Cardio-ankle vascular index as an arterial stiffness marker improves prediction of cardiovascular events in patients without cardiovascular diseases

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Abstract

Several studies reported that cardio-ankle vascular index (CAVI), a non-invasive measurement of arterial stiffness, was associated with the incidence of cardiovascular events. We investigated whether adding CAVI to a risk score improves the prediction of cardiovascular events in the setting of primary prevention. This retrospective observational study included consecutive 554 outpatients with cardiovascular disease risk factors but without known cardiovascular disease (68 ± 9 years, 64% men). CAVI was measured with VaSera vascular screening system. Major adverse cardiovascular events (MACE) included cardiovascular death, myocardial infarction, stroke, hospitalization for heart failure and coronary revascularization. During a median follow-up of 4.3 years, cardiovascular events occurred in 65 patients (11.7%). Multivariate Cox analysis showed that abnormal CAVI (> 9.0) was significantly associated with the incidence of MACE (Hazard ratio 2.31, 95%confidence interval 1.27-4.18). The addition of CAVI to the Suita score, a conventional risk score of coronary heart disease in Japan, significantly improved the C statics from 0.642 to 0.713 ($p = 0.04$). CAVI in addition to a conventional risk score improved prediction of cardiovascular events in patients with cardiovascular disease risk factors but without known cardiovascular diseases.

Introduction

Arterial stiffness is closely associated with cardiovascular disease (CVD) risks and mortality (1). Carotid-femoral pulse wave velocity (PWV) was reported to be associated with increased risk for first cardiovascular events in the general population and improved risk prediction when added to standard risk factors (2). Brachial-ankle PWV, which can be performed more easily than carotid-femoral PWV measurement, while both carotid-femoral PWV and brachial-ankle PWV are affected by blood pressure (1,3), which is an important confounding factor for CVD. To overcome the limitation, The cardio-ankle vascular index (CAVI), a marker of arterial stiffness based on the stiffness parameter β, developed in Japan in 2004 (4). CAVI can be obtained automatically by wrapping pressure cuffs around the upper arms and lower legs and is less dependent on blood pressure. Previous studies have reported the association between a greater CAVI and a high incidence of cardiovascular events in patients with diabetes mellitus, obesity, and several CVD risk factors (5-16).

The measures of arterial stiffness benefit the prevention of cardiovascular disease, while these have not been widely incorporated into routine clinical practice. To facilitate the use of CAVI, we proposed a criterion of CAVI as the expert consensus from the Physiological Diagnosis Criteria for Vascular Failure Committee in the Japan Society for Vascular Failure (17). In the document, we set three ranges; normal range (CAVI $\leq$ 8.0), borderline range (8.0 < CAVI $\leq$ 9.0), and abnormal range (CAVI > 9.0). Abnormal CAVI was considered as a cutoff value for discriminating the presence of cardiovascular disease or a risk of future cardiovascular events. However, the cutoff value of CAVI has not been adequately validated.

For the risk assessment of CVD, the pooled cohort risk equations have been introduced by the American College of Cardiology (18) and the European Society of Cardiology (19) to estimate the 10-year atherosclerotic cardiovascular disease. Meanwhile, the Suita score proposed and

validated to estimate 10-year risk of coronary heart disease for the Japanese population (20). These risk scores are beneficial to assess patients' risk stratification in the setting of primary prevention. As CAVI has been reimbursed by insurance in Japan, the measurement of CAVI has been included in the routine clinical practice. However, usefulness of CAVI in addition to the Suita score has not been evaluated.

This study aimed to investigate (1) whether abnormal CAVI (> 9.0) is a good predictor of cardiovascular events in patients with CVD risk factors but without known CVD and (2) whether CAVI offers incremental value in addition to the Suita score for predicting cardiovascular events in a retrospective cohort.

Methods

Study population

This was a retrospective, single-center, cohort study that evaluated the impact of CAVI on its prognosis. We enrolled 554 consecutive outpatients from May 2012 to December 2016. They had no history of CVD but had at least one CVD risk and had been referred to our hospital for the examination of coronary artery disease. Patients were excluded for the following reasons: peripheral artery disease defined as ankle–brachial pressure index < 0.9, left ventricular ejection fraction< 50%, a history of CVD, Atrial fibrillation, and hemodialysis. Hypertension was defined as systolic blood pressure ≥ 140mmHg or diastolic blood pressure ≥ 90mmHg and/or the use of antihypertensive medication. Diabetes mellitus was defined as a fasting blood glucose concentration of 126 mg/dL and/or the use of insulin or oral hypoglycemic medication. Dyslipidemia was defined as low density lipoprotein cholesterol (LDL-C) ≥ 140mg/dL, triglyceride ≥ 150mg/dL, high density lipoprotein cholesterol (HDL-C) < 40mg/dL and/or taking

antidyslipidemic medication. The estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease equation with the Japanese coefficient (21).

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the ethics committees of the Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences. The requirement for informed patient consent was waived owing to the low-risk nature of the study and the inability to obtain consent directly from all study subjects.

Measurement of CAVI

Arterial stiffness was evaluated using CAVI as previously described (6). After a 5-min rest and with the subject seated, extremity blood pressure was measured by the oscillometric method. CAVI was measured automatically using a VaSera vascular screening system (Fukuda Denshi, Tokyo, Japan) from the measurement of blood pressure and pulse wave velocity (PWV), while monitoring the electrocardiogram and heart sound. PWV was calculated by dividing the distance from the aortic valve to the ankle artery by sum of the time between the aortic valve closing sound and notch of the brachial pulse wave, and the time between the rise of the brachial pulse wave and rise of the ankle pulse wave. CAVI was determined using the following equation: $CAVI=a[(2\rho /\Delta P)\times In(Ps/Pd)\times PWV^2]+b$, where Ps and Pd are systolic and diastolic blood pressure, respectively, PWV is the pulse wave velocity between the heart and ankle, ΔP is Ps-Pd, ρ is blood density, and a and b are constants. The average of right and left CAVI was used for analysis. Patients were classified into three groups based on CAVI levels as previously described (17): normal group ($CAVI \leq 8.0$); borderline group ($8.0 < CAVI \leq 9.0$), and abnormal group ($CAVI > 9.0$).

The Suita score

For predicting the risk of CVD development, we used the Suita score (20). The Suita score is an established CVD risk score based on risk factor categories for predicting coronary heart disease in the Japanese population. The Suita score LDL-C version was calculated using age, sex, HDL-C and LDL-C levels, systolic blood pressure, diastolic blood pressure, smoking, diabetes mellitus, and eGFR according to a previous report (21). A high, medium, and low risk were classified as the Suita score ≥56, 41-55, <40. Estimated risk of developing coronary heart disease in 10 years of high, medium, and low risk groups was >9%, 2-9%, <2%, respectively.

Outcome data

A follow-up information was obtained from a review of medical records or telephone interviews blinded to CAVI data. The major adverse cardiovascular events (MACE) included cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and heart failure requiring hospitalization. Stroke included ischemic stroke and hemorrhagic stroke. The details of definitions of MACE were previously described (6). The time to the first primary endpoint was evaluated retrospectively.

Statistical analysis

Data are expressed as mean ± standard deviation. Dichotomous variables are expressed as a number and percentage. Categorical data were compared using $\chi 2$ analysis or Fisher's exact test. We used one-way analysis of variance to compare normally distributed continuous variables, and Bonferroni correction was used for post hoc testing. The relationship between continuous variables was investigated by means of Spearman's correlation coefficient. Cumulative survival estimates were calculated using the Kaplan–Meier method and compared with the log-rank test. To ascertain the associations of CAVI with MACE, we performed univariate and multivariate Cox regression analyses, and the results were reported as hazard ratios (HRs) with 95% confidence interval (CI). A multivariate Cox regression analysis included variables with $P < 0.05$

in the univariate analysis. The incremental prognostic value of CAVI was assessed using the receiver-operating characteristic (ROC) curve analysis continuous net reclassification improvement, and integrated discrimination improvement. All reported p-values were two-sided, and statistical significance was set at $p<0.05$. Statistical analyses were performed using SPSS statistical software (Version 28; IBM Corp., Armonk, NY, USA) and the R statistical package (version 3.5.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Comparison of baseline characteristics

Of all, the patients' mean age was 68 ± 9 years, and 64% were male. The average CAVI was 8.8±1.3. Baseline characteristics of 554 patients were shown according to CAVI (normal group, CAVI < 8; borderline group, CAVI 8.0–9.0; abnormal group, CAVI > 9.0) are shown in Table 1. Patients with higher CAVI levels were older and were more likely to be men. The mean systolic blood pressure and prevalence of hypertension increased significantly with a higher CAVI. The mean diastolic pressure and HDL-C levels, triglyceride levels, hemoglobinA1c, the prevalence of diabetes mellitus, dyslipidemia, smoking habits, and use of statins, did not differ among the groups.

Association between Cumulative incidence of major adverse cardiovascular events (MACE) and CAVI

During this follow-up period (median 4.3 years), 65 patients had the MACE, including cardiac death (n = 2), myocardial infarction (n = 3), stroke (n = 13), heart failure with hospitalization (n = 14), or coronary revascularization (n = 34). The cumulative incidence rates of the MACE according to the CAVI levels are shown in the Figure 1, and the rates were significantly higher in

the abnormal group than in the other groups (p value for trend < 0.001). Figure 2 shows the ROC curve analysis of CAVI for predicting MACE. The sensitivity and specificity of CAVI at the cut-off value of 9.0 were 75% and 54%, respectively (area under the curve, 0.688; $p < 0.001$). The multivariable-adjusted Cox proportional hazard model, CAVI (> 9.0) was associated with increased risk of the MACE after adjusting for covariates (HR, 1.941 [95% CI, 1.092–3.448]; $p = 0.024$) (Table 2)

Incremental predictive value of CAVI over the Suita score

As shown in Figure 2A, CAVI had weak correlation with the Suita score ($\rho = 0.351$, $p < 0.01$). When patients were classified into three groups (low-risk group, medium-risk group, high-risk group) according to Suita score, The CAVI value was stepwisely increased from low-risk group to high-risk group (8.1 ± 0.2, 8.9 ± 0.1, and 9.3 ± 0.2, respectively; p value for trend < 0.01) (Figure 2B). To determine the incremental value of the CAVI for predicting MACE, ROC curve analysis was performed (Figure 3). The addition of CAVI to the Suita Score significantly improved the C statics from 0.642 to 0.713 ($p = 0.04$). Addition of the CAVI yielded a continuous net reclassification index of 0.293 (95% CI, 0.036–0.551; $p = 0.025$) and an integrated discrimination improvement of 0.0479 (95% CI, 0.0218–0.0740; $p < 0.001$).

Discussion

This study demonstrated that abnormal CAVI (> 9.0) was significantly associated with the incidence of MACE in patients with CVD risk factors but without known CVD. Furthermore, CAVI in addition to the Suita score improved prediction of MACE in these patients. To our knowledge, this is the largest study showing incremental value of CAVI in addition to a clinical risk score for predicting cardiovascular events in the setting of primary prevention.

Several studies showed that CAVI was associated with the incidence of cardiovascular events in patients with known CVD (5-9) and without CVD (10-16). However, evidence on incremental value of CAVI for predicting cardiovascular events over a clinical risk score has been limited. Satoh-Asahara et al. showed that, in 300 obese patients without CVD, CAVI in addition to atherosclerotic cardiovascular disease risk score moderately improved the prediction of cardiovascular events (16). We showed that incremental value of CAVI for predicting cardiovascular events in a large cohort study, while one third of participants had a history of CVD (6). The present study are in line with these two previous studies, and clearly demonstrated that the usefulness of CAVI for predicting cardiovascular events in patients with CVD risk factors but without known CVD.

This study showed that the best cutoff value of CAVI for predicting cardiovascular events was 9.0, which was consistent with our proposal of abnormal CAVI (> 9.0) (17). However, the report by Satoh-Asahara et al. showed that, including 300 obese patients, the threshold of CAVI for cardiovascular events was 7.8 (16). Compared to the by Satoh-Asahara et al., the patients in our study were heterogenous patients with hypertension, diabetes, or dyslipidemia, who visiting to the Department of Cardiovascular Medicine. In addition, mean age was in their study was 52 years, being younger than that in ours (mean age was 66 years). Therefore, these differences may be the reason for the higher cut-off value in the present study. Although our study validated that CAVI of 9.0 was a cutoff for predicting cardiovascular events in the setting of primary prevention, further study will be needed to confirm the optimal threshold of CAVI to predict cardiovascular events with respect to each population.

Several measures of arterial stiffness such as carotid-femoral PWV and brachial-ankle PWV has been introduced (1). However, there are notable differences among arterial stiffness measurements. Carotid-femoral PWV is obtained by applanation tonometry, which is a

complicated technique compared with CAVI and brachial-ankle PWV (3). CAVI and brachial-ankle PWV are derived from plethysmography cuff automatically (1). CAVI has an advantage over PWV for measuring arterial stiffness as it is less dependent on blood pressure at the time of measurement (4). An assessment of arterial properties in a reproducible manner may allow detailed monitoring of changes in arterial stiffness in clinical practice. CAVI is easily obtained automatically with a device, leading to its widespread use in clinical situations if cost constraints are ignored. Further investigations will be needed to elucidate this matter, with due consideration given to cost-effectiveness.

This study had several limitations. First, we acknowledge that an observational study cannot definitively prove that there is a causal link underlying the association between increased CAVI and increased CVD events. Second, the study population included only Asians. Although several studies of non-Asian populations have recently been reported (12,14), the generalizability of our data to other races/ethnicities remains uncertain. Third, we failed to estimate a cutoff value of CAVI for each event because of the small number of events. Hence, a further study with a larger sample is warranted.

In conclusion, we demonstrated that abnormal CAVI (>9) was significantly associated with the incidence of cardiovascular events in patients with CVD risk factors but without known CVD. Furthermore, CAVI in addition to the Suita score improved prediction of cardiovascular events in these patients. The data of this study suggest that measurement of CAVI is a clinically useful means to predict the development of cardiovascular events in the setting of primary prevention.

Author Contributions

Conceptualization, Y.O. and T.M.; methodology, T.M.; formal analysis, Y.O. and T.M.; investigation, Y.O., T.M., K.I., Y.T., K.N., and H.M; writing—original draft preparation, Y.O. and T.M.; writing—review and editing, H.I. All authors have read and agreed to the published version of the manuscript.

Funding

This study was supported by the Japan Society for the Promotion of Science KAKENHI (grant number JP 19K08558).

Institutional Review Board Statement

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the ethics committees of the Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences (2203-024).

Informed Consent Statement

The requirement for informed patient consent was waived owing to the low-risk nature of the study and the inability to obtain consent directly from all study subjects.

Data Availability Statement

The data presented in this study are available upon request from the corresponding author. The data is not publicly available because of privacy concerns.

Conflicts of Interest

T.M. revived honorarium from Fukuda Denshi Inc. All authors declare no conflict of interest associated with this manuscript.

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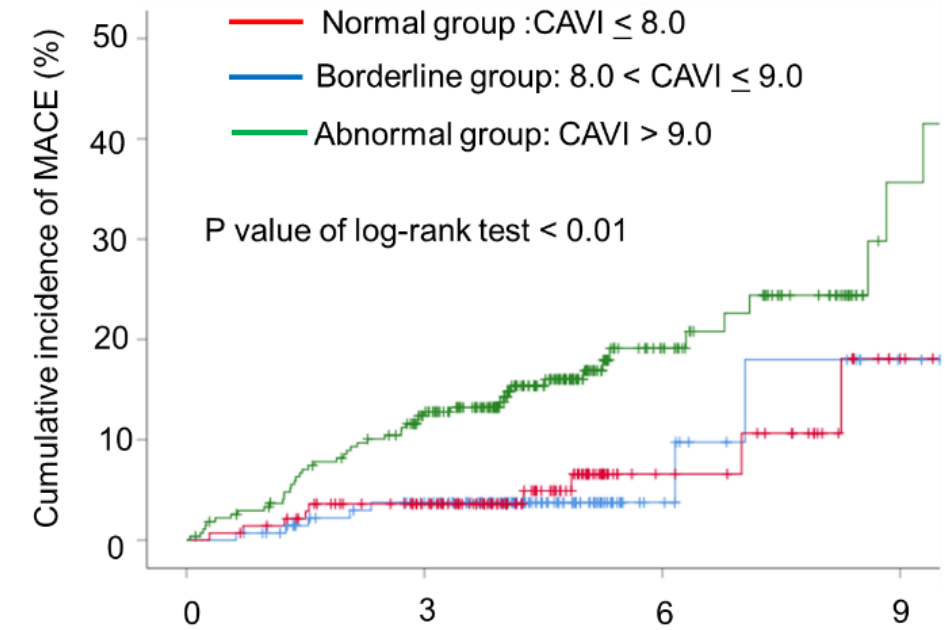


Number at risk:

CAVI				
<8	140	117	19	5
8-9	141	114	24	4
>9	273	217	53	10

Figure 1. Kaplan-Meier plot of cumulative probability of cardiovascular events by cardio-ankle vascular index (CAVI) levels.

Time to cardiovascular events, including cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, heart failure requiring hospitalization, and coronary revascularization according to baseline CAVI. The cumulative incidence rates of cardiovascular events according to the CAVI levels were significantly higher in the abnormal group (CAVI> 9.0) than in the normal (CAVI ≤ 8) and abnormal groups (8 < CAVI ≤ 9) (P value for trend < 0.01).

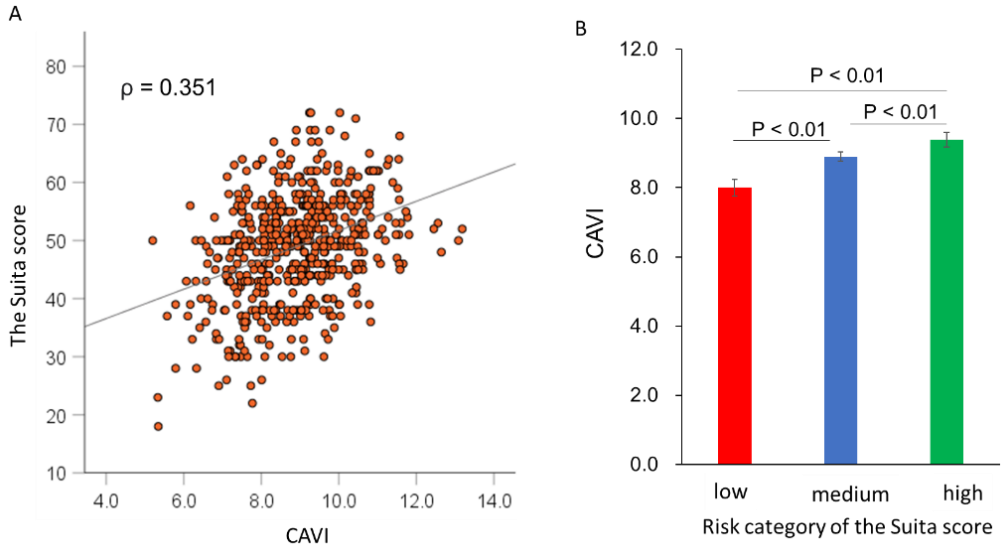
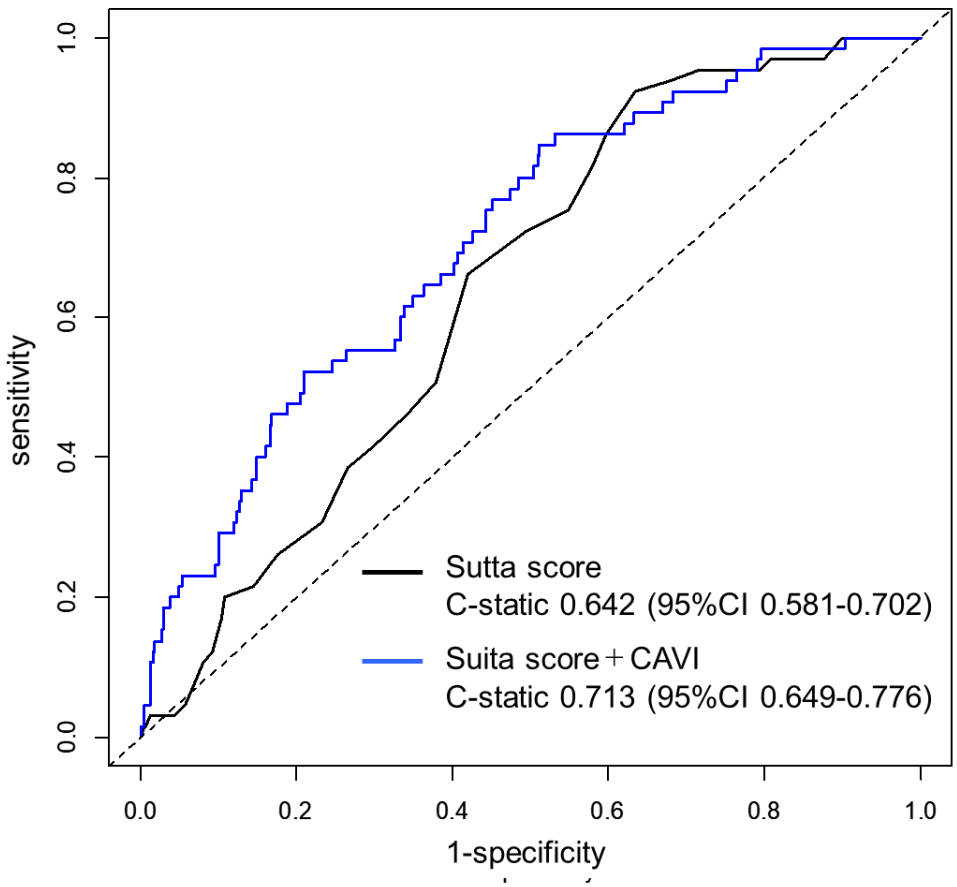


Figure 2. Correlation between CAVI and the Suita score

Scatter plot showing the correlation between CAVI and the Suita score (A), and CAVI according to the risk category of the Suita score (B)



Fgiure 3 Comparison of the receiver-operating characteristic (ROC) curves

Black curve: predictive ability by the Suita score. Blue curve: predictive ability by the Suita score and CAVI. CI, confidence interval.

Table 1. Baseline Characteristics According to the CAVI.

Variables	All (*n* = 554)	Normal CAVI (CAVI < 8) (*n* = 140)	Borderline CAVI (8 < CAVI < 9) (*n* = 141)	Abnormal CAVI (9 < CAVI) (*n* = 273)	*p*-Value for Trend
Age, year	66 ± 9	62 ± 10	67 ± 9	71 ± 7	<0.01
Male, *n* (%)	353 (64)	92 (66)	76 (54)	185 (68)	0.01
Body mass index, kg/m^2	23.4 ± 3.9	24.7 ± 4.6	23.9 ± 3.8	22.9 ± 3.5	<0.01
Hypertension, *n* (%)	418 (75)	84 (60)	110 (78)	224 (82)	<0.01
Diabetes mellitus, *n* (%)	283 (51)	69 (43)	76 (54)	138 (51)	0.72
Dyslipidemia, *n* (%)	343 (62)	82 (59)	92 (65)	169 (62)	0.52
Current smoking, *n* (%)	159 (29)	44 (31)	41 (29)	74 (27)	0.65
Systolic blood pressure, mmHg	129 ± 19	122 ± 19	128 ± 16	133 ± 18	<0.01
Diastolic blood pressure, mmHg	74 ± 11	72 ± 11	74 ± 10	75 ± 11	0.04
Laboratory data					
Triglyceride, mg/dl	140 ± 119	136 ± 126	137 ± 94	144 ± 126	0.78
HDL-C, mg/dl	55 ± 17	58 ± 19	54 ± 18	545 ± 16	0.08
LDL-C, mg/dl	109 ± 31	113 ± 33	110 ± 31	107 ± 32	0.17
HemoglobinA1c, %	6.4 ± 1.4	6.3 ± 1.5	6.5 ± 1.4	6.5 ± 1.4	0.69
eGFR, mL/min/1.73 m^2	66.1 ± 19.4	70.0 ± 17.3	68.0 ± 20.9	63.3 ± 18.2	0.02
Medications					
Antihypertensive agents, *n* (%)	406 (73)	85 (61)	107 (76)	214 (78)	<0.01
Antidiabetic agents, *n* (%)	178 (42)	34 (37)	52(47)	92 (42)	0.31
Lipid-lowering agents, *n* (%)	310 (56)	64 (46)	86 (61)	160 (59)	0.01

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

Table 2. Association Between the CAVI and Cardiovascular Events.

	Univariate		Multivariate	
	HR (95% CI)	***p*-Value**	**HR (95% CI)**	***p*-Value**
CAVI > 9	3.07 (1.78–5.41)	<0.01	2.31 (1.27–4.18)	<0.01
Age per year	1.05 (1.01–1.08)	<0.01	1.02 (0.98–1.06)	0.18
Male	1.97 (1.09–3.57)	0.02	1.86 (1.02–3.39)	0.04
Hypertension	2.56 (1.16–5.62)	0.01	0.86 (0.38–2.27)	0.86
Diabetes mellitus	1.44 (0.87–2.37)	0.14		
Dyslipidemia	1.68 (0.96–2.93)	0.06		
Current smoking	1.34 (0.80–2.25)	0.25		
Antihypertensive agents	5.36 (1.94–14.78)	<0.01	4.16 (1.29–13.40)	0.01
Antidiabetic agents	1.41 (0.32–2.40)	0.20		
Lipid-lowering agents	1.79 (1.05–3.07)	0.03	1.56 (0.91–2.68)	0.10

The multivariate analysis included CAVI > 9, age, male sex, hypertension, antihypertensive agents, and lipid-lowering agents. CAVI, cardio-ankle vascular index; HR, hazard ratio; CI, confidence interval.