

Prevalence and Clinical Implications of Newly Revealed, Asymptomatic Abnormal Ankle-Brachial Index in Patients With Significant Coronary Artery Disease

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Objectives This study sought to evaluate the association between newly revealed abnormal ankle-brachial index (ABI) and clinical outcomes in patients with significant coronary artery stenosis.

Background Little is known about the prevalence and clinical implications of ABI in patients with no claudication or previous history of peripheral artery disease who undergo diagnostic coronary angiography.

Methods Between January 1, 2006, and December 31, 2009, ABI was evaluated in 2,543 consecutive patients with no clinical history of claudication or peripheral artery disease who underwent diagnostic coronary angiography. Abnormal ABI was defined as ≤ 0.9 or ≥ 1.4 . The primary endpoint was the composite of death, myocardial infarction, and stroke over 3 years.

Results Of the 2,543 patients, 390 (15.3%) had abnormal ABI. Of the 2,424 patients with at least 1 significant stenosis ($\geq 50\%$) in a major epicardial coronary artery, 385 (15.9%) had abnormal ABI, including 348 (14.4%) with ABI ≤ 0.9 and 37 (1.5%) with ABI ≥ 1.4 . During a median follow-up of 986 days, the 3-year major adverse event rate was significantly higher in patients with abnormal than normal ABI (15.7% vs. 3.3%, $p < 0.001$). After multivariate analysis, abnormal ABI was identified as a predictor of primary endpoint (hazard ratio [HR]: 1.87; 95% confidence interval [CI]: 1.23 to 2.84; $p = 0.004$). After adjustment by propensity-score matching, abnormal ABI could predict adverse clinical events in patients with established coronary artery disease (HR: 2.40; 95% CI: 1.41 to 4.10; $p = 0.001$).

Conclusions The prevalence of newly revealed abnormal, asymptomatic ABI among patients who have significant CAD on coronary angiography was 15.9%. The presence of abnormal ABI was associated with a higher incidence of adverse clinical outcomes over 3 years. (J Am Coll Cardiol Intv 2013;6:1303–13) © 2013 by the American College of Cardiology Foundation

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The ankle-brachial index (ABI), the ratio of systolic blood pressure measured at the ankle to systolic blood pressure measured at the brachial artery, is used in the noninvasive diagnosis of lower-extremity peripheral artery disease (PAD). Individuals with an abnormal ABI, ≤ 0.90 or ≥ 1.40 , should be considered at increased risk for lower extremity PAD, independent of symptoms and other cardiovascular events (1–5). Both individuals in the general population and patients with established cardiovascular disease who have an abnormal ABI are at higher risk of adverse events than those with normal ABI (6–8). More than 50% of

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individuals with PAD are unaware of their disease due to atypical, vague, or nonspecific symptoms (9). Little is known about the actual incidence and clinical implications of newly revealed abnormal ABI in patients who undergo coronary angiography. We investigated whether an abnormal ABI was an independent risk factor for atherosclerotic events in patients with significant coronary artery disease (CAD).

Abbreviations and Acronyms

ABI = ankle-brachial index

CAD = coronary artery disease

CI = confidence interval

DP = dorsalis pedis

HR = hazard ratio

MI = myocardial infarction

PAD = peripheral artery disease

PT = posterior tibial

RR = repeat revascularization

Methods

Study population. Between January 2006 and December 2009, eligible patients with no clinical history or previous evaluation of PAD who underwent diagnostic coronary angiography were prospectively enrolled in the Asan

ABI Registry at Asan Medical Center, Seoul, Republic of Korea. All patients who were admitted for coronary angiography were recommended to undergo an ABI test during hospitalization. Patients who have never been evaluated for existence of PAD using the ABI test or managed for PAD were enrolled, after detailed review of all available medical records. Those patients were defined as having asymptomatic status, which means no clinical history of claudication was confirmed by the dedicated claudication questionnaire (10). Coronary angiography was recommended for these patients on the basis of the results of noninvasive stress tests (i.e., an exercise treadmill test or a thallium radionuclide scan), showing inducible ischemia (with or without ischemic chest pain) or a high probability of ischemic symptoms. Significant stenosis on coronary angiography was defined as $>50\%$ stenosis of an epicardial coronary artery. Treatment of significant stenosis was on the basis of lesion severity, morphology, comorbidities, clinical characteristics, and preference. Patients with $>50\%$ stenosis and non-ischemic-

producing lesions were managed with medical therapy if functional assessment by fractional flow reserve or noninvasive stress tests such as the treadmill test or myocardial perfusion imaging was negative. All enrolled patients provided written informed consent, and the ethics committee of the Asan Medical Center approved the design of this study and allowed the use of clinical data.

Data collection and follow-up. Clinical, angiographic, procedural or operative, and outcome data were collected with the use of a dedicated Internet-based reporting system. For validation of complete follow-up data, information about vital status or clinical event was obtained through February 28, 2013, from the National Population Registry of the Korea National Statistical Office using a unique personal identification number. Patients were re-examined after 3, 6, 9, and 12 months and semiannually thereafter by office visit or telephone contact. To ensure accurate assessment of clinical endpoints, additional information was obtained from visits or telephone contacts with living patients or family members and from medical records obtained from other hospitals, as necessary.

Measurement of ABI. The ABI for each leg was measured as described elsewhere (11) using a Doppler ultrasound device (Nicolet VasoGuard, Viasys Healthcare, Conshohocken, Pennsylvania). The sequence of limb pressure measurements consisted of the first arm, the first posterior tibial (PT) artery, the first dorsalis pedis (DP) artery, the second PT artery, the second DP artery, and the second arm. Each pressure was measured twice, and the average for each was used in the calculations. The ABI of each leg was calculated by dividing the PT or DP pressure, whichever was higher, by the systolic blood pressure for the right or left arm, whichever was higher. The ABI selected was the lower of the values for the left and right legs. If the ABI was found to be between 0.80 and 1.00, measurements were repeated with the same principles.

Definition of abnormal ABI. The ABI threshold most commonly used is ≤ 0.90 , which is based on studies showing that this threshold has about 80% sensitivity and $>90\%$ specificity to detect PAD when compared with angiography (12–14). Also, high ABI could predict the incidence of PAD from 60% to 80% (15,16). In addition to low ABI (≤ 0.90), high ABI (>1.40) may be associated with increased mortality and other adverse events (2,17). Abnormal ABI was therefore defined as ≤ 0.9 or ≥ 1.4 .

Endpoints. The primary endpoint of this study was the composite of death, myocardial infarction (MI), and stroke. Secondary endpoints were each clinical outcome (death, MI, or stroke) and repeat revascularization (RR). All events were on the basis of clinical diagnoses by each patient's physician and were centrally adjudicated by an independent group of clinicians. Death was defined as death from any cause. MI during follow-up was defined as an increase in cardiac biomarkers, with at least 1 value above the 99th percentile

Table 1. Baseline Clinical Characteristics of the Overall Population and of Patients With Abnormal and Normal ABI

	Overall (n = 2,424)	Abnormal ABI (n = 385)	Normal ABI (n = 2,039)	p Value
Demographic characteristics				
Age, yrs	62.9 ± 9.1	66.5 ± 8.5	62.2 ± 9.1	<0.001
Male	1,779 (73.4)	317 (82.3)	1,462 (71.7)	<0.001
Cardiac or co-existing conditions				
Diabetes mellitus	1,401 (57.8)	246 (63.9)	1,155 (56.6)	0.008
Hypertension	1,644 (67.8)	308 (80.0)	1,336 (65.5)	<0.001
Hyperlipidemia	2,001 (82.5)	284 (73.8)	1,717 (84.2)	<0.001
Current smoker	631 (26.0)	129 (33.5)	502 (24.6)	<0.001
Previous stroke	261 (10.8)	91 (23.6)	170 (8.3)	<0.001
Previous PCI	549 (22.6)	103 (26.8)	446 (21.9)	0.036
Previous CABG	91 (3.8)	22 (5.7)	69 (3.4)	0.023
Previous MI	192 (7.9)	38 (9.9)	154 (7.6)	0.122
Renal failure	156 (6.4)	70 (18.2)	86 (4.2)	<0.001
LMCA disease	339 (14.0)	64 (16.6)	275 (13.5)	0.108
Multivessel disease	1,496 (61.7)	289 (75.1)	1,207 (59.2)	<0.001
Ejection fraction, %	58.5 ± 9.1	55.6 ± 10.9	59.2 ± 8.5	<0.001
Heart failure, EF < 40%	84 (5.6)	32 (11.2)	52 (4.3)	<0.001
Coronary revascularization	1,910 (78.8)	291 (79.0)	1,619 (79.4)	0.103
PCI	1,518 (62.6)	192 (49.9)	1,326 (65.0)	<0.001
CABG	392 (16.2)	99 (29.1)	293 (14.4)	<0.001
Clinical indication				0.008
Silent/stable angina	1,646 (67.9)	239 (62.1)	1,407 (69.0)	
Unstable angina	626 (25.8)	111 (28.8)	515 (25.3)	
NSTEMI	97 (4.0)	24 (6.2)	73 (3.6)	
STEMI	55 (2.3)	11 (2.9)	44 (2.2)	
Medications				
Aspirin	2,118 (87.4)	323 (84.2)	1,794 (88.0)	0.044
Clopidogrel	1,596 (65.8)	234 (60.8)	1,323 (66.8)	0.022
Cilostazol	210 (8.7)	64 (16.6)	146 (7.2)	<0.001
Statin	1,872 (77.2)	252 (65.5)	1,620 (79.5)	<0.001
ACEI/ARB	935 (38.6)	172 (44.7)	763 (37.4)	0.008
Beta-blocker	1,281 (52.8)	181 (47.0)	1,100 (53.9)	0.014
CCB	1,812 (74.8)	265 (68.8)	1,547 (75.9)	0.002
Nitrate	1,356 (55.9)	209 (54.3)	1,147 (56.3)	0.501

Values are mean ± SD or n (%).
 ABI = ankle-brachial index; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; CCB = calcium channel blocker; EF = ejection fraction; LMCA = left main coronary artery; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

and with at least 1 of the following: 1) symptoms of ischemia; 2) new or presumed new significant ST-segment-T-wave changes or new left bundle branch block; 3) development of pathological Q waves on an electrocardiogram; 4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; or 5) identification of an intracoronary thrombus by angiography or autopsy (18). Stroke, indicated by the rapid onset of a focal or global neurological deficit with signs or symptoms, was confirmed by a neurologist on the basis of neuroimaging results (19).

RR was defined as any reintervention using percutaneous coronary intervention or coronary artery bypass graft of a de novo and/or restenotic lesion that occurred after completion of the planned current index procedure. All events were adjudicated by an independent clinical events committee.

Statistical analysis. All data analyses were performed using R software (version 2.10.1, R Foundation for Statistical Computing, Vienna, Austria) and SAS software (version 9.1, SAS Institute, Cary, North Carolina). Patient demographic characteristics, cardiac or co-existing conditions, and medication information were compared using Student *t* tests for continuous variables and chi-square or Fisher exact test for categorical variables. Survival curves according to ABI were constructed with Kaplan-Meier estimates and compared by the log-rank test. To estimate the effect, we also performed the univariate Cox proportional hazards model. Regarding the primary endpoint of death, MI, and stroke, we performed univariate and multivariate Cox regression analysis for the risk factor analysis. All baseline characteristics in Table 1 were tested and if the p value was ≤0.1 in univariate analysis, the variables were included in a multivariate analysis. We obtained the final model on the basis of the backward stepwise method where the least significant variables were discarded 1 by 1 from the full model. Furthermore, to reduce the effect of potential confounding in this observational study, we performed rigorous adjustment for significant differences in the baseline characteristics of patients with the use of propensity-score matching (20). The details of the propensity-score method, with the resulting models and their predictive characteristics, are described in the Online Appendix. After all the propensity-score matches were performed, we compared the baseline covariates between the 2 groups to check the comparability. Continuous variables were compared using the paired Student *t* test or the Wilcoxon signed-rank test, and categorical variables were compared using the McNemar test. Statistical significance and the estimated effect of treatment on outcomes were obtained using Cox regression models, with robust standard errors that accounted for the clustering of matched pairs. Among the propensity-matched cohort, survival curves according to ABI were constructed with Kaplan-Meier estimates and compared by the log-rank test.

Finally, multivariate binary logistic regression analysis was used to identify predictors of abnormal ABI. Noncorrelated variables with p values of <0.05 on univariate analyses were included in the multivariate analysis, and backward stepwise variable selection approach was employed. All reported p values are 2-sided, and p values of <0.05 were considered statistically significant.

Results

Prevalence of abnormal ABI. Between January 2006 and December 2009, 2,543 consecutive patients with no clinical

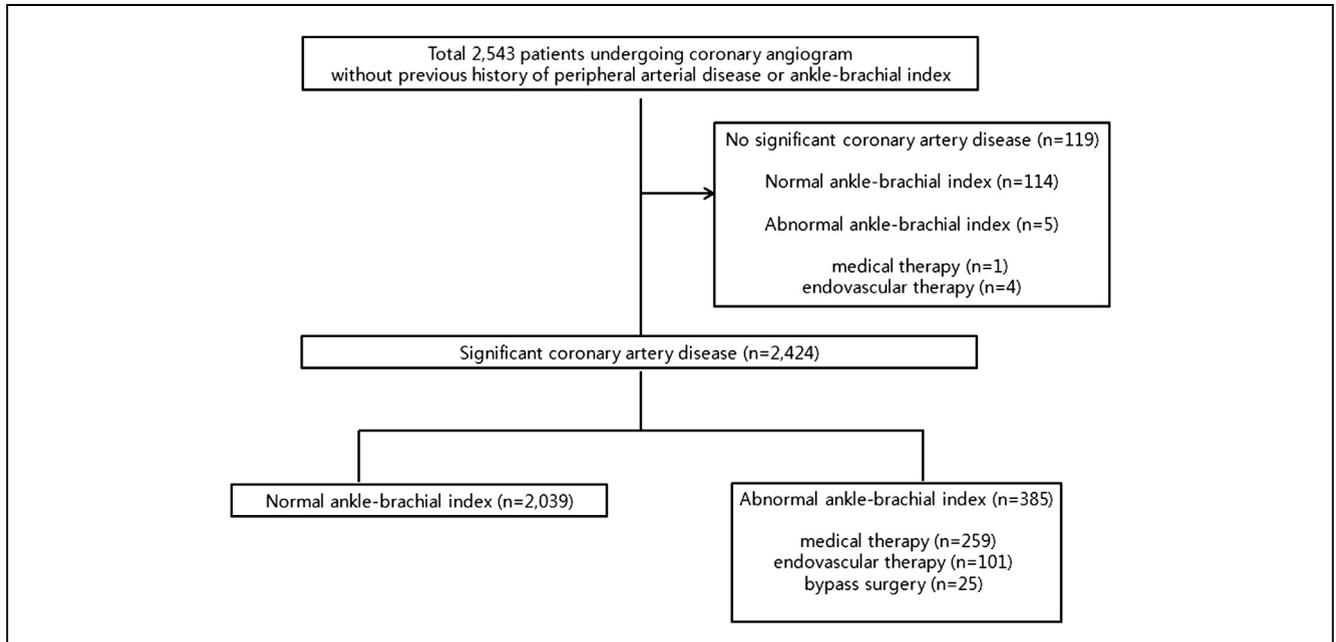


Figure 1. Overall Study Profile

Of the 2,543 patients, 390 (15.3%) had abnormal ABI. Of the 2,424 patients with at least one significant stenosis ($\geq 50\%$) in a major epicardial coronary artery, 385 (15.9%) had abnormal ABI, including 348 (14.4%) with $ABI \leq 0.9$ and 37 (1.5%) with $ABI \geq 1.4$.

claudication or previous evaluation of PAD, including ABI, underwent diagnostic coronary angiography. The study design is illustrated in Figure 1. When patients were stratified according to the presence of significant CAD, of the 2,424 patients with significant CAD, 385 (15.9%) had

abnormal ABI, including 348 (14.4%) with $ABI \leq 0.9$ and 37 (1.5%) with $ABI \geq 1.4$. By contrast, of the 119 patients without significant CAD, only 5 (4.2%) had abnormal ABI ($p < 0.001$ compared with the incidence of abnormal ABI in patients with significant CAD), with all having $ABI \leq 0.9$.

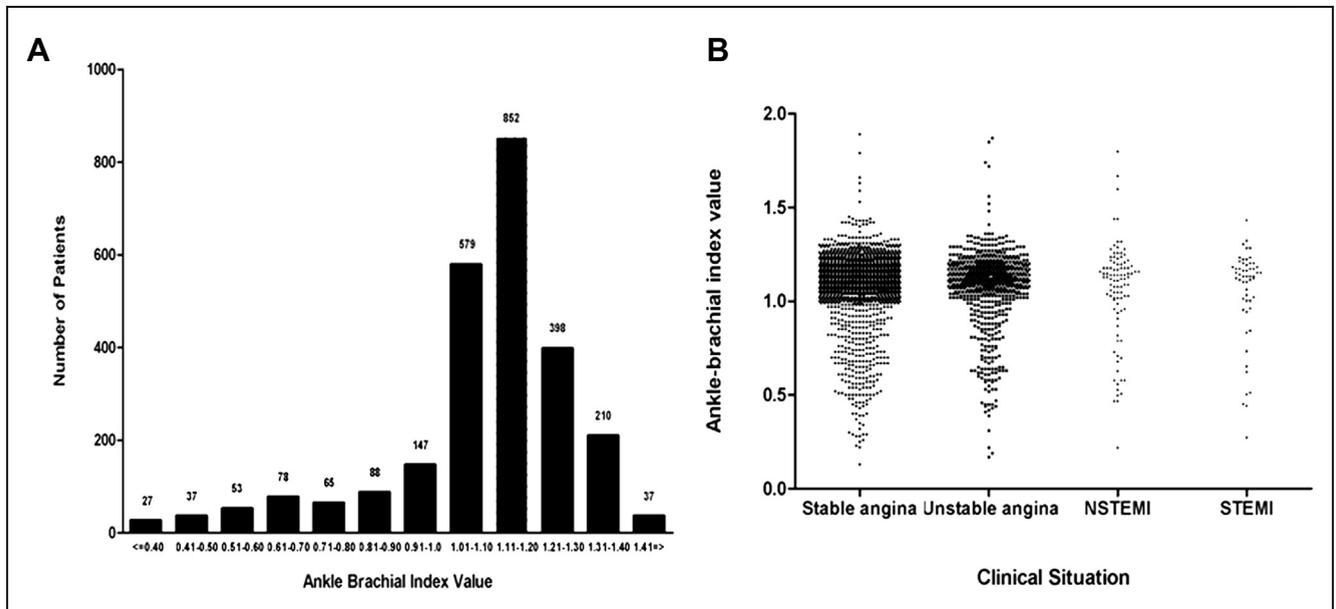


Figure 2. Distribution of ABI Values

The distribution of ankle-brachial index values in the entire cohort (A) and according to the clinical situation (B). NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

Table 2. Baseline Clinical Characteristics of the Propensity Score-Matched Patients With Abnormal and Normal ABI

	Abnormal ABI (n = 359)	Normal ABI (n = 359)	p Value
Demographic characteristics			
Age, yrs	66.1 ± 8.4	66.8 ± 8.3	0.25
Male	291 (81.1)	281 (78.3)	0.40
Cardiac or co-existing conditions			
Diabetes mellitus	227 (63.2)	224 (62.4)	0.82
Hypertension	283 (78.8)	282 (78.6)	0.93
Hyperlipidemia	271 (75.5)	266 (74.1)	0.73
Current smoker	118 (32.9)	117 (32.6)	0.94
Previous stroke	74 (20.6)	74 (20.6)	1.00
Previous PCI	96 (26.7)	95 (26.5)	0.93
Previous CABG	19 (5.3)	12 (3.3)	0.27
Previous MI	36 (10.0)	37 (10.3)	0.90
Renal failure	54 (15.0)	47 (13.1)	0.45
LMCA disease	58 (16.2)	57 (15.9)	0.91
Multivessel disease	265 (73.8)	256 (71.3)	0.50
Ejection fraction, %	55.7 ± 10.9	57.3 ± 8.8	0.15
Heart failure, EF <40%	23 (6.4)	12 (5.0)	0.13
Coronary revascularization	285 (79.4)	275 (76.6)	0.40
PCI	184 (51.3)	188 (52.4)	0.82
CABG	101 (28.1)	87 (24.2)	0.27
Clinical indication			0.99
Silent/stable angina	225 (62.7)	224 (62.4)	
Unstable angina	104 (29.0)	105 (29.2)	
Acute MI	30 (8.4)	30 (8.4)	
Medications			
Aspirin	302 (84.1)	301 (83.8)	0.92
Clopidogrel	219 (61.0)	219 (61.0)	1.00
Cilostazol	61 (17.0)	24 (6.7)	<0.001
Statin	240 (66.9)	250 (69.6)	0.47
ACEI/ARB	155 (43.2)	156 (43.5)	0.94
Beta-blocker	173 (48.2)	182 (50.7)	0.50
CCB	245 (68.2)	258 (71.9)	0.33
Nitrate	195 (54.3)	190 (52.9)	0.76

Values are mean ± SD or n (%).
 Abbreviations as in Table 1.

The prevalence of significant CAD was significantly higher among patients with abnormal than normal ABI (98.7% vs. 94.7%, $p < 0.001$). Among 385 patients with abnormal ABI who had significant CAD, 259 patients (67.3%) were managed with medical therapy and 126 patients (32.7%) with revascularization (endovascular therapy, 101 [26.2%] and bypass surgery, 25 [6.5%]); contrarily, among 5 patients with abnormal ABI who had no significant CAD, 4 patients were managed with endovascular therapy and 1 with medical therapy.

Distribution of ABI values. The distribution of ABI values in the entire cohort were illustrated (Fig. 2A) and provided according to the clinical situation (Fig. 2B). There were no significant differences in ABI values according to

Table 3. Predictors of Composite of Death, MI, or Stroke After Multivariate Cox Proportional Hazard Analysis

Variable	Univariate			Multivariate		
	Hazard Ratio	95% CI	p Value	Hazard Ratio	95% CI	p Value
Age, yrs	1.06	1.04–1.08	<0.001	1.05	1.03–1.07	0.001
Abnormal ABI	3.94	2.77–5.61	<0.001	1.87	1.23–2.84	0.004
Hypertension	1.40	0.94–2.09	0.094			
Hyperlipidemia	0.56	0.38–0.83	0.004			
Previous stroke	2.66	1.76–4.02	<0.001			
Previous CABG	2.94	1.27–4.53	0.007			
Renal failure	5.53	3.70–8.30	<0.001	3.43	2.17–5.41	<0.001
Multivessel disease	1.80	1.16–2.77	0.008			
Ejection fraction, %	0.97	0.95–0.99	<0.001	0.98	0.96–0.99	0.025
Clinical indication	1.50	1.16–1.93	0.002			
Aspirin	0.006	0.35–0.84	0.006			
ACEI/ARB	1.35	0.95–1.92	0.091			
Beta-blocker	0.70	0.49–0.99	0.045			
CCB	0.60	0.42–0.87	0.006			

CI = confidence interval; other abbreviations as in Table 1.

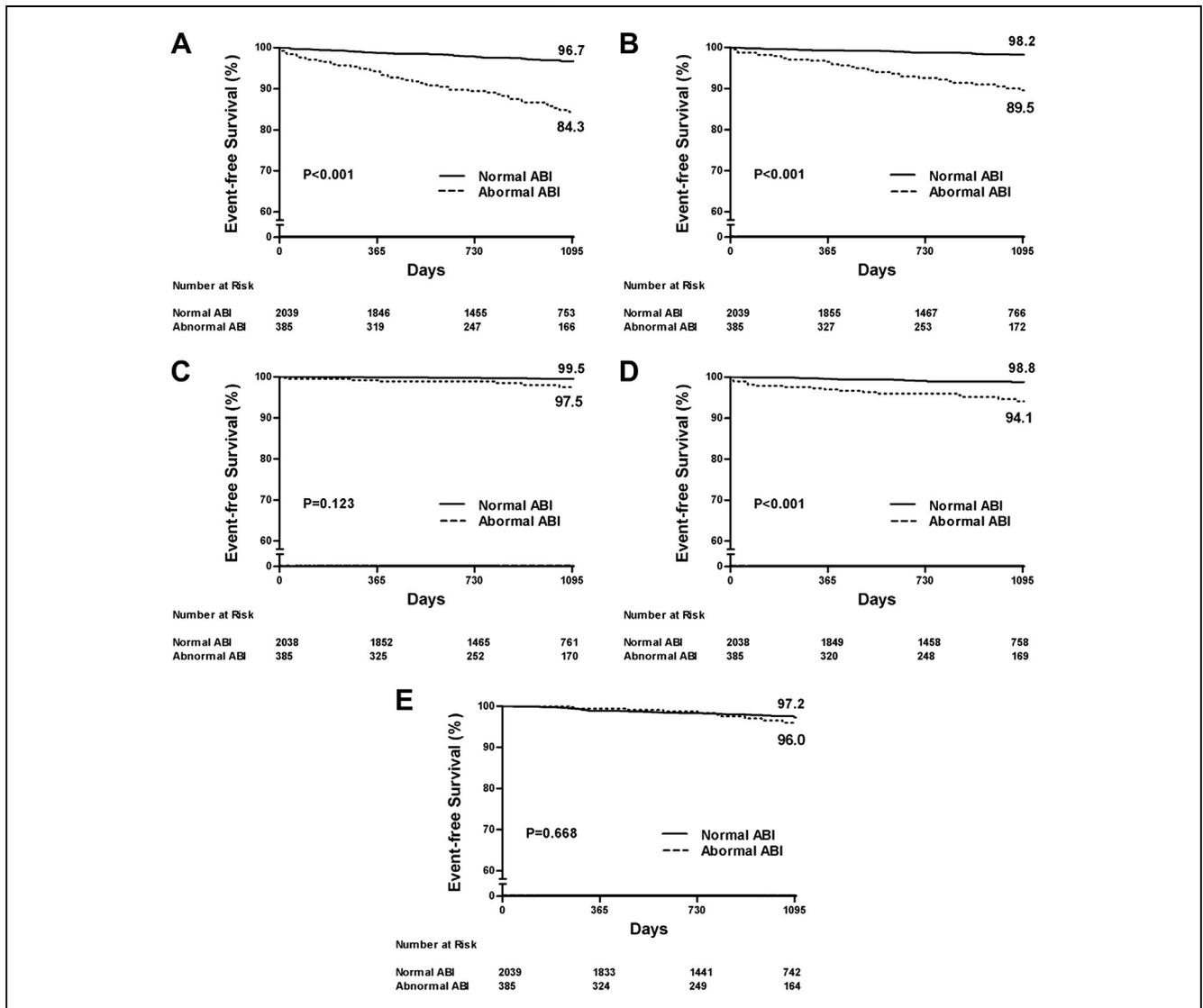
individual clinical situation (1.08 ± 0.19 in silent or stable angina, 1.06 ± 0.21 in unstable angina, 1.06 ± 0.26 in non-ST-segment elevation myocardial infarction and 1.05 ± 0.25 in ST-segment elevation myocardial infarction, respectively; p value = 0.26).

Patient characteristics. The baseline characteristics of the study patients who have significant CAD, categorized by their ABI values, are shown in Table 1. In general, the abnormal ABI group was associated with higher risk profiles than the normal ABI group was. Of the 2,424 patients with significant CAD, 1,973 (81.4%) had coronary revascularization, as determined by functional assessment of stenotic lesions.

Propensity-score matching of the entire population with significant CAD yielded 359 matched pairs (Table 2). In these matched cohorts, there were no significant differences in baseline characteristics between those with normal and abnormal ABI, except for more frequent use of cilostazol in patients with abnormal ABI, due to its use in the management of PAD.

Clinical outcomes. UNADJUSTED OUTCOMES IN THE ENTIRE COHORT. The median follow-up duration was 986 days (interquartile range: 673 to 1,483 days).

During follow-up, 78 patients died, 26 had MI, 45 had a stroke, and 67 underwent RR due to progressive ongoing ischemia in previously treated or untreated coronary arteries. As a result, the primary endpoint of the composite of death, MI, and stroke occurred in 128 patients. After multivariate analysis, several risk factors including abnormal ABI (hazard ratio [HR]: 1.87; 95% confidence interval [CI]: 1.23 to 2.84;



$p = 0.004$) were identified as the predictors of primary endpoint (age: HR: 1.05; 95% CI: 1.03 to 1.07; $p < 0.001$; renal failure: HR: 3.43; 95% CI: 2.17 to 5.41; $p < 0.001$; and left ventricle ejection fraction: HR: 0.98; 95% CI: 0.96 to 0.99; $p = 0.025$) (Table 3).

Those with abnormal ABI had significantly higher rates of the composite of death, MI, and stroke (15.7% vs. 3.3%, $p < 0.001$), all-cause death (10.5% vs. 1.8%, $p < 0.001$), and stroke (5.9% vs. 1.2%, $p < 0.001$), over 3 years than did those with normal ABI (Table 4, Fig. 3).

ADJUSTED OUTCOMES IN THE PROPENSITY-MATCHED COHORT. Figure 4 and Table 5 show the incidences of clinical outcomes over 3 years, relative to ABI, in the matched

cohort. Among the 359 matched pairs, the primary endpoint defined as composite of death, MI, and stroke was significantly higher in the abnormal ABI group (HR: 2.40; 95% CI: 1.41 to 4.10; $p = 0.001$). Among the secondary endpoint, stroke (HR: 4.68; 95% CI: 1.59 to 13.76; $p = 0.005$) was also significantly higher in the abnormal group than in the normal ABI group. But, the risk of death, MI, and RR did not differ between those with normal and abnormal ABI.

Dose-response gradient between ABI values and adverse events. The risk for death, MI, or stroke at 3-year follow-up for different levels of ABI compared with a normal ABI of 0.91 to 1.40 formed a reverse J-shaped curve. For levels of ABI ≤ 0.90 , the unadjusted HR increased consistently

Table 4. Incidence of Clinical Outcomes According to ABI in the Entire Cohort

Outcome	Outcome Rates			Multivariate Adjusted*	
	Normal ABI (n = 2,039)	Abnormal ABI (n = 385)	p Value†	Hazard Ratio (95% CI)*	p Value
Primary endpoint					
Death, MI, or stroke	53 (3.3)	48 (15.7)	<0.001	1.87 (1.23–2.84)	0.004
Secondary endpoint					
Death	30 (1.8)	32 (10.5)	<0.001	1.71 (0.99–2.94)	0.054
MI	8 (0.5)	7 (2.5)	0.123	1.05 (0.32–3.45)	0.93
Stroke	20 (1.2)	18 (5.9)	<0.001	2.86 (1.42–5.77)	0.003
Repeat revascularization	43 (2.8)	10 (4.0)	0.668	0.92 (0.45–1.88)	0.81

Values are the number of events (estimated cumulative incidence rate based on Kaplan-Meier curve) for 3-year follow-up. *Hazard ratios of patients having abnormal ABI compared with those having normal ABI were measured using the multivariate backward stepwise Cox proportional hazard models, which included all variables listed in Table 1. †The p values are based on the log-rank test.
 Abbreviations as in Tables 1 and 3.

with decreasing ABI. For an ABI >1.40, the HR also increased (HR: 3.73; 95% CI: 1.51 to 9.24) (Fig. 5A). According to the low, normal, and high ABI groups, there were significant differences in 3-year event rates (3.3% in normal, 10.2% in high, and 16.2% in low ABI groups, log-rank p value <0.001) (Fig. 5B). Compared with the normal ABI group, the low ABI group showed significant risk after multivariate Cox proportional hazard analysis (adjusted HR: 1.59; 95% CI: 1.10 to 2.50; p = 0.047) and propensity-matched analysis in 331 matched pairs (HR: 1.50; 95% CI: 1.08 to 2.36; p = 0.046). But compared with the normal ABI group, the high ABI group showed a higher trend without statistical significance in multivariate Cox proportional hazard analysis (adjusted HR: 1.72; 95% CI: 0.65 to 4.54; p = 0.27) (Fig. 5C).

Also, we classified 3 groups of low ABI according to the ABI values using 0.60 and 0.76 as cutoff points. Finally, we analyzed the total 5-group cohort as low tertile (≤0.60, n = 117), middle tertile (>0.60 and ≤0.76, n = 119), high tertile (>0.76 and ≤0.90, n = 112) in the low ABI group, normal ABI group (>0.90 and ≤1.40, n = 2,039), and high ABI (>1.40, n = 37). The cumulative incidences of primary endpoint at 3-year follow-up were 26.6%, log-rank p value <0.001; 13.2%, log-rank p value <0.001; 11.3%, log-rank p value = 0.021; 3.3%, normal ABI as reference; 10.2%, log-rank p value = 0.002, respectively. After multivariate Cox proportional hazard analysis, there were dose-response gradients between ABI values and adverse events (HR: 2.14; 95% CI: 1.28 to 3.70 in the low tertile; HR: 1.79; 95% CI: 1.09 to 3.32 in the middle tertile; HR: 1.13; 95% CI: 0.58 to 2.10 in the high tertile; HR: 1.65; 95% CI: 0.62 to 4.37 in the high ABI group, in comparison with normal ABI group as reference) (Fig. 5D).

Predictors of abnormal ABI. Multivariate analysis showed that older age, male sex, multivessel CAD, current smoking,

hypertension, previous stroke, and renal failure were significant predictors of abnormal ABI (Table 6).

Discussion

We have shown here that the prevalence of abnormal ABI among patients who had a significant CAD on coronary angiogram was 15.9% and that abnormal ABI in patients with significant CAD was associated with higher rates of adverse clinical outcomes over 3 years. Also, we could see a definite dose-response gradient between ABI values and adverse events. We could not determine whether abnormal ABI is a marker or cause of adverse outcomes, but our findings indicate that abnormal ABI among patients with significant CAD could predict 3-year adverse outcomes in a large observational cohort, independent of the severity of CAD.

In the present study, we found that patients who had significant CAD with abnormal ABI had higher incidences of cardiovascular events than those with normal ABI did. We hypothesize that abnormal ABI could increase risk, even in high-risk patients. Of the entire cohort, the abnormal ABI group showed higher adverse clinical events. Also, we analyzed using propensity-score matching due to the considerable differences in baseline characteristics between patients with normal and abnormal ABI. Furthermore, among propensity-score-matched patients, abnormal ABI was associated with significantly higher risks of 3-year composite death, MI, and stroke (HR: 2.40), and stroke (HR: 4.68) compared with normal ABI. Although not statistically significant, patients with abnormal ABI also were at higher risk for death (HR: 1.78), MI (HR: 5.95), and RR (HR: 1.96).

The most common ABI threshold for abnormality is ≤0.90, based on studies showing that this ABI has >90% sensitivity and specificity to detect PAD compared with angiography (12,13). A high ABI (≥1.4) suggests the

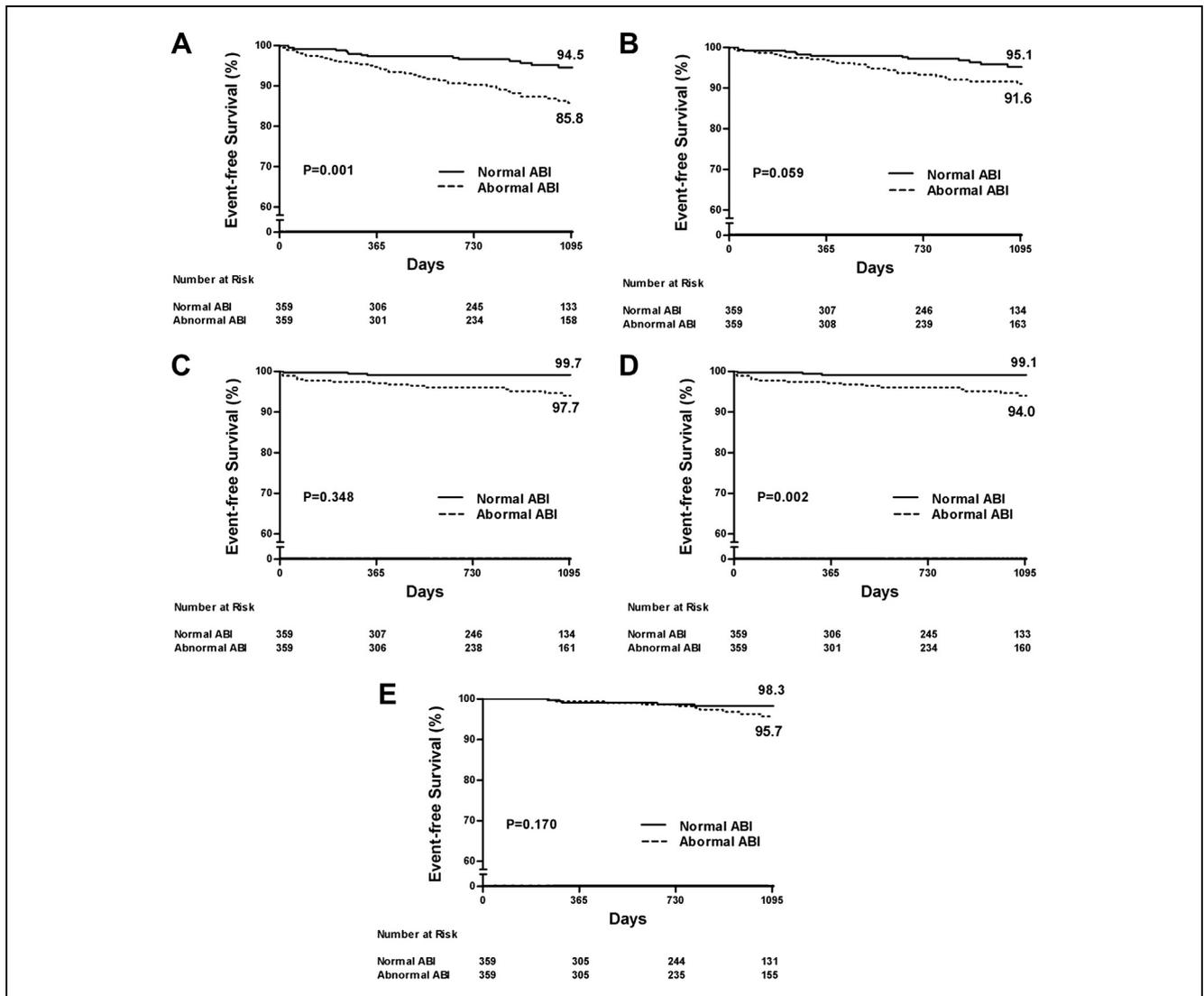


Figure 4. Kaplan-Meier Curves of Outcomes in Propensity-Matched Patients With Normal and Abnormal ABI

Propensity matching of patients in the entire cohort yielded 349 matched pairs. (A) Outcomes for death, myocardial infarction, and stroke. Outcomes for freedom from death (B), myocardial infarction (C), stroke (D), and repeat revascularization (E). Event-free survival rates (at 3 years) were derived from paired Kaplan-Meier curves. ABI = ankle-brachial index.

presence of calcified vessels, which may occur in patients with medical calcinosis, diabetes mellitus, or end-stage renal disease. Although vascular calcification could allow PAD to be detected by ABI, high ABI could predict a 60% to 80% incidence of PAD (15,16,21). So, we defined abnormal ABI as ≤ 0.9 or ≥ 1.4 .

Because ABI is associated with higher atherosclerotic risk factors and the prevalence of vascular disease in other vascular systems, ABI may be a surrogate marker for systemic atherosclerosis. A low ABI is associated with higher rates of cardiovascular risk factors and, therefore, higher rates of coronary heart disease, stroke, transient ischemic attack, progressive renal insufficiency, and all-cause

mortality (22–27). These results, however, were derived primarily from population-based cohort studies that included patients with existing disease (28–32). Similar to low ABI, abnormally high ABI has been associated with higher cardiovascular risk (17,33–36). The MESA (Multi-Ethnic Study of Atherosclerosis) showed that both high and low ABI were associated with higher cardiovascular risk in patients without clinical cardiovascular disease (2,37). The Strong Heart Study also demonstrated that the adjusted HR for all-cause mortality and cardiovascular mortality rates were 1.8 and 2.0, respectively, for high ABI and 1.7 and 2.5, respectively, for low ABI relative to normal ABI ($0.9 < \text{ABI} < 1.4$) (24). Most of these findings were obtained in

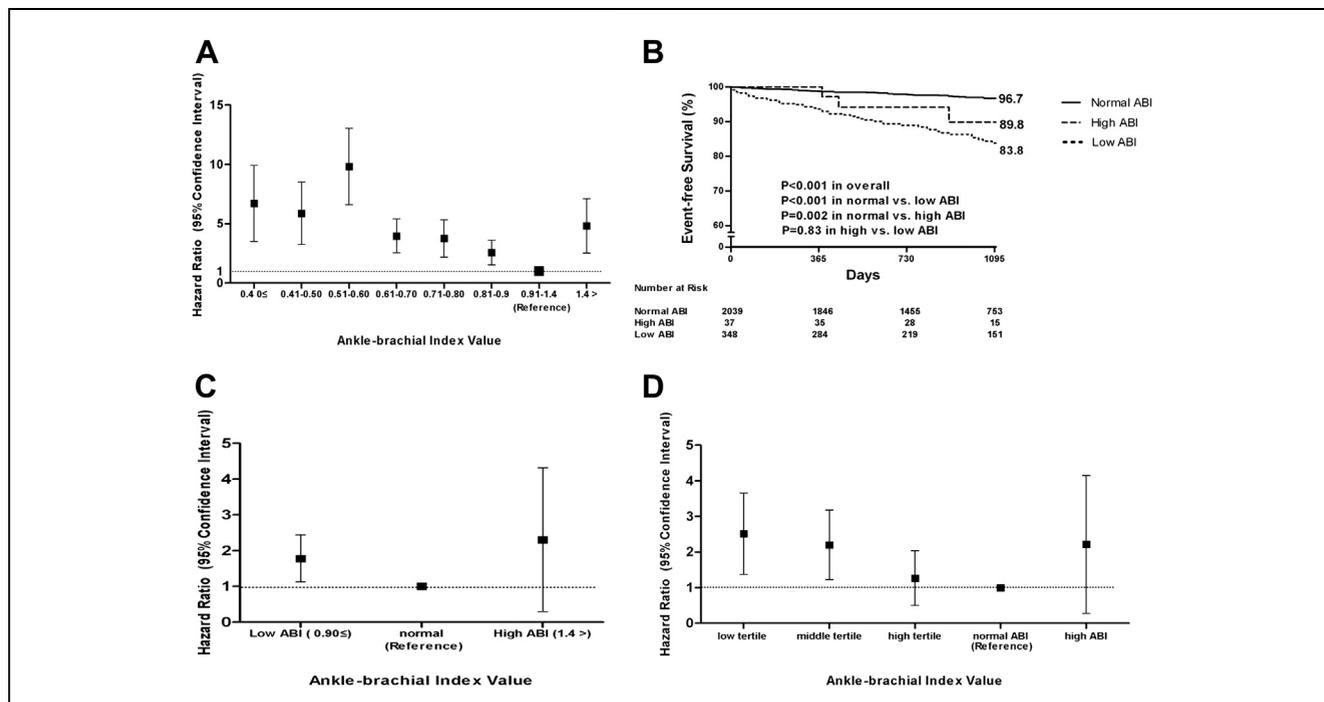


Figure 5. Dose-Response Gradient Between ABI Values and Adverse Events

(A) Hazard ratios for death, myocardial infarction, and stroke at 3-year follow-up according to the ankle-brachial index (ABI) values at baseline. Hazard ratios are not adjusted for cardiovascular risk factors. **(B)** Kaplan-Meier curves of death, myocardial infarction, and stroke outcomes according to the ABI values at baseline (low, normal, and high groups). Event-free survival rates (at 3 years) were derived from paired Kaplan-Meier curves. **(C)** Adjusted hazard ratios for death, myocardial infarction, and stroke at 3-year follow-up according to ABI values at baseline (low, normal, and high groups). Hazard ratios are derived from multivariate Cox proportional hazard analysis. **(D)** Adjusted hazard ratios for death, myocardial infarction, and stroke at 3-year follow-up according to the ABI at baseline (low, middle, high tertiles in low, normal, and high groups). Hazard ratios are derived from multivariate Cox proportional hazard analysis.

populations with variable risk profiles, making it necessary to determine whether abnormal ABI would be a risk factor in individual populations. In addition, abnormal ABI has been associated with future cardiovascular events in patients with established cardiovascular disease (6-8,31,38-44), suggesting that abnormal ABI may independently predict the risk of vascular events in patients with established cardiovascular disease. Because traditional risk factors are frequently present in patients with both high and low ABI, abnormal ABI may increase not only the prevalence but also

the risk of future cardiovascular events. These findings, however, are limited by the ambiguous definition of PAD, the relatively small numbers of patients surveyed, and the lack of adjustment for different characteristics. We therefore analyzed patients with significant coronary stenosis who were undergoing coronary angiography. On the basis of updated guidelines, we used universal definitions of clinical events and abnormal ABI with standardized measurements (11,18,19). Finally, to minimize biases, we aggressively adjusted our patient population using propensity-matched

Table 5. Clinical Outcomes in the Propensity-Matched Cohort According to ABI

	Normal ABI (n = 359)		Abnormal ABI (n = 359)	
	Event Rate for 3-Year Follow-Up		Event Rate for 3-Year Follow-Up	Hazard Ratio (95% CI)* p Value
Death/MI/stroke	15 (5.5)		41 (14.2)	2.40 (1.41-4.10) 0.001
Death	13 (4.9)		25 (8.4)	1.78 (0.98-3.24) 0.059
MI	1 (0.3)		6 (2.3)	5.95 (0.71-49.52) 0.099
Stroke	3 (0.9)		17 (6.0)	4.68 (1.59-13.76) 0.005
Repeat revascularization	5 (1.7)		10 (4.3)	1.96 (0.73-5.23) 0.178

Values are the number of events (estimated cumulative incidence rate based on Kaplan-Meier curve) for 3-year follow-up. *Hazard ratios of patients having abnormal ABI compared with those having normal ABI were measured using the Cox proportional hazard models. Abbreviations as in Tables 1 and 3.

Table 6. Predictors of Abnormal ABI

	Odds Ratio (95% CI)	p Value
Renal failure	4.13 (2.83–6.04)	<0.001
Previous stroke	2.43 (1.77–3.33)	<0.001
Male	2.00 (1.34–3.00)	0.001
Current smoking	1.83 (1.39–2.41)	<0.001
Hypertension	1.74 (1.30–2.32)	<0.001
Multivessel disease	1.54 (1.18–2.02)	0.001
Age, yrs	1.06 (1.04–1.07)	<0.001

Abbreviations as in Tables 1 and 3.

analysis (45,46). Matching according to propensity score eliminates a greater proportion of baseline differences between 2 groups than stratification or adjustment for covariates does (47). Our data are therefore an updated analysis of abnormal ABI and cardiovascular events in patients with established CAD.

Study limitations. Our evaluation of observational cohort data, not randomized patients, is a major limitation. Moreover, our definition of “newly revealed ABI” may be faulty, because the initial evaluation with ABI may be arbitrary and may depend on the characteristics of the physician or patient. This may lead to an unintended under- or overestimation of the prevalence of ABI. We attempted to minimize any errors in estimation of incidence by standardizing inclusion criteria using available resources such as a detailed review of all available medical records and questionnaire with patients and their families (10). From an analytical standpoint, our findings are subject to selection bias and confounding with respect to the patients’ symptoms and history of previous evaluation. Using propensity-score matching, the rigorous adjustment was performed to reduce unexpected bias. It is difficult to perform randomized trials to evaluate the impact of abnormal ABI for future clinical outcomes, but our analysis should be meaningful.

Conclusions

The prevalence of newly revealed, asymptomatic abnormal ABI among patients who have significant CAD on coronary angiography was 15.9%. The presence of abnormal ABI was independently associated with a higher incidence of adverse clinical outcomes over 3 years. Measurement of ABI could provide an important insight into the prognosis of patients with significant CAD.

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Key Words: ankle-brachial index ■ asymptomatic ■ clinical outcome ■ coronary artery disease.

▶ APPENDIX

For the details of the propensity-score method, with the resulting models and their predictive characteristics, please see the online version of this paper.