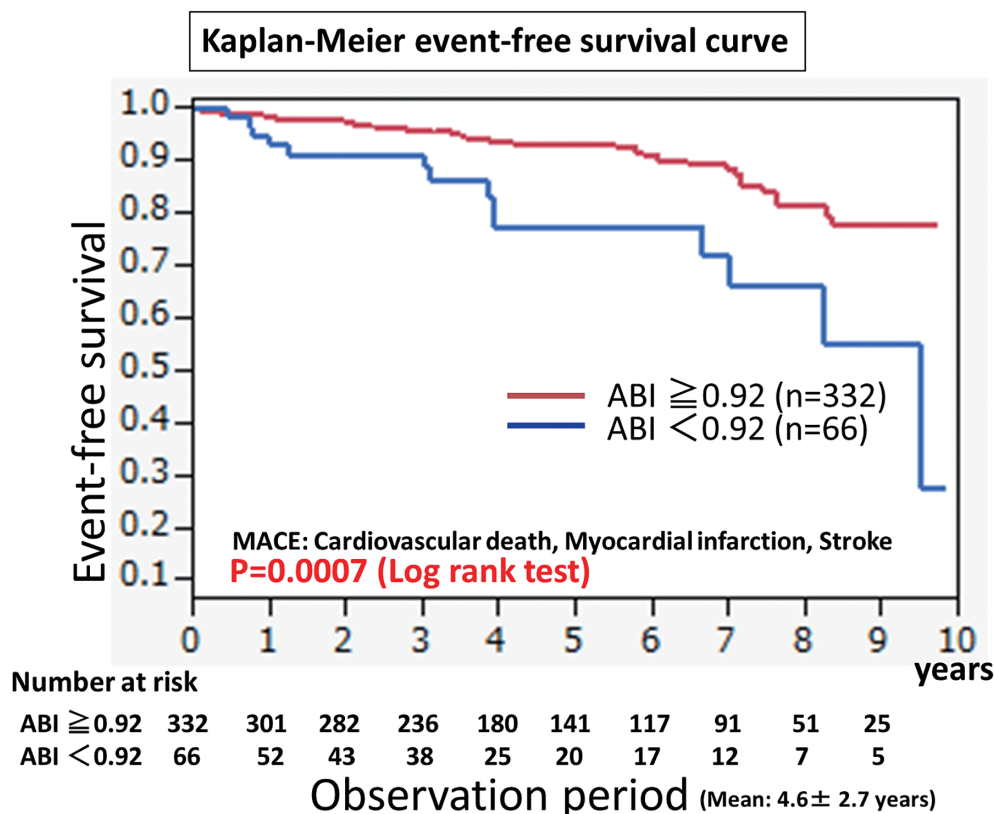**Kaplan-Meier event-free survival curve**

Fig. 2   Kaplan-Meier plot
Kaplan-Meier plot for cardiovascular death, myocardial infarction [MI], and stroke (MACE).
Two groups of patients were included in the analysis. The patients were assigned to a group
according to their ankle-brachial index (ABI) value.

time of hospitalization, so the data might not be right in patients with AF. Reports suggest that the accuracy of ABI in patients with atrial fibrillation decreases; however, other reports suggest that atrial fibrillation does not affect ABI data[22]. Finally, we have no data regarding changes of medication or habits that could affect the prognosis during the observation period.

V   Conclusion

We found that ABI measured at the time of ad-mission can predict the prognosis of patients with AF, similar to the $CHADS_2$ or CHA_2DS_2-VASc scores and can be useful to predict cardiovascular events and prevent progression of cardiovascular diseases.

VI   Acknowledgement

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