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ORIGINAL RESEARCH

Long-Term (7-Year) Clinical Implications of Newly Unveiled Asymptomatic Abnormal Ankle–Brachial Index in Patients With Coronary Artery Disease

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BACKGROUND: The long-term impact of newly discovered, asymptomatic abnormal ankle–brachial index (ABI) in patients with significant coronary artery disease is limited.

METHODS AND RESULTS: Between January 2006 and December 2009, ABI was evaluated in 2424 consecutive patients with no history of claudication or peripheral artery disease who had significant coronary artery disease. We previously reported a 3-year result; therefore, the follow-up period was extended. The primary end point was a composite of all-cause death, myocardial infarction (MI), and stroke over 7 years. Of the 2424 patients with significant coronary artery disease, 385 had an abnormal ABI (ABI ≤0.9 or ≥1.4). During the follow-up period, the rate of the primary outcome was significantly higher in the abnormal ABI group than in the normal ABI group (P<0.001). The abnormal ABI group had a significantly higher risk of composite of all-cause death/MI/stroke than the normal ABI group, after adjustment with multivariable Cox proportional hazards regression analysis (hazard ratio [HR], 2.07; 95% CI, 1.67–2.57; P<0.001) and propensity score–matched analysis (HR, 1.97; 95% CI, 1.49–2.60; P<0.001). In addition, an abnormal ABI was associated with a higher risk of all-cause death, MI, and stroke, but not repeat revascularization.

CONCLUSIONS: Among patients with significant coronary artery disease, asymptomatic abnormal ABI was associated with sustained and increased incidence of composite of all-cause death/MI/stroke, all-cause death, MI, and stroke during extended follow-up over 7 years.

Key Words: ankle–brachial index ■ asymptomatic diseases ■ atherosclerosis ■ coronary artery disease

The ankle–brachial index (ABI) is a simple, noninvasive, risk-free, and cost-effective diagnostic tool.[1] Observational studies[2–7] and meta-analyses[8,9] have shown that individuals with an abnormal ABI have an increased risk of lower extremity peripheral artery disease (PAD), independent of symptoms and other cardiovascular events. In addition to patients with known cardiovascular disease, individuals in the general population with an abnormal ABI are at a higher risk of cardiovascular events than those with a normal ABI.[10–12] However, >50% of individuals with PAD are unaware of their disease because of atypical, vague, or nonspecific symptoms.[13] We previously reported that an abnormal, newly revealed, asymptomatic ABI

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CLINICAL PERSPECTIVE

What Is New?

- This study has shown that patients with significant coronary artery disease accompanied by asymptomatic abnormal ankle–brachial index have an increased risk of death, myocardial infarction, and stroke during a long-term follow-up period (beyond 3 years and up to 7 years).

What Are the Clinical Implications?

- Routine ankle–brachial index measurement of patients with significant coronary artery disease may provide prognostic parameters of future atherosclerotic events for adequate management.

Nonstandard Abbreviations and Acronyms

PSM	propensity-score matching
PVD	polyvascular disease
RR	repeat revascularization

among patients with significant coronary artery disease (CAD) was associated with a higher incidence of composite all-cause death/myocardial infarction (MI)/stroke and stroke over a 3-year period.[14] Therefore, ABI may be strongly considered not only for PAD diagnosis, but also for future cardiovascular risk prediction. To further characterize the long-term impact of abnormal ABI on clinical outcomes in patients with significant CAD, we present the 7-year follow-up results of this study.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. The study design, method, and 3-year outcomes were reported previously.[14] Among 2543 patients who underwent diagnostic coronary angiography, 2424 patients with significant CAD were enrolled in the present study. All patients who were admitted for diagnostic coronary angiography underwent an ABI test during the same hospitalization period. The selected patients had no history of claudication, previous assessment, or diagnosis of PAD. Patients who had never been evaluated for PAD using an ABI test, or who had never been treated for PAD, were enrolled after a detailed review of all available medical records or a dedicated claudication questionnaire.[15] The 2424 patients with significant CAD (>50% stenosis in major epicardial coronary arteries, size ≥2.5 mm) were categorized into normal ABI (n=2039, 84.1%) and abnormal ABI groups (n=385, 15.9%). All enrolled patients provided written informed consent, and the ethics committee of Asan Medical Center approved the study design and allowed the use of clinical data.

End Points, Definitions, and Follow-Up

The primary end points were a composite of all-cause death, MI, and stroke. The secondary end points were all-cause death, MI, stroke, and repeat revascularization (RR). Deaths from any cause (cardiovascular or noncardiovascular) were also included. The diagnosis of MI during follow-up was based on the universal definition of MI.[16] Stroke, represented by a new neurological deficit, was confirmed by a neurologist.[17] RR was defined as any interventional procedure using percutaneous coronary intervention or coronary artery bypass graft after the planned index procedure. All events were based on the clinical diagnosis of each patient by their physicians and were adjudicated by an independent group of clinicians.

The ABI for each leg was measured as described previously[18] using a Doppler ultrasound device (Nicolet VasoGuard; Viasys Healthcare, Conshohocken, PA). The sequence of limb pressure measurements consisted of the first arm, first posterior tibial artery, first dorsalis pedis artery, second posterior tibial artery, second dorsalis pedis artery, and second arm. Each pressure was measured twice, and the average of each pressure was used in calculations. The ABI of each leg was calculated by dividing the posterior tibial or dorsalis pedis pressure, whichever was higher, by the right or left arm systolic blood pressure, whichever was higher. The selected ABI was the lowest of the values for the left and right legs. If the ABI was between 0.80 and 1.00, the measurements were repeated. An abnormal ABI was defined as ≤0.90 or ≥1.4.[19,20] The ABI threshold for detecting PAD was defined as ≤0.90, based on studies showing ≈80% sensitivity and >90% specificity,[21–23] and a high ABI (>1.40) was defined as abnormal, because it could predict the incidence of PAD with 60% to 80% accuracy.[24,25] This definition includes the possibility that a low ABI (≤0.90) and a high ABI (>1.40) may be associated with increased mortality and other adverse events.[2,26]

To validate the complete follow-up data, information about vital status or clinical events was obtained from the National Population Registry of the Korea National Statistical Office on February 28, 2019 using a unique personal identification number. To ensure accurate assessment of clinical end points, additional information was obtained from visits or telephone interviews with living patients or family members, as well as from medical records obtained from other hospitals.

Statistical Analysis

All statistical analyses were performed using SPSS software (version 24; IBM, Armonk, NY) or R software (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria). Analyses of the baseline characteristics were reported previously.[14] Patient demographics, cardiac and other coexisting conditions, and information on medication were compared using the Student *t* test for continuous variables and the χ^2 or Fisher exact test for categorical variables. Based on previous studies, ABI survival curves were drawn using Kaplan-Meier analysis and compared using the log-rank test. In addition, the univariate Cox proportional hazards model was used to estimate the effects of the variables on survival. Univariate and multivariate Cox regression analyses were used for risk factor analysis of the primary end points. All baseline characteristics were tested in a previous study, and the variables were applied to multivariate analysis if the *P* value was ≤0.01 in univariate analysis. The final model was obtained using a backward stepwise method. To reduce the effect of potential confounding variables in an observational study, we performed rigorous adjustments for differences in the baseline characteristics of patients using propensity-score matching (PSM).[27] The variables and details related to PSM analysis are described in Data S1. The validity of the propensity scores was checked using the Hosmer-Lemeshow test (*P*>0.2). To conduct PSM, observations within a 0.1-caliper range were matched, and finally, 359 matched pairs of subjects were selected. Following PSM, the baseline covariates were compared between the 2 groups to check for comparability (Table S1). Statistical significance and the estimated effect of treatment on outcomes were obtained using conditional Cox regression models, with robust standard errors that accounted for the clustering of matched pairs. Likewise, in the propensity-score matched cohort, survival curves according to the ABI were drawn using Kaplan-Meier estimates and compared using the log-rank test. Two-sided *P* values <0.05 indicated statistical significance.

RESULTS

Between January 2006 and December 2009, 2543 patients underwent diagnostic coronary angiography. Among them, 119 patients with no significant CAD were excluded (114 patients in the normal ABI group and 5 patients in the abnormal ABI group). The remaining 2424 patients (95.3%) with significant CAD and without clinical claudication and no previous diagnosis of PAD or intermittent claudication (including ABI) were enrolled in the study. Of the 2424 patients with significant CAD, 1973 (81.4%) had coronary revascularization, and 385 (15.9%) had abnormal ABIs, including 348 (14.4%) with ABI ≤0.90 and 37 (1.5%) with ABI ≥1.40. Among the 385 patients with abnormal ABIs who had significant CAD, 259 (67.3%) were managed with medical therapy, and 126 (32.7%) required revascularization (endovascular therapy, 101 [26.2%]; bypass surgery, 25 [6.5%]). In contrast, among the 5 patients with abnormal ABIs who had no significant CAD, 4 were managed with endovascular therapy, and one was managed with medical therapy (Figure 1).

The baseline characteristics of the 2424 patients according to ABI categorization have been reported previously (Table 1).[14] In general, the abnormal ABI group was associated with higher risk profiles than the normal ABI group.

Of the patients with significant CAD, 359 matched pairs were selected by PSM (Table S1). After PSM, there were no significant differences in the baseline characteristics between the 2 groups, except that cilostazol was more frequently used in the abnormal ABI group.

Outcomes

Unadjusted Outcomes in the Entire Cohort

The median follow-up time was 6.73 years (interquartile range, 4.84–8.00). During follow-up, 346 patients died, 77 had MI, 123 had a stroke, and 264 underwent RR. Consequently, the primary composite end point was confirmed in 429 patients. The number of events increased steadily throughout the follow-up period. Kaplan-Meier curves showed that there was an increasing divergence between the 2 groups during the follow-up period.

Patients with an abnormal ABI had significantly higher rates of composite all-cause death/MI/stroke (40.8% versus 13.3%, *P*<0.001), all-cause death (31.9% versus 9.2%, *P*<0.001), MI (6.5% versus 2.2%, *P*<0.001), and stroke (9.6% versus 3.4%, *P*<0.001) over the course of 7 years. However, the RR rate was not significantly different between the 2 groups (11.2% versus 10.3%, *P*=0.302) (Table 2, Figure 2). There were no significant differences in ABI values between individual clinical situations (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 MI, and 1.05±0.25 in ST-segment–elevation MI, respectively; *P*=0.26).

After multivariate analysis, the primary end point was significantly higher in the abnormal ABI group (hazard ratio [HR], 2.07; 95% CI, 1.67–2.57; *P*<0.001). Among the secondary end points, all-cause death (HR, 1.97; 95% CI, 1.53–2.53; *P*<0.001), MI (HR, 2.40; 95% CI, 1.43–4.04; *P*=0.001), and stroke (HR, 2.17; 95% CI, 1.41–3.34; *P*<0.001) were also significantly higher in the abnormal group than in the normal ABI group.

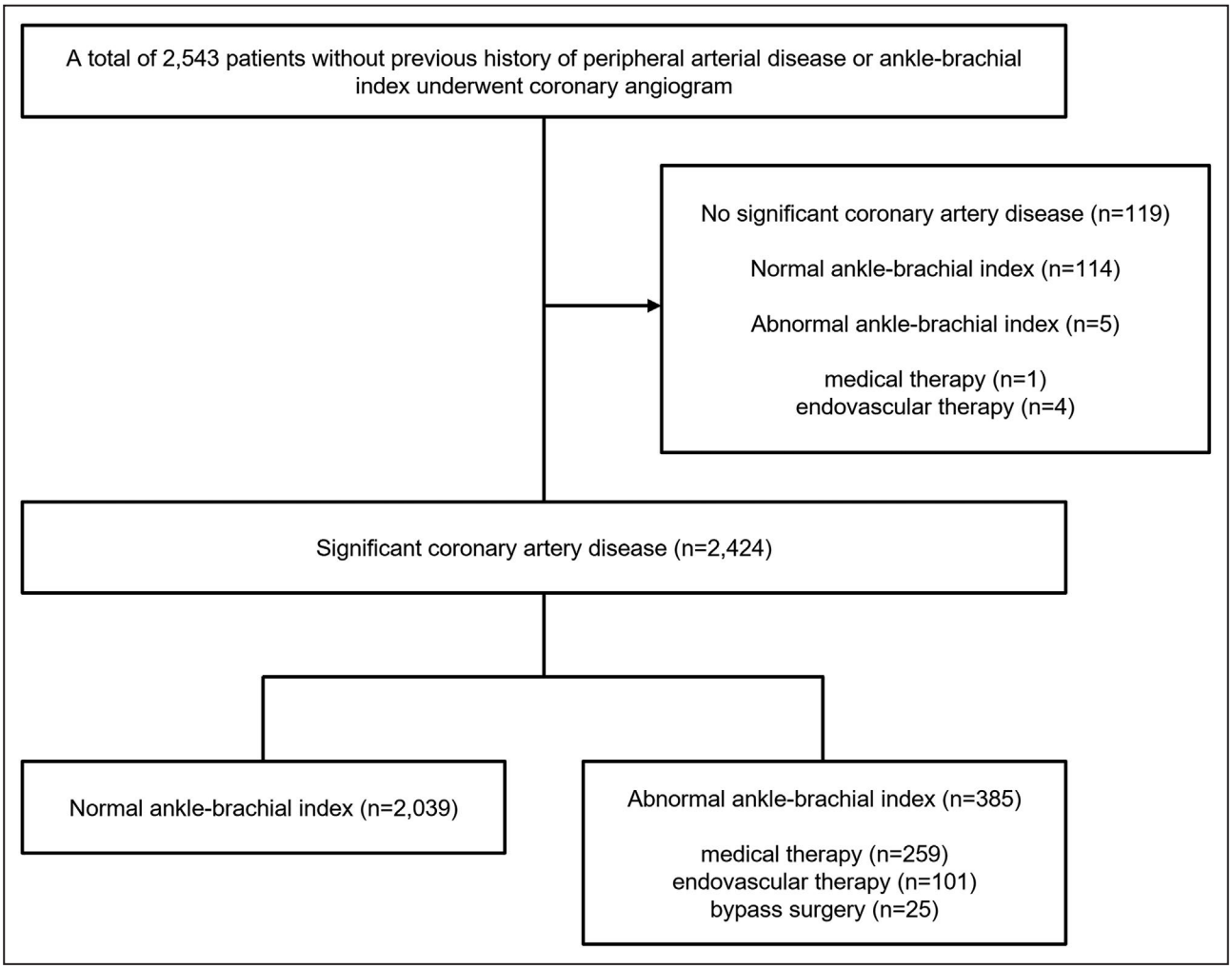

Figure 1. Flow diagram illustrating the selection of the study population.
Of the 2543 patients, 390 (15.3%) had an abnormal ankle–brachial index (ABI). Of the 2424 patients with at least 1 significant stenosis (≥50%) in a major epicardial coronary artery, 385 (15.9%) had an abnormal ABI, including 348 (14.4%) with ABI ≤0.9 and 37 (1.5%) with ABI ≥1.4.

Adjusted Outcomes in the Propensity-Matched Cohort

The incidence of clinical outcomes over the course of 7 years was analyzed in 359 propensity score–matched pairs. Compared with patients with a normal ABI, those with an abnormal ABI had a significantly higher incidence rate of composite all-cause death/MI/stroke (38.4% versus 21.2%; HR, 1.97; 95% CI, 1.49–2.60; *P*<0.001), all-cause death (29.2% versus 17.5%; HR, 1.72; 95% CI, 1.26–2.35; *P*=0.001), MI (6.4% versus 2.2%; HR, 3.07; 95% CI, 1.37–6.86; *P*=0.004), and stroke (9.7% versus 4.2%; HR, 2.45; 95% CI, 1.34–4.49, *P*=0.003). However, the risk of RR was not significantly different between the normal and abnormal ABI groups (11.4% versus 7.5%, *P*=0.058) (Table 3, Figure 3).

Dose-Response Gradient Between ABI Values and Adverse Events

The risk for composite all-cause death/MI/stroke over a 7-year follow-up period for abnormal ABI formed a reverse J-shaped curve according to the ABI values. For ABIs ≤0.90, the unadjusted HR increased as ABI decreased. Similarly, the HR increased in the group with ABI >1.40 (HR, 2.54; 95% CI, 1.43–4.53) (Figure S1). When the ABI groups were divided into 3 categories (low, normal, and high), there were significant differences in event rates over the 7-year period (13.3% in normal, 32.4% in high, and 41.7% in low ABI groups; log-rank *P* value <0.001) (Figure 4A). After multivariate Cox proportional hazard analysis, the low-ABI group showed a significantly higher risk (adjusted HR, 2.19; 95% CI, 1.76–2.73; *P*<0.001) than the normal-ABI

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

Variable	Overall, n=2424	Abnormal ABI, n=385	Normal ABI, n=2039	*P* value
Demographic characteristics				
Age, y	62.9±9.1	66.5±8.5	62.2±9.1	<0.001
Male sex	1779 (73.4)	317 (82.3)	1462 (71.7)	<0.001
Cardiac or coexisting conditions				
Diabetes	1401 (57.8)	246 (63.9)	1155 (56.6)	0.008
Hypertension	1644 (67.8)	308 (80.0)	1336 (65.5)	<0.001
Hyperlipidemia	2001 (82.5)	284 (73.8)	1717 (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
LM disease	339 (14.0)	64 (16.6)	275 (13.5)	0.108
Multivessel disease	1496 (61.7)	289 (75.1)	1207 (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	1910 (78.8)	291 (79.0)	1619 (79.4)	0.103
PCI	1518 (62.6)	192 (49.9)	1326 (65.0)	<0.001
CABG	392 (16.2)	99 (29.1)	293 (14.4)	<0.001
Clinical indication				0.008
Silent/stable angina	1646 (67.9)	239 (62.1)	1407 (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	2118 (87.4)	323 (84.2)	1794 (88.0)	0.044
Clopidogrel	1596 (65.8)	234 (60.8)	1323 (66.8)	0.022
Cilostazol	210 (8.7)	64 (16.6)	146 (7.2)	<0.001
Statin	1872 (77.2)	252 (65.5)	1620 (79.5)	<0.001
ACEI/ARB	935 (38.6)	172 (44.7)	763 (37.4)	0.008
β-blocker	1281 (52.8)	181 (47.0)	1100 (53.9)	0.014
CCB	1812 (74.8)	265 (68.8)	1547 (75.9)	0.002
Nitrate	1356 (55.9)	209 (54.3)	1147 (56.3)	0.501

Data are shown as mean (SD) for continuous variables and as absolute numbers (percentages) for dichotomous variables. ABI indicates ankle–brachial index; ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft surgery; CCB, calcium channel blocker; EF, ejection fraction; LM, left main coronary artery; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

group; the same result was observed in the PSM analysis (HR, 2.04; 95% CI, 1.53–2.71; *P*<0.001). In contrast to the low-ABI group, the high-ABI group showed no statistical significance in either the multivariate Cox proportional hazard analysis (adjusted HR, 1.16; 95% CI, 0.64–2.10; *P*=0.63) or PSM analysis (adjusted HR, 1.35; 95% CI, 0.70–2.62; *P*=0.37), compared with the normal-ABI group (Figure 4B).

The low-ABI group was classified into 3 subgroups according to ABI values, using 0.60 and 0.76 as cutoff points. We also analyzed the entire 5-group cohort as low (≤0.60, n=117), middle (>0.60 and ≤0.76, n=119), and high tertial (>0.76 and ≤0.90, n=112) in the low-, normal- (>0.90 and ≤1.40, n=2039), and high-ABI groups (>1.40, n=37). The incidence of the primary end point at the 7-year follow-up was 50.4% in the low tertial (log-rank *P* value <0.001), 40.3% in the middle tertial group (log-rank *P* value <0.001), 33.9% in the high tertial group (log-rank *P* value <0.001), 13.3% in the normal-ABI reference group, and 32.4% in the high-ABI group (log-rank *P*=0.001). After multivariate Cox proportional hazard analysis, dose-response gradients were found between ABI values and adverse events (HR, 2.78; 95% CI, 2.06–3.76 in the low tertial; HR,

Table 2. Clinical Outcomes of the Entire Cohort According to ABI

Outcome	Outcome rates			Multivariate adjusted*	
	Normal ABI, n=2039	Abnormal ABI, n=385	*P* value†	Hazard ratio (95% CI)*	*P* value
Primary end point					
All-cause death, MI, or stroke	272 (13.3)	157 (40.8)	<0.001	2.07 (1.67–2.57)	<0.001
Secondary end point					
All-cause death	187 (9.2)	123 (31.9)	<0.001	1.97 (1.53–2.53)	<0.001
MI	45 (2.2)	25 (6.5)	<0.001	2.40 (1.43–4.04)	0.001
Stroke	69 (3.4)	37 (9.6)	<0.001	2.17 (1.41–3.34)	<0.001
Repeat revascularization	209 (10.3)	43 (11.2)	0.302	N/A	N/A

Data are shown as the number of events (estimated cumulative incidence rate based on Kaplan-Meier curve) over 7 years. ABI indicates ankle–brachial index; and MI, myocardial infarction.

N/A, not available.

**P* values are based on log-rank tests.

†Hazard ratios of patients with an abnormal ABI compared with those with a normal ABI were measured using multivariate backward stepwise Cox proportional hazard models, which included all variables listed in Table 1.

2.40; 95% CI, 1.76–3.29 in the middle tertial; HR, 1.52; 95% CI, 1.07–2.16 in the high tertial; and HR, 1.15; 95% CI, 0.64–2.08 in the high-ABI group), compared with the normal-ABI group as a reference (Figure 4C).

DISCUSSION

Our extended study clearly demonstrated that newly revealed, asymptomatic abnormal ABI was significantly associated, in a dose-dependent manner, with long-term adverse clinical outcomes (composite all-cause death/MI/stroke, all-cause death, MI, and stroke) in patients with CAD over a 7-year follow-up period. This was a more obvious result compared with previous research, because our previous 3-year study showed that an abnormal ABI was related only to a composite of all-cause death, MI, and stroke, and stroke alone. The prevalence of abnormal ABI was 15.9% among patients with significant CAD. These findings suggest that an abnormal ABI can be used as a surrogate marker for future atherosclerotic events in patients with significant CAD.

We reported that abnormal ABIs had a higher incidence of cardiovascular events, including all-cause death/MI/stroke or stroke, than those with normal ABI, in significant CAD over 3 years.[14] The results of the current extended 7-year follow-up study were more apparent than the previous 3-year study. Our previous short-term data showed that abnormal ABI could increase cardiovascular risk significantly only in the composite end point (all-cause death/MI/stroke) and stroke, but not in all-cause death, MI, or RR. However, a long-term follow-up study showed that there was an increasing divergence between the normal and abnormal ABI groups during the entire follow-up period. In summary, long-term data demonstrated that an abnormal ABI was significantly associated with worse outcomes in terms of all-cause death/MI/stroke as well as all-cause death, MI, and stroke. Our extended follow-up study made it clear that an abnormal ABI was able to predict future cardiovascular event risk in patients with significant CAD. This study is one of the longest follow-up studies to investigate the association between abnormal ABI and clinical outcomes in patients with CAD.

The ABI may be the most important tool for identifying polyvascular disease (PVD).[28] Generally, the incidence of PVD is 13% to 22% in patients with CAD, and the presence of PVD in these populations appears significant in predicting interventions or exacerbations, suggesting an overall unique subtype of patients with high risks of morbidity and mortality. It confers a much higher atherothrombotic burden, which necessitates more aggressive medical management, including more potent antithrombotics or lipid-lowering therapy.[29–32] Our data showed that the prevalence of an asymptomatic, latent abnormal ABI was 15.9%, which was associated with significantly worse outcomes than a normal ABI with respect to death, MI, and stroke. This phenomenon has been demonstrated using other data from Japanese patients, in which the ABI provided additional information for the prediction of future cardiovascular events in patients undergoing percutaneous coronary intervention at 4 years.[33] In addition, a recent meta-analysis showed that an abnormal ABI can predict the incidence of major adverse cardiac events and all-cause mortality in patients with CAD.[34] Furthermore, ABI measurement has been shown to improve the accuracy of cardiovascular risk prediction beyond the traditional Framingham Risk Score in high-risk patients. A low ABI was associated with approximately twice the 10-year total mortality, cardiovascular mortality, and major coronary event rates than the overall rate in each Framingham Risk Score category.[8] Despite this, recent

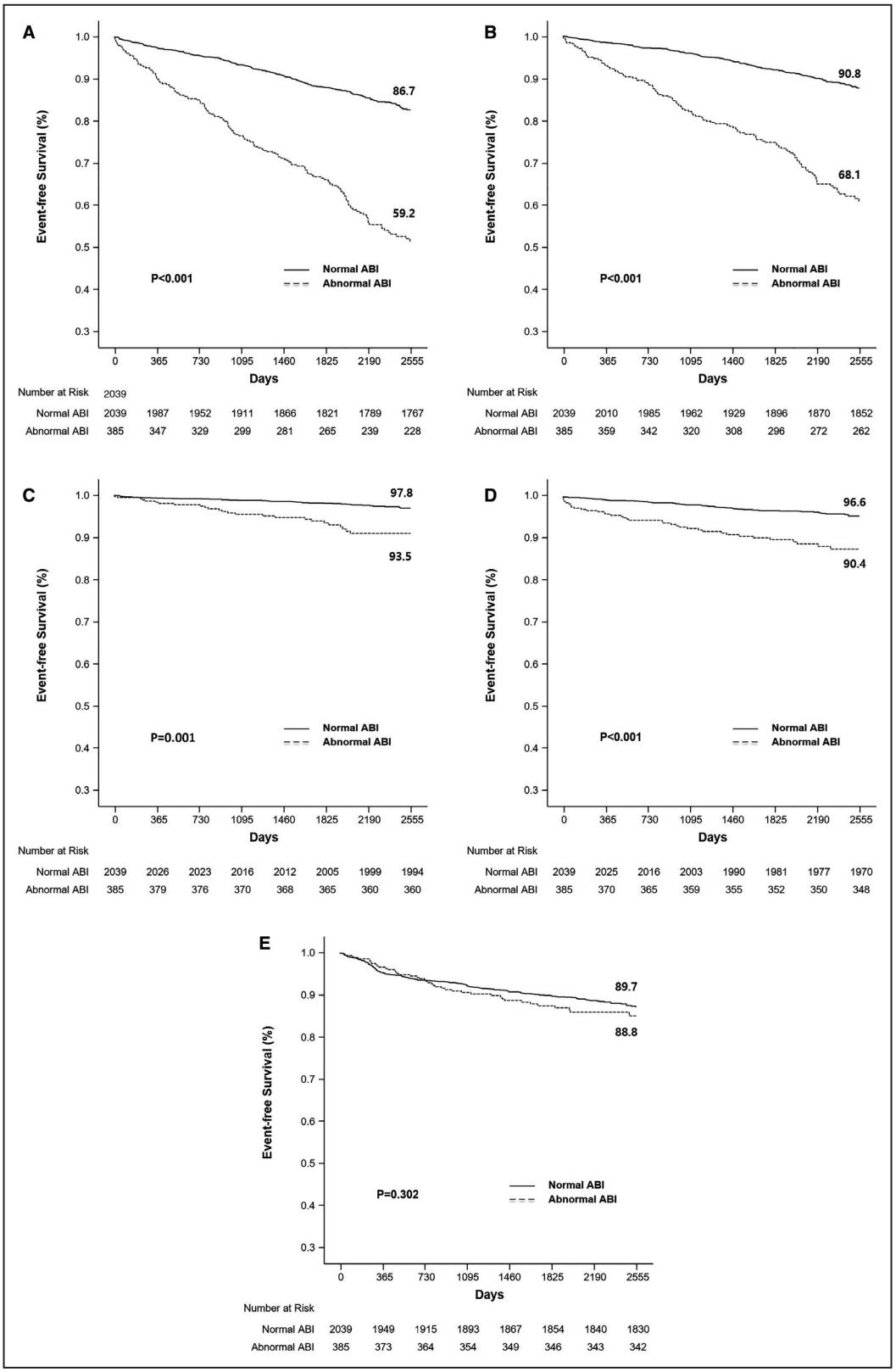

Figure 2. Kaplan-Meier curves of the outcomes of the entire cohort of patients with normal and abnormal ankle–brachial index (ABI).
A, Outcomes for death, myocardial infarction, and stroke. **B**, Outcomes for event-free survival. **C,** Myocardial infarction. **D,** Stroke. **E**, Repeat revascularization event-free survival rates (at 7 years) were derived from paired Kaplan-Meier curves.

Table 3. Clinical Outcomes of the Propensity-Score Matched Cohort According to ABI

Outcome	Normal ABI, n=359	Abnormal ABI, n=359	Hazard ratio (95% CI)*	*P* value
	Event rate for 7-year follow-up	Event rate for 7-year follow-up		
All-cause death, MI, or stroke	76 (21.2)	157 (38.4)	1.97 (1.49–2.60)	<0.001
All-cause death	63 (17.5)	105 (29.2)	1.72 (1.26–2.35)	0.001
MI	8 (2.2)	23 (6.4)	3.07 (1.37–6.86)	0.004
Stroke	15 (4.2)	35 (9.7)	2.45 (1.34–4.49)	0.003
Repeat revascularization	27 (7.5)	41 (11.4)	1.59 (0.98–2.59)	0.058

Data are shown as the number of events (estimated cumulative incidence rate based on Kaplan-Meier curve) for the 7-year follow-up. ABI indicates ankle–brachial index; and MI, myocardial infarction.

*Hazard ratios of patients with an abnormal ABI compared with those with a normal ABI were measured using Cox proportional hazard models.

guidelines do not encourage routine screening for PVD. We must gather newer evidence concerning the potential benefits of targeted screening and therapy for PVD. To enhance the likelihood of evaluation of PVD, routine ABI measurement should be recommended in appropriate patients for adequate risk stratification and management.

Study Limitations

The major limitation of this study is that our evaluation used observational cohort data and was not randomized. This may have led to an unintended underestimation or overestimation of the prevalence of ABI, clinical events, and hidden confounding variables, which could have resulted in a biased outcome. We attempted to minimize any errors in the estimation of incidence by standardizing the inclusion criteria using available resources, such as a detailed review of all available medical records. Next, we defined significant coronary stenosis as >50% stenosis of the epicardial coronary artery. However, the current standard definition is >50% stenosis of the left main coronary artery, >70% stenosis in a major coronary artery, or 30% to 70% stenosis with fractional flow reserve ≤0.8. This is inconsistent with the definition of our study, and another limitation is that the fractional flow reserve threshold that requires intervention for intermediate stenotic lesions has not been presented. Third, ≈38% of patients with abnormal ABI had revascularization (either endovascular therapy or bypass surgery). According to the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines, asymptomatic patients with PAD are generally not indicative of revascularization. If there is damage to the lower extremity nerves because of diabetes, symptoms may not be felt properly or a patient may complain of atypical pain although the ABI value is low (ie, PAD is present). Patients with physical disability may not complain of pain because their walking performance is not enough to cause pain. In addition, even in the case of aorto-iliac artery disease discovered by chance, the collateral artery may develop well, and symptoms may not be discovered if additional tests such as the treadmill test are not performed. However, it is known that asymptomatic PAD has a worse prognosis than intermittent claudication.[35] More than 60% of our subjects had diabetes, and there were a considerable number of elderly patients. Therefore, our study subjects may have included patients in the above example. Based on this evidence, we selected and treated PAD patients with no symptoms through a multidisciplinary approach to revascularization only when the ABI value was extremely low, there was definite aorto-iliac artery disease, and the symptoms were ambiguous, although the peripheral circulation was poor.

From an analytical perspective, our study is an observational cohort study, which may mask confounding variables resulting in selection bias with respect to patients' symptoms and prior evaluation history. Modification of inclusion and exclusion criteria may improve the importance of the study through a better evaluation. Using multivariate analysis and PSM, a rigorous adjustment was performed to reduce unexpected bias. Nevertheless, the PSM method using the log-rank test to compare Kaplan-Meier survival curves may fail to account for potential variables, such as lifestyle modifications, which could have affected the results of the study. However, considering the difficulty in performing randomized trials to evaluate the impact of abnormal, asymptomatic ABI on future clinical outcomes, our analysis is meaningful.

CONCLUSIONS

Abnormal ABI in patients with significant CAD was associated with an increased incidence of major cardiovascular events, including the composite of all-cause death/MI/stroke, all-cause death, MI, and stroke, for long-term follow-up. Abnormal ABI could be a valuable

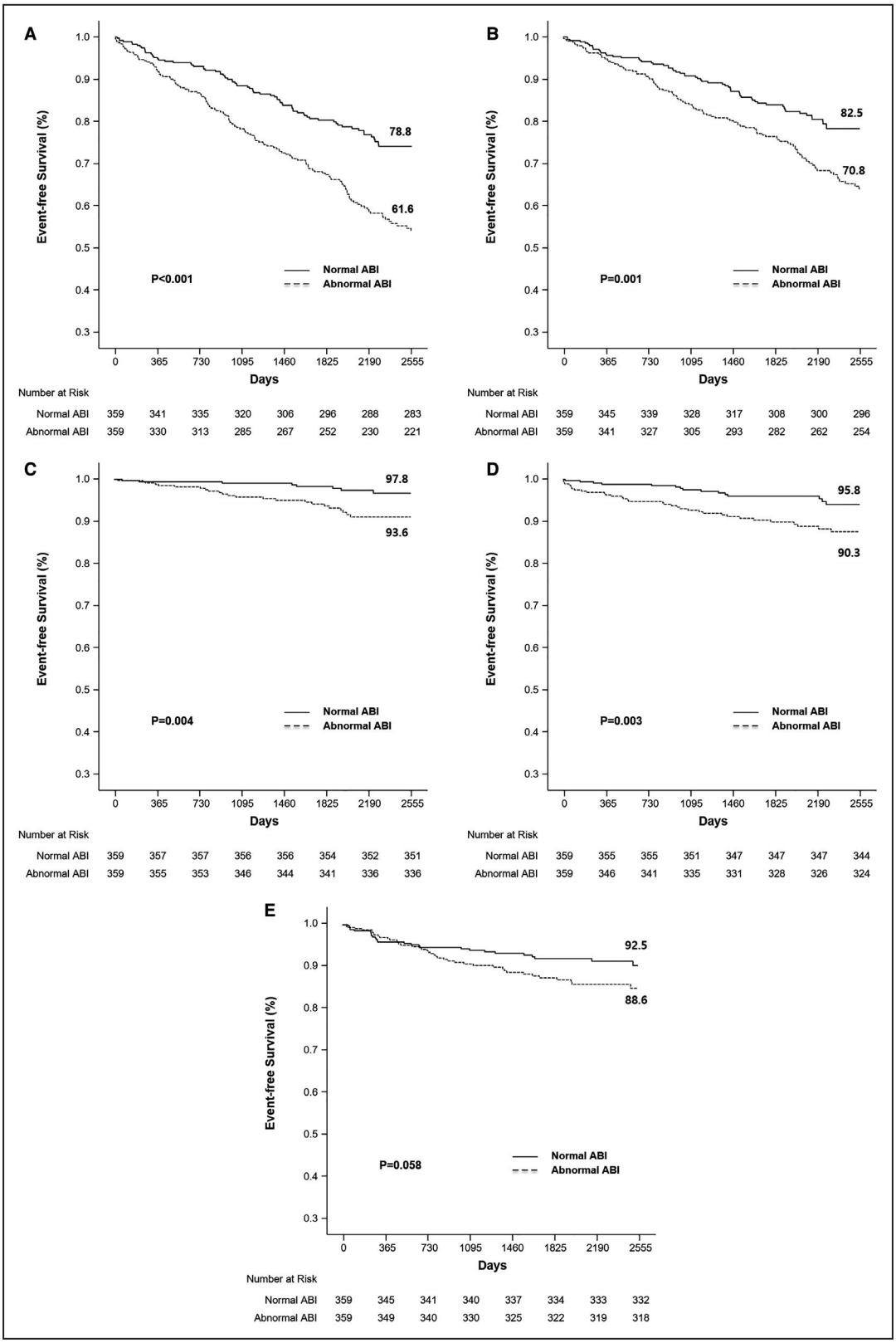

Figure 3. Kaplan-Meier curves of the outcomes of propensity-score matched patients with normal and abnormal ankle–brachial index (ABI).
Propensity-score matching of the entire cohort of patients yielded 359 matched pairs. **A**, Outcomes for all-cause death, myocardial infarction, and stroke. **B**, Outcomes for event-free survival **C**, Myocardial infarction. **D**, Stroke. **E**, Repeat revascularization event-free survival rates (at 7 years) were derived from paired Kaplan–Meier curves.

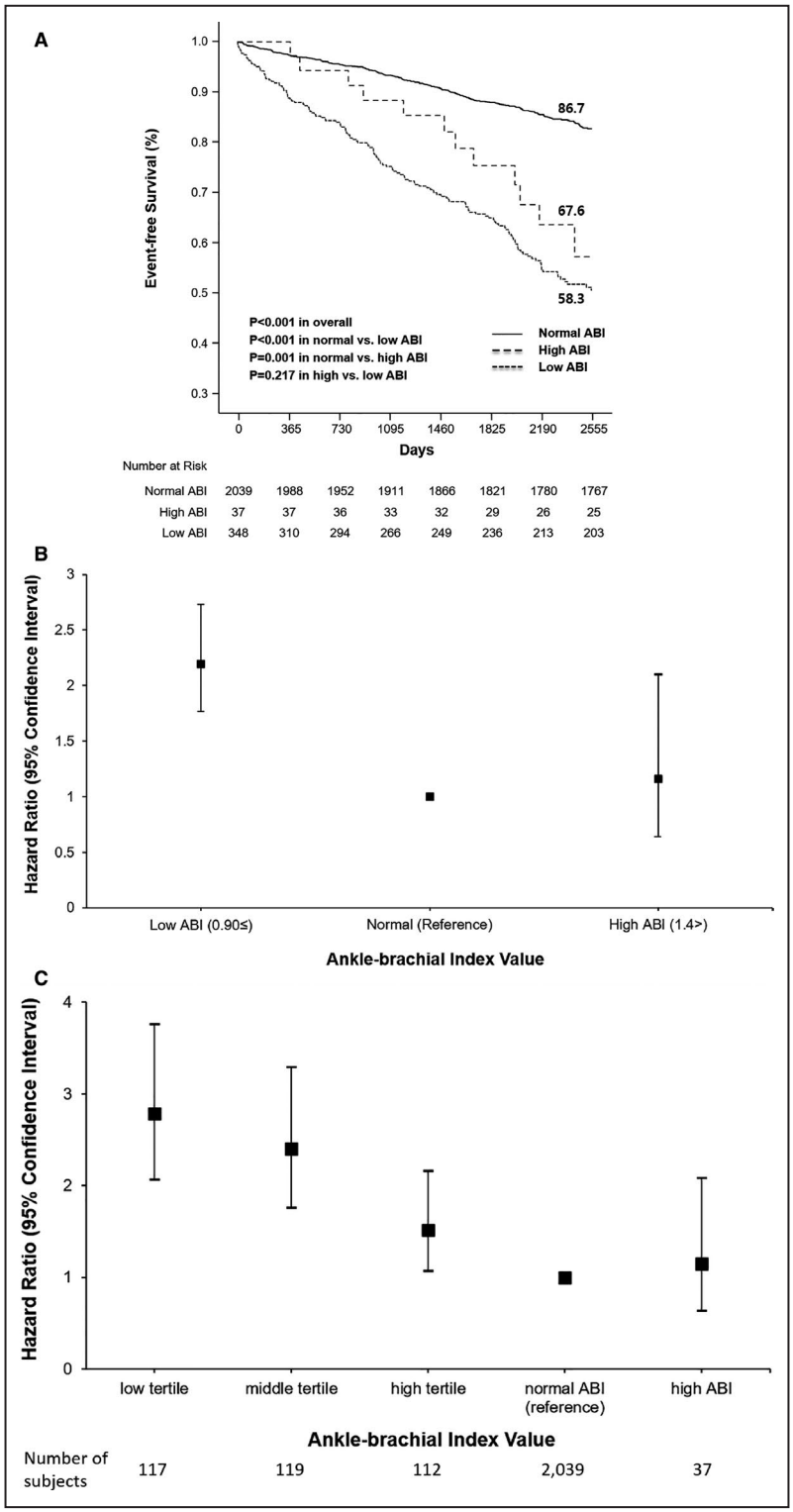

Figure 4. Dose-response gradient between ankle–brachial index (ABI) values and adverse events.
A, Kaplan-Meier curves for all-cause death, myocardial infarction, and stroke outcomes according to the ABI values at baseline (low, normal, and high groups). Event-free survival rates (at 7 years) were derived from paired Kaplan-Meier curves. **B**, Adjusted hazard ratios for all-cause death, myocardial infarction, and stroke at the 7-year follow-up according to ABI values at baseline (low, normal, and high groups). Hazard ratios were derived from multivariate Cox proportional hazards analysis. **C**, Adjusted hazard ratios for all-cause death, myocardial infarction, and stroke at the 7-year follow-up according to the ABI at baseline (low, middle, high tertials in low, normal, and high groups). Hazard ratios were derived from multivariate Cox proportional hazards analyses.

tool for evaluating the prognosis of patients with significant CAD.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Data S1
Figure S1
Table S1

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SUPPLEMENTAL MATERIAL

Data S1. Propensity-Score Matching Method

We conducted propensity-score matching (PSM) in R using the MatchIt package. The considered covariables are listed in Table 1, including age, sex, clinical diagnosis, diabetes mellitus, hypertension, hyperlipidemia, smoking status, previous stroke, previous percutaneous coronary intervention, previous coronary artery bypass grafting, previous myocardial infarction, renal failure, left main disease, multi-vessel disease, left ventricular ejection fraction, coronary revascularization, and medications. The validity of the propensity scores was checked using the Hosmer-Lemeshow test ($p>0.2$). To conduct PSM, observations within a range of ± 0.1 calipers were matched; finally, 359 observations were matched. We checked the profile distances such as means or proportions between the two groups and found that patient profiles between the groups were close based on Table S1. The predictive ability of each propensity-score model was assessed by means of the C statistic (0.88) for the entire cohort, indicating good discrimination between the two groups.

Table S1. Baseline clinical characteristics of the propensity score-matched patients with normal and abnormal ankle-brachial indexes.

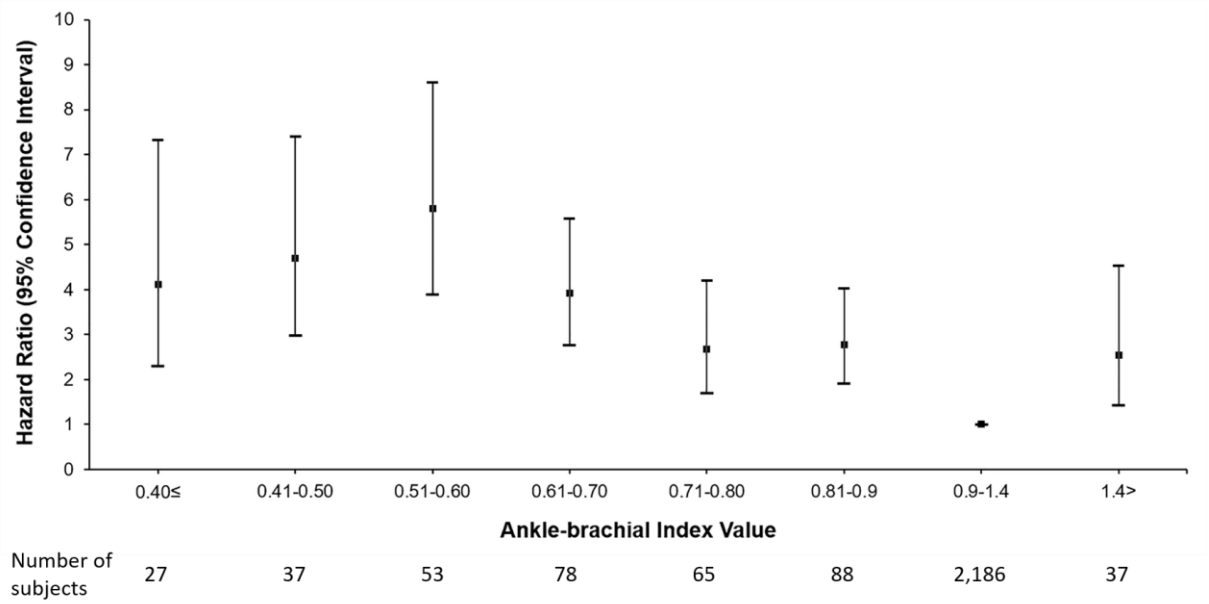
Variable	Abnormal ABI (n=359)	Normal ABI (n=359)	p-value
Demographic characteristics			
Age (years)	66.1±8.4	66.8±8.3	0.25
Male sex	291 (81.1)	281 (78.3)	0.40
Cardiac or coexisting conditions			
Diabetes mellitus	227 (63.2)	224 (62.4)	0.82
Hypertension	283 (78.8)	282 (78.6)	0.93
Hyperlipidemia	271 (75.5)	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
LM disease	58 (16.2)	57 (15.9)	0.91
Multi-vessel 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

Data are shown as means (SDs) for continuous variables and as absolute numbers (percentages) for dichotomous variables.

PCI, percutaneous coronary intervention; MI, myocardial infarction; CABG, coronary artery bypass graft surgery; LM, left main coronary artery; EF, ejection fraction; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Figure S1. **Dose-response gradient between ABI values and adverse events.**



Hazard ratios for all-cause death, myocardial infarction, and stroke at the 7-year follow-up according to the ABI values at baseline. Hazard ratios were not adjusted for cardiovascular risk factors.