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Predictive Value of Abnormal and Borderline Ankle-Brachial Index for Coronary Re-Intervention and Mortality in Patients with Coronary Artery Disease: An Observational Cohort Study

Sanghyun Ahn¹*, EunAh Jo¹*, Seung-Kee Min¹, Sangil Min¹, Jongwon Ha¹, Kyung Woo Park², and Kyoung-Bok Min³

¹Department of Surgery, Seoul National University Hospital, Seoul, ²Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, Seoul, ³Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea

Purpose: This study aimed to investigate the abnormal and borderline ABIs for predicting coronary re-intervention and mortality in patients with coronary artery disease (CAD).

Materials and Methods: Data from a previous study were obtained and used to investigate the prevalence of peripheral arterial disease among Korean patients with CAD (n=285) in 2010. All patients underwent follow-up coronary angiography as scheduled (asymptomatic: 2-, 5-, and 7-month intervals) or as clinically indicated (symptomatic).

Results: In total, 33 patients had an abnormal ABI (ab-ABI: <1.0 or >1.4), and 252 had a normal ABI (nl-ABI: $1.0 \le ABI \le 1.4$). The mean follow-up was 47 months. The mortality was significantly higher in the ab-ABI group than in the nl-ABI group (18.2% vs. 6.7%, P=0.0233). MACEs were significantly more common in the ab-ABI group (60.6% vs. 34.5%, P=0. 0036). Moreover, the ab-ABI group had a greater CAD progression than the nl-ABI group (48.5% vs. 31.3%, P=0.0496). The incidence of clinically indicated coronary re-intervention was significantly higher in the ab-ABI group than in the nl-ABI group (33.3% vs. 13.1%, P=0.0025). After adjusting for age, diabetes, dyslipidemia, dialysis, smoking, and obesity, the incidence of clinically indicated re-intervention was significantly higher in the ab-ABI group than in the nl-ABI group (HR, 2.80; 95% CI, 1.24 to 6.34).

Conclusion: Abnormal and borderline ABI significantly increased the incidence of clinically indicated coronary revascularization and all-cause mortality during a 4-year follow-up among patients with CAD. Hence, ABI could be used to stratify extremely high-risk patients with CAD who may require aggressive surveillance or treatment.

Key Words: Coronary artery disease, Ankle brachial index, Borderline, Coronary intervention, Peripheral arterial disease

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Corresponding author: Kyoung-Bok Min

Department of Preventive Medicine, Seoul National University College of Medicine, 103 Daehak-ro, Jongno-gu, Seoul 03080, Korea

Tel: 82-2-2072-2817 Fax: 82-2-766-3975 E-mail: minkb@snu.ac.kr https://orcid.org/0000-0001-9576-0093

*These authors contributed equally to this work.

INTRODUCTION

The ankle-brachial index (ABI), the ratio of ankle to arm systolic blood pressure, is a simple diagnostic test that is available in any primary care setting [1]. In a previous study, approximately 15.9% of patients with significant coronary artery disease (CAD) on coronary angiography (CAG) presented with an asymptomatic abnormal ABI (ab-ABI) [2]. Moreover, our previous study of a Korean population showed that 15% of patients with CAD had peripheral arterial disease (PAD) [3].

Several studies have shown that an ABI <0.90 is a marker of future cardiovascular risk and is a diagnostic criterion of PAD [4]. In addition, an ab-ABI is associated with a high incidence of adverse clinical outcomes and poor cardiovascular outcomes in patients who underwent drug-eluting stent implantation [5].

A borderline ABI (0.91 to 0.99) is not included in the conventional diagnostic criteria for PAD. However, it increases the incidence of PAD and leads to a poor long-term prognosis [6]. Furthermore, it is associated with poor short-term clinical outcomes after coronary artery interventions, which can be correlated with endothelial dysfunction [7-9]. Such important outcomes should be considered. However, long-term studies of the mortality and prognosis of CAD patients with an abnormal or borderline ABI have not been published to date.

Hence, this study aimed to investigate the significance of abnormal and borderline ABI in terms of mortality, coronary re-intervention, and disease progression (DP) during a follow-up period of 4 years in Korean patients with CAD.

MATERIALS AND METHODS

1) Study population

The current observational cohort study was performed using data from a previous study [3] to investigate the prevalence of PAD among patients with CAD in 2010. Patients who were diagnosed with CAD and who underwent CAG at least twice (n=285) were included in this study. However, CAD patients who underwent coronary artery graft bypass surgery were excluded. Data about mortality rates in December 2014 were provided by the Korea National Statistical Office (https://kostat.go.kr). All patients underwent follow-up CAG (either scheduled or clinically indicated).

The group was divided based on two categories: 1) normal ABI (nl-ABI): $1.0 \le ABI \le 1.4$ and 2) ab-ABI, including PAD (ABI \le 0.9), non-compressible (ABI > 1.4), and borderline (0.90 < ABI < 1.00) [10,11]. Trained physician assistants mea-

sured ABI using a 10 to 20 cm sphygmomanometer and a handheld Doppler (Hadeco[®]; Hadeco, Tokyo, Japan).

The endpoints included all-cause mortality, major adverse cardiac events (MACEs), DP, repeated revascularization (RR), and DP pattern (DPP).

The institutional review board of Seoul National University Hospital approved this study, and the need for informed consent was waived (H-1602-059-740).

2) Definitions

MACE was defined as the composite of death, myocardial infarction (MI), or stroke. DP was defined as stenosis >30% or occlusion of any coronary artery on the latest CAG. The indication for RR was stenosis >50% on CAG or stenosis <50% with a correlated symptom. CAG was performed when scheduled (asymptomatic: 2-, 5-, and 7-month intervals) or clinically indicated (symptomatic with correlation with MI or angina). To evaluate DP, the target lesion was defined as the vessel segment containing the initially treated (stented or percutaneous transluminal angioplasty) lesion. The target vessel was defined as any other segment in the same epicardial vessel or one of its side branches. A non-target vessel or other was defined as the epicardial coronary arteries, not including the target lesion [12]. Data on mortality rates until December 2014 were obtained from the Korean National Statistical Office.

3) Statistical analysis

The baseline characteristics of the participants, who were categorized according to ABI (ab-ABI: <1.0 or >1.4



Fig. 1. Cumulative hazard of repeated revascularization stratified according to ankle-brachial index (ABI) categories (abnormal ABI [ab-ABI]: <1.0 or >1.4 and normal ABI [nl-ABI]: $1.0 \le ABI \le 1.4$).

versus nl-ABI: 1.0≤ABI≤1.4), were compared using the chisquare test. For the primary analysis of the association between ABI categories and health outcomes, we examined the proportion (%) of patients with ab-ABI and nl-ABI according to the incidence of MACE, DP, and RR and all-cause mortality during the follow-up period, and the possible association between them was determined using the chisquare test. The Kaplan-Meier curves were used to evaluate the cumulative hazard for RR in patients with ab-ABI and those with nl-ABI (Fig. 1). We conducted a multivariate Cox proportional hazards regression analysis of the health outcomes during the study period. The proportional hazards assumption for the model was confirmed. The hazard ratios (HRs) and 95% confidence intervals (Cls) for the incidence of MACE, DP, and RR and all-cause mortality in patients with ab-ABI and nl-ABI were evaluated. In the multivariate analyses, model 1 was adjusted for demographic variables (i.e., age and sex), and model 2 was further adjusted for cig-

 Table 1. Baseline characteristics of the participants according to ABI categories^a

Characteristic	Patients with	Patients with	D voluo ^b	
	ab-ABI (n=33)	nl-ABI (n=252)	r-value	
Age (y)				
50-59	5 (15.2)	63 (25.0)	0.1922	
60-69	12 (36.4)	108 (42.9)		
70-79	13 (39.4)	72 (28.6)		
≥80	3 (9.1)	9 (3.6)		
Sex				
Male	21 (63.6)	187 (74.2)	0.1985	
Female	12 (36.4)	65 (25.8)		
Cigarette smoking				
No	15 (45.5)	129 (51.2)	0.5354	
Yes	18 (54.5)	123 (48.8)		
BMI (kg/m ²)				
<25	16 (48.5)	112 (44.4)	0.6608	
≥25	17 (51.5)	140 (55.6)		
Number of diseased vessels				
1	6 (18.2)	98 (38.9)	0.0234	
2	10 (30.3)	78 (31.0)		
3	17 (51.5)	76 (30.2)		
Underlying disease				
Diabetes	17 (51.5)	83 (32.9)	0.0355	
Dyslipidemia	25 (75.8)	160 (63.5)	0.1650	
Hemodialysis	3 (9.1)	5 (2.0)	0.0201	

Values are presented as number (%).

ABI, ankle-brachial index; ab-ABI, abnormal ABI; nl-ABI, normal ABI; BMI, body mass index.

^aABI categories were defined as ab-ABI (<1.0 or >1.4) and nl-ABI (1.0 \leq ABI \leq 1.4). ^bP-value was determined using the chi-square test.

arette smoking, body mass index, number of diseased vessels, and underlying disease. All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA), and P-values <0.05 was considered statistically significant.

RESULTS

1) Demographic characteristics of the participants

Of 285 patients enrolled in this study, 33 (11.6%) had ab-ABI and 252 (88.4%) had nl-ABI. The mean follow-up was 47 months. The characteristics of the patients are shown in Table 1. The ab-ABI group had a significantly higher incidence of end-stage renal disease and three-vessel disease than the nl-ABI group. Half of the patients in the ab-ABI group had diabetes, and the intergroup difference was statistically significant.

2) Primary outcomes: all-cause mortality and incidence of MACE, DP, and RR

The all-cause mortality and incidence of MACE, DP, and RR were significantly higher in the ab-ABI group than in

 Table 2. Health outcomes of participants according to ABI categories^a during the follow-up period

Health outcomes	Patients with	Patients with	P. voluo ^b	
	ab-ABI (n=33)	nl-ABI (n=252)	r-value	
MACE ^c				
Yes	20 (60.6)	87 (34.5)	0.0036	
No	13 (39.4)	165 (65.5)		
Disease progression ^d				
Yes	16 (48.5)	79 (31.3)	0.0496	
No	17 (51.5)	173 (68.7)		
Repeated revascularization ^e				
Yes	11 (33.3)	33 (13.1)	0.0025	
No	22 (66.7)	219 (86.9)		
All-cause mortality				
Yes	6 (18.2)	17 (6.7)	0.0233	
No	27 (81.8)	235 (93.3)		

Values are presented as number (%).

ABI, ankle-brachial index; ab-ABI, abnormal ABI; nI-ABI, normal ABI; MACE, major adverse cardiac events.

^aABI categories were defined as ab-ABI (<1.0 or >1.4) and nl-ABI (1.0 \leq ABI \leq 1.4). ^bP-value was determined using the chi-square test. ^cMACE included disease progression, repeated revascularization, and all-cause mortality. ^dDisease progression was defined as stenosis >30% or occlusion of any coronary artery on the latest coronary angiography. ^cRepeated revascularization was defined as stenosis >50% on coronary angiography or stenosis <50% with a correlated symptom.

the nl-ABI group (Table 2). All-cause mortality and MACE occurred in 6 (18.2%) and 20 (60.6%) patients in the ab-ABI group and in 17 (6.7%) and 87 (34.5%) patients in the nl-ABI group (P=0.0233, P=0.0036) during the 4-year follow-up period. The all-cause rate and incidence rate of MACE was 2 to 3 times higher in the ab-ABI group than in the nl-ABI group. CAD progression was more common in the ab-ABI group (n=16, 48.5%) than in the nl-ABI group (n=79, 31.3%; P=0.0496). The incidence of clinically indicated coronary reintervention was significantly higher in the ab-ABI group

(n=11, 33.3%) than in the nl-ABI group (33, 13.1%; P=0.0025).

3) DP according to Scheduled or Clinically Indicated CAG

The overall DP based on scheduled and clinically indicated CAG was higher in the ab-ABI group than in the nl-ABI group. DP requiring RR was significantly higher in patients with ab-ABI and clinically indicated CAG, but not for those with scheduled CAG (Fig. 1). This cumulative incidence was nearly three times higher in patients with ab-ABI than in

Table 3. Hazard ratio (95% confidence intervals) for health outcomes a	according to ABI categories ^a
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Health outcomes	Unadjusted model	Adjusted model ^b		
	Unaujusteu mouer	Model 1	Model 2	
MACE ^c				
nI-ABI	Reference	Reference	Reference	
ab-ABI	1.99 (1.22-3.24)	1.74 (1.06-2.87)	1.50 (0.89-2.50)	
Disease progression ^d				
nl-ABI	Reference	Reference	Reference	
ab-ABI	1.54 (0.89-2.66)	1.44 (0.83-2.51)	1.19 (0.67-2.15)	
Repeated revascularization ^e				
nl-ABI	Reference	Reference	Reference	
ab-ABI	2.53 (1.25-5.12)	2.53 (1.20-5.34)	2.80 (1.24-6.34)	
All-cause mortality				
nI-ABI	Reference	Reference	Reference	
ab-ABI	2.98 (1.17-7.55)	2.53 (0.98-6.50)	2.24 (0.82-6.09)	

ABI, ankle-brachial index; MACE, major adverse cardiac events; nI-ABI, normal ABI; ab-ABI, abnormal ABI.

^aABI categories were defined as ab-ABI (<1.0 or >1.4) and nl-ABI ($1.0 \le ABI \le 1.4$). ^bModel 1 was adjusted for age and sex and model 2 was further adjusted for cigarette smoking, body mass index, number of diseased vessels, and underlying disease. ^cMACE included disease progression, repeated revascularization, and all-cause mortality. ^dDisease progression was defined as stenosis >30% or occlusion of any coronary artery that has newly appeared on the latest coronary angiography. ^cRepeated revascularization was identified as stenosis >50% on coronary angiography or stenosis <50% with a correlated symptom.



Fig. 2. Comparison of ankle-brachial index (ABI) cutoff values of 1.0 and 0.9 using the area under the curve (AUC). ROC, receiver operating characteristic.

those with nl-ABI. The most common disease pattern was in the target lesion (58.3% in the ab-ABI group, 50% in the nl-ABI group), and there was no intergroup difference (P=0.577).

4) Risk factors for RR

Using the Cox proportional hazards model for clinically indicated RR after adjusting for age and sex (model 1) and model 1 plus diabetes, dyslipidemia, dialysis, smoking, obesity, and number of affected vessels, the incidence of clinically indicated re-intervention was significantly higher in the ab-ABI group than in the nl-ABI group (HR, 2.80; 95% Cl, 1.24 to 6.34). In summary, the ABI remained an independent predictor of RR (Table 3).

The significance of ABI cutoff values of 1.0 and 0.9 was compared using the area under the curve (Fig. 2). The value measures a test's capability to accurately classify those with and without the disease. The area under the receiver operating characteristics curve for an ABI of 1.0 was 0.8264, and that for an ABI of 0.9, which is an excellent discrimination value for predicting RR was, 0.7988.

DISCUSSION

The current study investigated the significance of an ab-ABI (including a borderline ABI) with respect to mortality, coronary re-intervention, and DPP during a follow-up period of 4 years in patients with CAD. CAD patients with ab-ABI had higher rates of all-cause mortality (18.2% vs. 6.7%, P=0.0233) and clinically indicated coronary RR (33.3% vs. 13.1%, P=0.0025) than those with nl-ABI during the longterm follow-up (47 months).

Previous studies have shown that ABI is an important screening and diagnostic tool for PAD and future cardiovascular events [4]. Thus, this study evaluated the longterm outcomes in patients with CAD and PAD. ABI was an important tool for predicting poor outcomes in patients with CAD. We recommend that routine ABI measurements should be used more actively to predict the outcomes of CAD patients and to identify silent PAD.

Commonly, a low ABI (<0.9) is associated with all-cause mortality, cardiovascular mortality, and incidence of major coronary event [8]. In recent studies, borderline ABI values (0.91 to 0.99) were also a risk factor for CAD, stroke, and mortality [12,13]. However, the clinical impact of a borderline ABI in a population treated with percutaneous coronary intervention has rarely been assessed [14]. Further, such a long-term study of this population has rarely been conducted.

Our study showed that an ABI <1.0 remained a signifi-

cant risk factor for RR (HR, 2.80; 95% Cl, 1.24 to 6.34) after adjusting for known risk factors. When predicting RR, an ABI <1.0 had a better area under the curve than an ABI <0.9 in patients with CAD. Therefore, an ABI reference of 1.0 may be more effective in predicting the need for RR for CAD than the conventional reference of 0.9. Therefore, we recommend that more precautions for cardiac events should be taken among CAD patients with a borderline or ab-ABI.

A low ABI reflects systemic atherosclerosis and polyvascular disease [15,16]. Accordingly, in terms of DPP, patients with ab-ABI have a greater progression than those with nl-ABI, since the systemic manifestations increased with decreased ABI [17]. However, our study did not show a significant difference between the two groups in terms of DPP. Hence, a 4-year follow-up period might have been insufficient.

ABI was initially used as a diagnostic tool for PAD. However, recent studies have shown a correlation between ABI and prognosis as well as its capability to predict various cardiovascular diseases and PAD [18]. For example, a low ABI predicts an early risk of recurrent stroke in patients with acute cerebral ischemia [19-21]. Moreover, there is a strong correlation between ABI level and MI [22]. Hence, cardiovascular disease physicians should be aware of ABI and should use this test in clinical practice.

The current study had some limitations. The results were based on a single-center cohort study; hence, a relatively small number of patients were enrolled, and the proportion of patients with ab-ABI was even lower. Thus, the categorization of normal, borderline, and ab-ABI according to the American College of Cardiology/American Heart Association guidelines was modified into two groups. A high proportion of patients with CAD was excluded due to the lack of follow-up CAG, which might have caused inherent selection bias.

Nevertheless, this study showed that ABI, which is simple and cost-effective, can be an important prognostic tool for patients with CAD. Similarly, Hashizume et al. [13] showed that patients with an ab-ABI had a significantly higher incidence of PCI-related complications and a less favorable 1-year prognosis. Our long-term study included data with high credibility from the Korean National Statistical Office.

CONCLUSION

An ab-ABI (including low and borderline values) significantly increased the incidence of clinically indicated coronary RR (HR, 2.80; 95% Cl, 1.24 to 6.34) and all-cause mortality (18.2%) during the 4-year follow-up in patients with CAD. Hence, ABI could be used to further stratify extremely high-risk patients with CAD who may require aggressive surveillance or further treatment.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

ORCID

Sanghyun Ahn https://orcid.org/0000-0003-2094-3586 EunAh Jo https://orcid.org/0000-0002-9324-4877 Seung-Kee Min https://orcid.org/0000-0002-1433-2562 Sangil Min https://orcid.org/0000-0002-0688-0278 Jongwon Ha https://orcid.org/0000-0003-2285-3517 Kyung Woo Park https://orcid.org/0000-0003-2432-4432 Kyoung-Bok Min https://orcid.org/0000-0001-9576-0093

AUTHOR CONTRIBUTIONS

Concept and design: SA. Analysis and interpretation: EAJ. Data collection: SA, KWP. Writing the article: EAJ. Critical revision of the article: SKM, SM, JH. Final approval of the article: SKM. Statistical analysis: KBM. Obtained funding: none. Overall responsibility: SA.

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