Original Article

Cardio-Ankle Vascular Index is Independently Associated with Future Cardiovascular Events in Outpatients with Metabolic Disorders

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***Aim*: We investigated whether cardio-ankle vascular index (CAVI), an arterial stiffness marker, independently predicts future cardiovascular events in subjects with metabolic disorders.**
***Methods*: 1562 outpatients underwent CAVI between April 2004 and March 2006 at Toho University, Sakura Medical Center in Chiba, Japan. Patients who already had cardiovascular events at baseline, patients with low ankle brachial index (<0.9), and patients with atrial fibrillation were excluded. After exclusion, 1080 subjects with metabolic disorders including diabetes mellitus, hypertension and dyslipidemia were screened and followed prospectively.**
***Results*: Eventually, 1003 subjects (92.9% of 1,080 subjects) followed until March 2012 (follow-up duration 6.7±1.6 years) were analyzed. During the observation period, 90 subjects had new-onset myocardial infarction or angina pectoris confirmed by angiography. All subjects were stratified into quartiles by baseline CAVI (Q1: CAVI ≤8.27, Q2: CAVI 8.28-9.19, Q3: CAVI 9.20-10.08, Q4: CAVI ≥10.09). Age, male ratio and future cardiovascular events increased as CAVI quartile became higher. In Cox proportional hazards regression analysis, the factors independently associated with higher risk of future cardiovascular events were every 1.0 increment of CAVI [hazard ratio (HR) 1.126, p=0.039], male gender (HR 2.276, p=0.001), smoking (HR 1.846, p=0.007), diabetes mellitus (HR 1.702, p=0.020), and hypertension (HR 1.682, p=0.023).**
***Conclusion*: In individuals with metabolic disorders, CAVI was a predictor of future cardiovascular events, independent of traditional coronary risk factors. CAVI is a potentially valuable tool to identify persons likely to benefit from more intensive therapeutic approaches.**

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Key words: Cardio-ankle vascular index, Arterial stiffness, Metabolic disorders, Cardiovascular disease

Introduction

Many previous studies have demonstrated the significance of arterial stiffness as a surrogate marker for the prognosis of cardiovascular disease (CVD)[1, 2]. Aortic stiffness is due to the structural changes occurring prior to plaque or thrombus formation in muscular and elastic vessels. Increased arterial stiffness is observed in persons with coronary risk factors such as hypertension[3], diabetes mellitus[4], and dyslipidemia[5]. Estimation of the degree of atherosclerosis by examining arterial stiffness is therefore clinically significant for the prevention of cardiovascular events[6].

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A novel arterial stiffness diagnostic parameter called cardio-ankle vascular index (CAVI) has been developed in Japan, which essentially reflects the stiffness of the aorta, femoral artery, and tibial artery[7]. This stiffness parameter has been reported to be less affected by blood pressure at the time of measurement and adequately reproducible for clinical use[8, 9]. Kubozono *et al.* reported the reproducibility of CAVI measurements by analyzing 21 consecutive Japanese subjects. CAVI was measured twice for each patient with an interval of 2 weeks. Linear regression analysis showed a very strong correlation between the two measurements of CAVI ($r=0.93$, $p<0.0001$). In Bland−Altman plots, the mean difference of the two measurements was 0.2, and the 95% limits of agreement (mean ± 1.96 SD) was − 1.2 and 1.7[10]. CAVI is also known to be associated with traditional parameters of vascular structure and function, such as intima-media thickness (IMT), pulse wave velocity (PWV), and central augmentation index[11]. Furthermore, no special technique is required for the measurement of CAVI. Indeed, CAVI has been associated with a number of risk factors for cardiovascular disease and the severity of CVD[10, 12-15]. An increase in the number of risk factors for metabolic syndrome was also positively correlated with an increased CAVI, probably due to insulin resistance[16].

However, the predictive value of CAVI for future cardiovascular events in people with any form of metabolic disorder has not yet been fully elucidated. The aim of this study was to investigate whether CAVI independently predicts future cardiovascular events in persons with metabolic disorders.

Subjects and Methods

Study Design

We performed a prospective study at a single center on outpatients with metabolic disorders such as diabetes mellitus, hypertension, and dyslipidemia. The study was approved by the Ethics Committee of Sakura Hospital, School of Medicine, Toho University (No. 2012-084).

Subjects

Between April 2004 and March 2006, a total of 1562 outpatients with metabolic disorders such as diabetes mellitus, hypertension and dyslipidemia underwent CAVI measurement at Toho University, Sakura Medical Center in Chiba, Japan. Patients who already had cardiovascular events at baseline were excluded. To obtain correct CAVI measurements[7], patients with low ankle brachial index (<0.9) and patients with atrial fibrillation were excluded. Eventually, 1080 subjects with metabolic disorders were screened and followed prospectively. At the end of follow-up in March 2012, 77 subjects were lost to follow-up. Among them, 46 died (8, hemorrhagic stroke; 24, cancer; 6, infection; and 8, unknown reason), 13 moved to another city, and 18 were lost for unknown reason. The remaining 1003 subjects were analyzed (follow-up duration, 6.7 ± 1.6 years) (**Fig. 1**).

Data Collection

The primary end point of this study was new-onset cardiovascular events such as myocardial infarction and stable/unstable angina pectoris. Cardiovascular event was defined as ≥75% stenosis in an epicardial coronary artery confirmed angiographically. Sudden cardiac death, heart failure, and intermittent claudication without coronary angiography were not included in the end point. Angina pectoris and myocardial infarction were diagnosed according to the European Society of Cardiology guidelines[17]. Baseline parameters analyzed included age, gender, body mass index (BMI, kg/m^2), systolic blood pressure (sBP, mmHg), diastolic blood pressure (dBP, mmHg), heart rate (bpm), CAVI, diabetes mellitus rate (%), hypertension rate (%), dyslipidemia rate (%), smoking rate (%), fasting plasma glucose (FPG, mg/dL), total cholesterol (TC, mg/dL), triglyceride (TG, mg/dL), and high-density lipoprotein cholesterol (HDL-C, mg/dL). Glycated hemoglobin (HbA1c, %), including stable and unstable fractions, was measured by high pressure liquid chromatography using the Hi-Auto A1c (Kyoto Daiichi Kagaku, Kyoto, Japan). HbA1c values obtained using the Japan Diabetes Society (JDS) method were converted to NGSP values (%) by the following formula: HbA1c (NGSP) (%) = HbA1c (JDS) (%) + 0.4%[18]. Diabetes mellitus was diagnosed according to the Treatment Guide for Diabetes 2014 edited by JDS, defined as fasting plasma glucose ≥126 mg/dL and/or 75-g oral glucose tolerance test 2-h plasma glucose ≥200 mg/dL and/or random (casual) plasma glucose ≥200 mg/dL. Alternatively, patients who already received antidiabetic agents were also diagnosed. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. Patients treated with antihypertensive agents at baseline were included. Dyslipidemia was defined as TC ≥220 mg/dL or HDL-C <40 mg/dL or TG ≥150 mg/dL or subjects treated with lipid-lowering agents at baseline.

Measurement of CAVI

CAVI was measured with a VaSera CAVI instru-

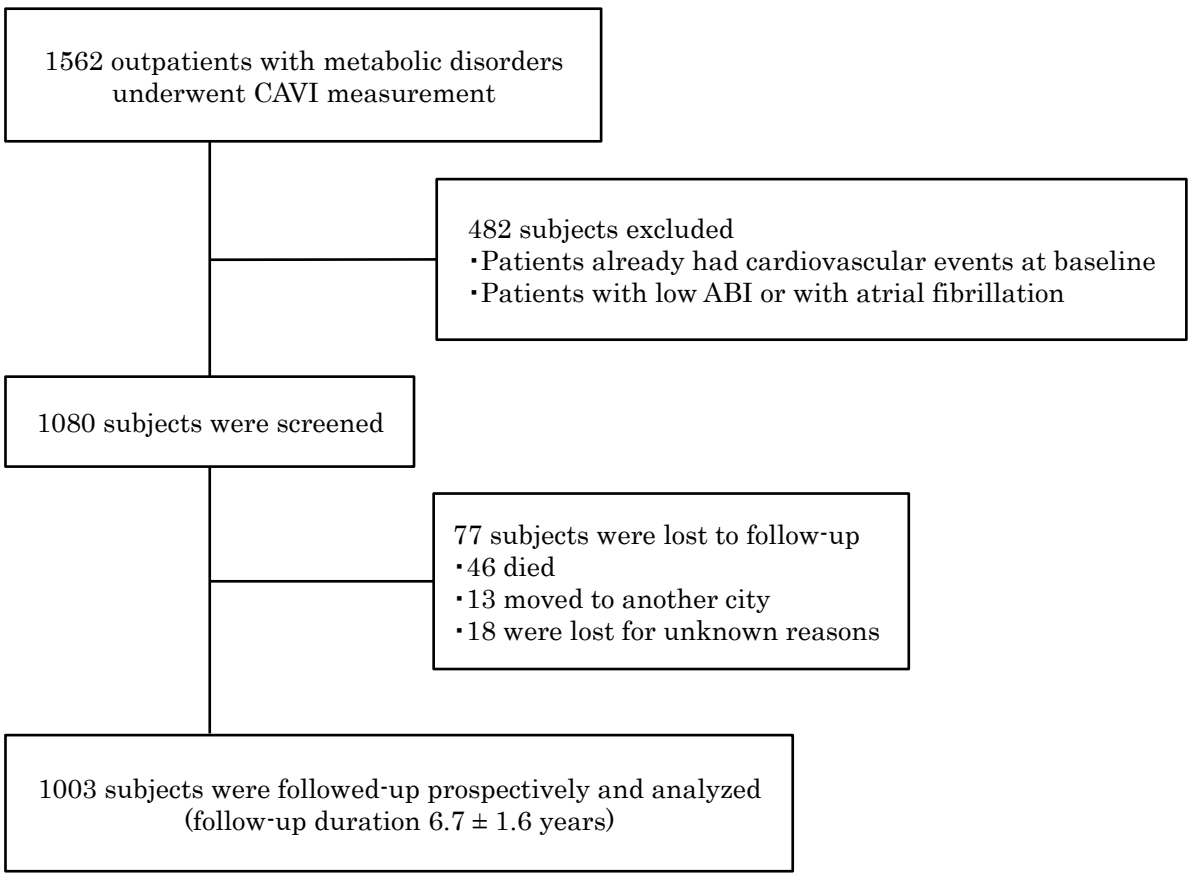

Fig. 1. Patients description.

ment (Fukuda Denshi Co Ltd, Tokyo, Japan) by the methods described previously[7]. In brief, cuffs were applied to bilateral upper arms and ankles with the subject lying supine and the head held in midline position. After resting for 10 min, the examinations were performed. To detect the brachial and ankle pulse waves with cuffs, a low cuff pressure of 30−50 mmHg was used to ensure minimal effect of cuff pressure on hemodynamics. Furthermore, blood pressure was measured thereafter. CAVI was calculated by the following formula: $CAVI = a\{(2\rho/\Delta P) \times \ln(Ps/Pd)\ PWV2\} + b$, where Ps is systolic blood pressure, Pd is diastolic blood pressure, PWV is pulse wave velocity, ΔP is Ps − Pd, ρ is blood density, and a and b are constants. Blood pressure was measured using the cuff at the upper arm. PWV was obtained by dividing the vascular length by the time taken for the pulse wave to propagate from the aortic valve to the ankle and was measured using cuffs at the upper arms and ankles. All the measurements and calculations were performed automatically by the VaSera. The mean coefficient of variation of CAVI measured by this method is $<5\%$, which is sufficiently small for clinical usage and indicates that CAVI has good reproducibility[10].

Measurement of Body Weight and Blood Sampling

Body weight was measured, and blood samples were collected in the morning after 12 h of fasting. Serum was separated within 1 h and used for measurements of HbA1c and serum lipids.

Measurement of HbA1c and Plasma Lipid Concentrations

For HbA1c measurement, blood was collected in tubes containing EDTA. Stable and unstable fractions of HbA1c were measured by high pressure liquid chromatography using the Hi-Auto A1c (Kyoto Daiichi Kagaku, Kyoto, Japan). Data of the stable form were used in the present analysis. TC and TG were measured enzymatically using kits from Nippon Shoji Co., Ltd. (Osaka, Japan) and a Hitachi 7150 analyzer (Hitachi, Ltd., Tokyo, Japan). HDL-C was measured by a selective inhibition method (Daiichi Pure Chemicals Co., Ltd, Tokyo, Japan)[19].

Statistical Analysis

Statistical analysis were performed using IBM SPSS statistics (version 20, Armonk, NY, USA), except for Cochran−Armitage test, which was performed using EZR (Jichi Medical University), a graphical user interface for R software (The R Foundation for Statistical Computing)[20]. Fisher's exact test and Mann−Whitney's *U* test were performed to determine whether intra group differences were statistically significant. ANOVA and Cochran−Armitage test were also used to assess whether there was a linear trend across groups. Kaplan−Meier survival analysis was employed to estimate the differences of time to end point between the four groups. Cox proportional hazards regression analysis was used to identify the predictors of cardiovascular events and expressed as hazard ratio with 95% confidence interval. Data are presented as mean ± standard deviation or numbers or percentage. In all statistical procedures, two-sided p values <0.05 were considered statistically significant.

Results

Characteristics of Participants at Baseline

In this study, a total of 1003 subjects (initial age: 62.5 ± 11.2 years, 514 males and 489 females, BMI: 23.9 ± 3.9) completed follow-up (duration: 6.7 ± 1.6 years) and were included as the population for analysis. Baseline CAVI was 9.25 ± 1.61, and smoking prevalence was 21.8%. For underlying diseases, 51.1% of the subjects had diabetes mellitus, 52.4% had hypertension, and 62.6% had dyslipidemia. Coronary risk factors described in this study included the following six components: elderly (age: >65 years), obesity (BMI: >25 kg/m^2), smoking, diabetes mellitus, hypertension, and dyslipidemia. Resultantly, 2.6 ± 1.3 risks were possessed in all subjects. Other clinical data and medications are shown in **Table 1**.

Table 1. Characteristics of participants at baseline

	Total (n = 1003)
CAVI	9.25 ± 1.61
Future Cardiovascular events (%)	9.0
Age (years)	62.5 ± 11.2
Male ratio (%)	51.2
BMI (kg/m^2)	23.9 ± 3.9
sBP (mmHg)	137 ± 22
dBP (mmHg)	81 ± 12
Heart rate (bpm)	68 ± 13
FPG (mg/dL)	136 ± 57
HbA1c (NGSP, %)	6.9 ± 1.6
TC (mg/dL)	206 ± 42
TG (mg/dL)	145 ± 138
HDL-C (mg/dL)	55 ± 17
Smoking (%)	21.8
Diabetes mellitus (%)	51.1
Hypertension (%)	52.4
Dyslipidemia (%)	62.6
Number of coronary risks	2.6 ± 1.3
Medication use:	
Insulin (%)	12.5
Sulphonylurea (%)	20.7
Biguanide (%)	9.4
α-GI (%)	9.9
Thiazolidine (%)	6.8
ARB or ACE-I (%)	32.3
Calcium channel blocker (%)	33.4
Statin (%)	26.3
Fibrate (%)	4.0

Data are presented as mean ± standard deviation. CAVI indicates cardio-ankle vascular index; BMI, body mass index; sBP, systolic blood pressure; dBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; α-GI, α-glucosidase inhibitor; ARB, angiotensin receptor blocker; and ACE-I, angiotensin converting enzyme inhibitor.
Coronary risks include the 6 components; elderly (aged 65 years and over), obesity (BMI 25 kg/m^2 and over), smoking, diabetes mellitus, hypertension and dyslipidemia.

Primary End Point

During the observation period, 46 of 1003 subjects died. Six subjects died of CVD and 40 died of other causes. After the follow-up period to reach an end point of 96 months, cardiovascular events occurred in 90 subjects (8.97%), including 41 (45.6%) of acute myocardial infarction, 20 (22.2%) of unstable angina pectoris, and 29 (32.2%) of stable angina pectoris.

Characteristics of Participants Stratified by Quartile of CAVI

The analysis population (n = 1003) was stratified into quartiles by CAVI (**Table 2**). Q1: CAVI, ≤8.27 (n = 252); Q2: CAVI, 8.28−9.19 (n = 253); Q3: CAVI, 9.20−10.08 (n = 248); and Q4: CAVI, ≥10.09 (n = 250). Age (Q1: Q2: Q3: Q4 = 54.3 ± 12.2: 60.4 ± 8.6: 65.5 ± 8.5: 69.9 ± 8.5 years, $p<0.001$ for trend), male ratio (Q1: Q2: Q3: Q4 = 41.0: 50.2: 53.6: 60.4%, $p<0.001$ for trend), and the incidence of cardiovascular events (Q1: Q2: Q3: Q4 = 5.6: 7.1: 10.9: 12.4%, $p=0.025$ for trend) increased as CAVI became higher. BMI (Q1: Q2: Q3: Q4 = 24.5 ± 5.0: 24.0 ± 3.6: 23.8 ± 3.2: 23.4 ± 3.1 kg/m^2, $p=0.008$ for trend) decreased as CAVI became higher. Smoking rate and prevalence of dyslipidemia did not differ between quartiles. Preva-

Table 2. Characteristics of participants stratified by quartile of baseline CAVI

	CAVI				*p* value
	Q1 (≤8.27)	Q2 (8.28-9.19)	Q3 (9.20-10.08)	Q4 (≥10.09)	
n	252	253	248	250	–
Future cardiovascular events (%)	5.6	7.1	10.9	12.4	0.025[a]
Age (years)	54.3±12.2	60.4±8.6	65.5±8.5	69.9±8.5	<0.001[a]
Male ratio (%)	41.0	50.2	53.6	60.4	<0.001[b]
BMI (kg/m^2)	24.5±5.0	24.0±3.6	23.8±3.2	23.4±3.1	0.008[a]
sBP (mmHg)	130±21	134±20	140±22	145±23	<0.001[a]
dBP (mmHg)	79±13	81±16	82±10	82±12	0.002[a]
Heart rate (bpm)	67±14	67±12	68±12	69±13	0.421[a]
FPG (mg/dL)	125±52	134±52	138±63	147±59	<0.001[a]
HbA1c (NGSP, %)	6.5±1.6	6.9±1.7	7.0±1.6	7.2±1.6	<0.001[a]
TC (mg/dL)	212±49	207±36	205±44	199±39	0.007[a]
TG (mg/dL)	150±224	143±85	148±90	141±102	0.877[a]
HDL-C (mg/dL)	58±19	56±16	54±16	52±15	0.001[a]
Smoking (%)	21.0	21.3	21.8	23.2	0.552[b]
Diabetes mellitus (%)	36.9	49.0	54.8	64.0	<0.001[b]
Hypertension (%)	45.2	48.2	56.4	59.6	<0.001[b]
Dyslipidemia (%)	55.6	66.8	65.7	62.4	0.154[b]
Number of coronary risks	2.1±1.2	2.5±1.3	2.8±1.2	3.1±1.2	<0.001[a]

Data are presented as mean±standard deviation, [a]: ANOVA, [b]: Cochran–Armitage test, *p* value for trend. Abbreviations are as in Table 1.

lence of diabetes mellitus and hypertension increased as CAVI became higher. Number of coronary risks (Q1: Q2: Q3: Q4=2.1±1.2: 2.5±1.3: 2.8±1.2: 3.1±1.2, $p<0.001$ for trend) also increased as CAVI became higher. More details are shown in **Table 2**.

Kaplan–Meier Survival Analysis to Estimate Differences between the Four Groups

Fig. 2 shows the event-free survival of cardiovascular events. There were significant differences among the quartile groups, and the cumulative incidence of events was higher in Q4 than in other groups.

Characteristics of Participants with and those without Cardiovascular Events

In subjects with cardiovascular events, baseline CAVI, male ratio, age, smoking rate, and prevalence of diabetes mellitus and hypertension were significantly higher, whereas TC and HDL-C were significantly lower than in subjects without future cardiovascular events. No significant difference in BMI, sBP, dBP, heart rate, TG, and prevalence of dyslipidemia were observed between the two groups. Other clinical data and medication use are shown in **Table 3**.

Cox Proportional Hazards Regression Analysis of the Association between Future Cardiovascular Events and Clinical Variables

We examined the factors associated with future cardiovascular events using Cox proportional hazards regression analysis. CAVI, gender, age, smoking, diabetes mellitus, and hypertension that showed significant differences between subjects with and those without cardiovascular events in **Table 3**, together with obesity (BMI ≥25 kg/m^2) and dyslipidemia were introduced in the model (**Table 4**). The model demonstrated that the factors independently associated with higher risk of future cardiovascular events were every 1.0 increment of CAVI [hazard ratio (HR): 1.126, $p=0.039$], male gender (HR: 2.276, $p=0.001$), smoking (HR: 1.846, $p=0.007$), diabetes mellitus (HR: 1.702, $p=0.020$), and hypertension (HR: 1.682, $p=0.023$). Older age (≥65 years), obesity, and dyslipidemia were not significant independent predictors of future cardiovascular events.

Discussion

In this prospective study that followed 1003 consecutive outpatients (92.9% of 1080 patients screened) with metabolic disorders for 6.7±1.6 years, the incidence of new-onset cardiovascular events was 8.97%

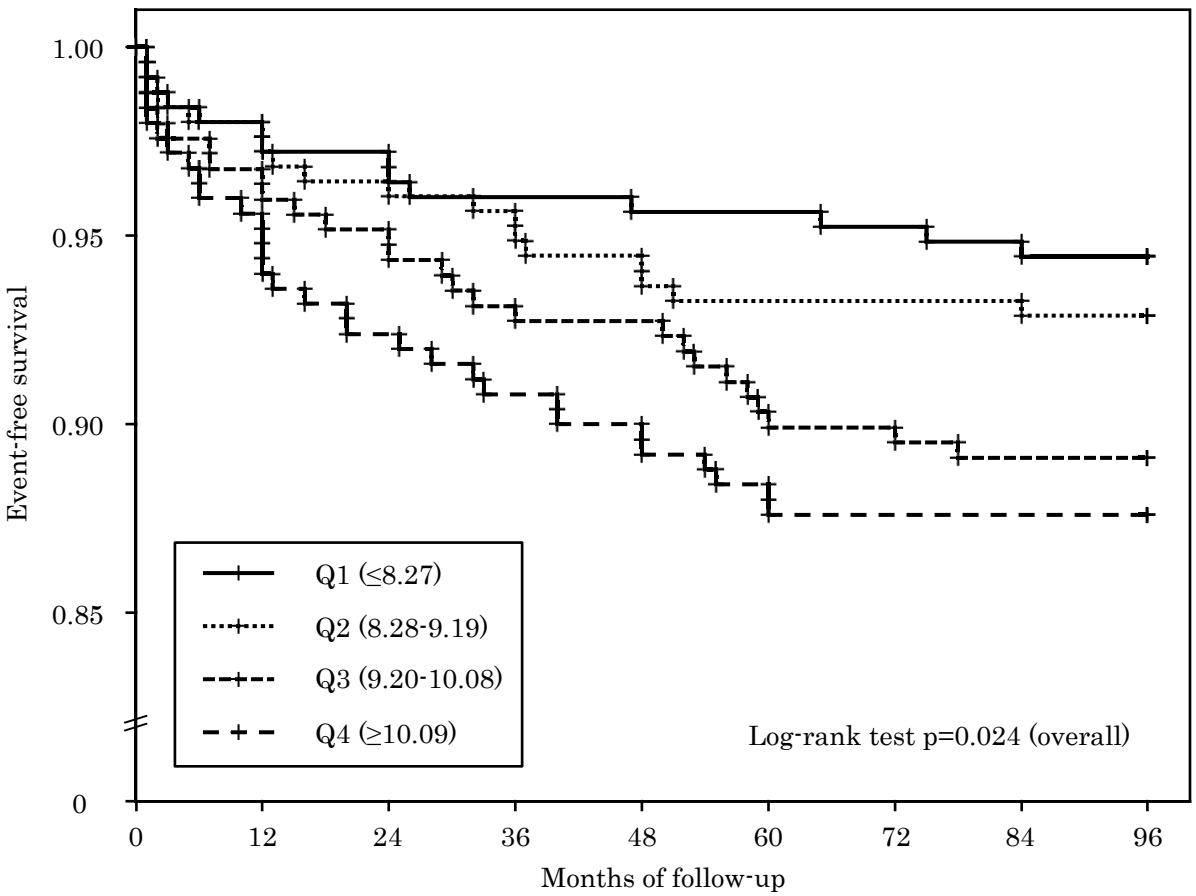

Fig. 2. Kaplan-Meier survival curves showing cardiovascular events according to quartiles of CAVI.

(90 subjects). Baseline CAVI correlated positively with the incidence of new-onset cardiovascular events as well as the prevalence of diabetes mellitus, hypertension, and dyslipidemia. In subjects with new-onset cardiovascular events, baseline CAVI, male ratio, age, smoking ratio, and prevalence of diabetes mellitus and hypertension were significantly higher. Cox proportional hazards regression analysis identified baseline CAVI, male gender, smoking, diabetes mellitus, and hypertension as independent predictors of future cardiovascular events. Kubota Y *et al.* already reported that higher CAVI was an independent predictor of vascular diseases, such as coronary artery diseases and strokes, in 400 patients of a three-year observation period[21]. However, CAVI was not extracted to be a significant predictor of alone coronary artery disease in the study. Consequently, the present study is the first report showing that CAVI was independently extracted to be an independent predictor of the occurrence of future coronary artery diseases.

The correlation between arterial stiffness and CVD is consistent with the hypothesis that coronary risk factors contribute to atherogenesis by damaging the aortic and coronary vessel walls through common pathophysiological pathways[22]. Furthermore, reduced aortic distensibility per se, as reflected by increased CAVI, constitutes a risk factor for CVD. Increased vascular resistance and central blood pressure are considered to increase left ventricular afterload and oxygen requirement, consequently accentuating myocardial ischemia. Several reports have confirmed the relationship between CAVI and left ventricular functions[23-25]. In addition, cardiorespiratory fitness was also reported to be associated with CAVI in hypertensive middle-aged and elderly Japanese men[26].

Increased CAVI is observed in many arteriosclerotic diseases such as coronary artery disease, carotid arteriosclerosis, chronic kidney disease, and cerebrovascular disease and is positively related to coronary risk factors such as hypertension, diabetes mellitus, dyslipidemia, and smoking[12, 13, 27]. Using CAVI, clinicians can evaluate the severity of arteriosclerosis in

Table 3. Characteristics of participants with and those without future cardiovascular events

	Cardiovascular event		*p* value
	+ (*n*=90)	− (*n*=913)	
CAVI	9.86 ± 2.03	9.19 ± 1.55	<0.001 [a]
Male ratio (%)	74.4	49.0	<0.001 [b]
Age (years)	65.7 ± 9.1	62.2 ± 11.3	0.001 [a]
BMI (kg/m^2)	24.0 ± 2.8	23.9 ± 3.9	0.458 [a]
sBP (mmHg)	139 ± 23	137 ± 22	0.237 [a]
dBP (mmHg)	81 ± 13	81 ± 12	0.433 [a]
Heart rate (bpm)	70 ± 15	68 ± 12	0.321 [a]
FPG (mg/dL)	158 ± 78	134 ± 54	0.003 [a]
HbA1c (NGSP, %)	7.4 ± 1.7	6.8 ± 1.6	0.001 [a]
TC (mg/dL)	194 ± 46	207 ± 42	0.003 [a]
TG (mg/dL)	145 ± 67	145 ± 143	0.046 [a]
HDL-C (mg/dL)	48 ± 16	56 ± 17	<0.001 [a]
Smoking (%)	40.0	20.0	<0.001 [b]
Diabetes mellitus (%)	66.7	49.6	0.003 [b]
Hypertension (%)	65.6	51.0	0.011 [b]
Dyslipidemia (%)	67.8	62.1	0.306 [b]
Medication use:			
Insulin (%)	16.7	12.0	0.176 [b]
Sulphonylurea (%)	28.9	19.9	0.056 [b]
Biguanide (%)	12.2	9.1	0.342 [b]
α-GI (%)	15.6	9.3	0.064 [b]
Thiazolidine (%)	8.9	6.6	0.380 [b]
ARB or ACE-I (%)	42.2	31.3	0.044 [b]
Calcium channel blocker (%)	41.1	32.6	0.127 [b]
Statin (%)	36.7	25.3	0.024 [b]
Fibrate (%)	5.6	3.8	0.396 [b]

Data are presented as mean ± standard deviation, [a]: Man-Whitney *U* test, [b]: Fisher's exact test. Abbreviations are as in Table 1.

patients with coronary risks. Furthermore, the present study suggests that CAVI can predict vascular events that may occur in the future. Moreover, CAVI has been shown to decrease following various interventions for coronary risks, including some medications for metabolic disorders, weight reduction, and smoking cessation[13, 28-33]. Therefore, CAVI is considered a good physiological surrogate marker for lifestyle changes such as smoking cessation and control of blood pressure and glucose level, which may be expected to contribute to the prevention of CVD. Clinicians should be encouraged to measure CAVI in their routine practice and care.

In 2002, brachial-ankle PWV (baPWV) was proposed as a marker of vascular damage and was reported to be a predictive factor of coronary artery disease[34]. Furthermore, baPWV was strongly correlated with aortic (carotid-femoral) PWV, an established index of central arterial stiffness[35]. However, PWV is known to depend on BP at the measuring time. Therefore, the validity of PWV in reflecting actual arterial stiffness is questionable, and this parameter is unsuitable for evaluating the effect of antihypertensive drugs in the arterial wall. On the other hand, CAVI is independent of BP, which makes it more precise and reproducible than PWV, whereas its predictive value of cardiovascular events is not established enough[20, 36]. Furthermore, Izuhara *et al.*[37] reported the multiple logistic analysis revealing that CAVI, but not baPWV, was associated with the presence of carotid and coronary arteriosclerosis.

Several studies have shown a strong association between increased IMT and CAD[38, 39]. Furthermore, strong correlation between CAVI and IMT were reported[40]. However, CAVI probably reflects the effect of therapy on vascular function and is measured swiftly

Table 4. Cox proportional hazards regression analysis of the association between future cardiovascular events and clinical variables

Variables	Hazard ratio	95% confidence interval	*p* value
CAVI (every 1.0 index)	1.126	1.006-1.259	0.039
Gender (male; 1, female; 0)	2.276	1.383-3.748	0.001
Elderly (Age ≧65; 1, <65; 0)	1.203	0.759-1.905	0.432
Obesity (BMI ≧25; 1, <25; 0)	0.778	0.483-1.252	0.301
Smoking (+; 1, −; 0)	1.846	1.184-2.879	0.007
Diabetes mellitus (+; 1, −; 0)	1.702	1.086-2.667	0.020
Hypertension (+; 1, −; 0)	1.682	1.073-2.636	0.023
Dyslipidemia (+; 1, −; 0)	1.376	0.875-2.165	0.167

Abbreviations are as in Table 1.

compared with IMT. The combination of CAVI and IMT may be a much significant predictor of cerebral thrombosis in highly atherosclerotic patients.

Gender difference in CAVI was previously reported[27]. Similarly, in this study, mean CAVI was higher in males (9.47 ± 1.74 in males, 9.02 ± 1.42 in females), whereas mean age did not differ (62.7 ± 11.7 years in males, 62.3 ± 10.7 years in females). From these findings, the favor of male in cardiovascular events is seemed to be consistent. However, in this study, male gender was extracted to be a predictor of cardiovascular events independently from CAVI. There may be some interaction between the factor of gender and CAVI. It remains unclear why the magnitude of the association between CAVI and cardiovascular events differs between males and females.

In this study, BMI decreased as CAVI became higher in **Table 2**. Furthermore, CAVI was correlated negatively with BMI in healthy Japanese subjects[41]. These data are consistent. Obesity is one of the risks of cardiovascular diseases, whereas this negative correlation between BMI and CAVI looks discrepant. We previously reported that weight reduction induced the decrease of CAVI[28] in 47 obese Japanese subjects (BMI: 33.3 ± 7.5 kg/m^2). In this study, only the change of visceral fat area contributed to the change of CAVI. We therefore hypothesize that systemic accumulation of adipose tissue, in itself, leads to the decrease of arterial stiffness in non-obese subjects, and excessive accumulation of visceral fat may induce an increase of arterial stiffness. However, the mechanism and the threshold of the effect of BMI on change in arterial stiffness are still unclear.

Regarding the structure of the multivariate analysis model shown in **Table 4**, only CAVI was left as part of the continuous volume when used as an independent variable. After leaving age (every 1 year) and BMI (every 1 kg/m^2) as part of the continuous volume when conducting multivariate analysis, they were not extracted similarly. On the other hand, CAVI was not unfortunately extracted as an independent predictor of cardiovascular disease if it was converted to dichotomous or quartile variable. Reluctantly, we adopted that model.

A limitation of this study was that some patients were lost to follow-up during the observation period, which may contribute to overall bias and lead to uncertainty concerning the conclusion. However, only 7.1% of the initially selected population was excluded from the analysis, and it is unlikely that their inclusion would have impacted the overall results. Moreover, the present prospective observational study cannot definitely demonstrate that there is a causal relationship underlying the association between arterial stiffness and cardiovascular events. We also cannot rule out residual confounders such as duration and severity of associated risk factors. In addition, in the present study, we evaluated mainly middle-aged to elderly subjects with any metabolic disorder at a single center only. Therefore, the results may not be generalizable to younger subjects without coronary risks. Furthermore, this study did not examine whether decreasing CAVI by appropriate treatments or interventions would translate into reduction of cardiovascular events. From these viewpoints, a multiple-center cohort study for CAVI is necessary.

In conclusion, in individuals with metabolic disorders, CAVI is a predictor of future cardiovascular events independent of traditional coronary risk factors. CAVI is a potentially valuable tool to identify people likely to benefit from more intensive therapeutic approaches.

Conflicts of Interest

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References

1) Oliver JJ, Webb DJ: Noninvasive assessment of arterial stiffness and risk of atherosclerotic events. Arterioscler Thromb Vasc Biol, 2003; 1; 23: 554-566
2) Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, Asmar R, Reneman RS, Hoeks AP, Breteler MM, Witteman JC: Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation, 2006; 113: 657-663
3) O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE: Clinical applications of arterial stiffness; definitions and reference values. Am J Hypertens, 2002; 15: 426-444
4) Koizumi M, Shimizu H, Shimomura K, Oh-I S, Tomita Y, Kudo T, Iizuka K, Mori M: Relationship between hyperinsulinemia and pulse wave velocity in moderately hyperglycemic subjects. Diabetes Res Clin Pract, 2003; 62: 17-21
5) ter Avest E, Holewijn S, Bredie SJ, van Tits LJ, Stalenhoef AF, de Graaf J: Pulse wave velocity in familial combined hyperlipidemia. Am J Hypertens, 2007; 20: 263-269
6) Mansour AS, Yannoutsos A, Majahalme N, Agnoletti D, Safar ME, Ouerdane S, Blacher J. Aortic stiffness and cardiovascular risk in type 2 diabetes. J Hypertens. 2013; 31: 1584-1592
7) Shirai K, Utino J, Otsuka K, Takata M: A novel blood pressure-independent arterial wall stiffness parameter; cardio-ankle vascular index (CAVI). J Atheroscler Thromb, 2006; 13: 101-107
8) Matsui Y, Kario K, Ishikawa J, Eguchi K, Hoshide S, Shimada K: Reproducibility of arterial stiffness indices (pulse wave velocity and augmentation index) simultaneously assessed by automated pulse wave analysis and their associated risk factors in essential hypertensive subjects. Hypertens Res, 2004; 27: 851-857
9) Yambe T, Yoshizawa M, Saijo Y, Yamaguchi T, Shibata M, Konno S, Nitta S, Kuwayama T: Brachio-ankle pulse wave velocity and cardio-ankle vascular index (CAVI). Biomed Pharmacother, 2004; 58: 95-958
10) Kubozono T, Miyata M, Ueyama K, Nagaki A, Otsuji Y, Kusano K, Kubozono O, Tei C: Clinical significance and reproducibility of new arterial distensibility index. Circ J, 2007; 71: 89-94
11) Gomez-Sanchez L, Garcia-Ortiz L, Patino-Alonso MC, Recio-Rodriguez JI, Frontera G, Ramos R, Martí R, Agudo-Conde C, Rodriguez-Sanchez E, Maderuelo-Fernández JA, Gomez-Marcos MA: The Association Between the Cardio-ankle Vascular Index and Other Parameters of Vascular Structure and Function in Caucasian Adults: MARK Study. J Atheroscler Thromb, 2015 May 20. [Epub ahead of print] PubMed PMID: 25994828
12) Nakamura K, Tomaru T, Yamamura S, Miyashita Y, Shirai K, Noike H: Cardio-ankle vascular index is a candidate predictor of coronary atherosclerosis. Circ J, 2008; 27: 598-604
13) Noike H, Nakamura K, Sugiyama Y, Iizuka T, Shimizu K, Takahashi M, Hirano K, Suzuki M, Mikamo H, Nakagami T, Shirai K: Changes in cardio-ankle vascular index in smoking cessation. J Atheroscler Thromb, 2010; 17: 517-525
14) Suzuki J, Kurosu T, Kon T, Tomaru T: Impact of cardiovascular risk factors on progression of arteriosclerosis in younger patients: evaluation by carotid duplex ultrasonography and cardio-ankle vascular index (CAVI). J Atheroscler Thromb, 2014; 21: 554-562
15) Dobsak P, Soska V, Sochor O, Jarkovsky J, Novakova M, Homolka M, Soucek M, Palanova P, Lopez-Jimenez F, Shirai K: Increased cardio-ankle vascular index in hyperlipidemic patients without diabetes or hypertension. J Atheroscler Thromb, 2015; 22: 272-283
16) Satoh N, Shimatsu A, Kato Y, Araki R, Koyama K, Okajima T, Tanabe M, Ooishi M, Kotani K, Ogawa Y: Evaluation of the cardio-ankle vascular index, a new indicator of arterial stiffness independent of blood pressure, in obesity and metabolic syndrome. Hypertens Res, 2008; 31: 1921-1930
17) Alpert JS, Thygesen K, Antman E, Bassand JP: Myocardial infarction redefined — a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol, 2000; 36: 959-969
18) The Committee of Japan Diabetes Society on the diagnostic criteria of diabetes mellitus: Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. J Jpn Diabetes Soc, 2010; 53: 450-467
19) Shirai K, Nema T, Hiroh Y, Itoh Y, Miyashita Y, Watanabe H: Clinical efficacy of the direct assay method using polymers for serum high density lipoprotein cholesterols. J Clin Lab Anal, 1992; 11: 82-86
20) Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013; 48: 452-458
21) Kubota Y, Maebuchi D, Takei M, Inui Y, Sudo Y, Ikegami Y, Fuse J, Sakamoto M, Momiyama, Y: Cardio-Ankle Vascular Index is a predictor of cardiovascular events. Artery Res, 2011; 5: 91-96
22) Schwartzkopff B, Motz W, Frenzel H, Vogt M, Knauer S, Strauer BE: Structural and functional alterations of the intramyocardial coronary arterioles in subjects with arterial hypertension. Circulation, 1993; 88: 993-1003
23) London GM, Pannier B, Guerin AP, Marchais SJ, Safar

ME, Cuche JL: Cardiac hypertrophy, aortic compliance, peripheral resistance, and wave reflection in end-stage renal disease. Comparative effects of ACE inhibition and calcium channel blockade. Circulation, 1994; 90: 2786-2796
24) Mizuguchi Y, Oishi Y, Tanaka H, Miyoshi H, Ishimoto T, Nagase N, Oki T: Arterial stiffness is associated with left ventricular diastolic function in subjects with cardiovascular risk factors: early detection with the use of cardio-ankle vascular index and ultrasonic strain imaging. J Card Fail, 2007; 13: 744-751
25) Zhang C, Ohira M, Iizuka T, Mikamo H, Nakagami T, Suzuki M, Hirano K, Takahashi M, Shimizu K, Sugiyama Y, Yamaguchi T, Kawana H, Endo K, Saiki A, Oyama T, Kurosu T, Tomaru T, Wang H, Noike H, Shirai K: Cardio-ankle vascular index relates to left ventricular ejection fraction in subjects with heart failure. A retrospective study. Int Heart J, 2013; 54: 216-221
26) Tanisawa K, Ito T, Sun X, Kawakami R, Oshima S, Gando Y, Cao ZB, Sakamoto S, Higuchi M: Cardiorespiratory Fitness is a Strong Predictor of the Cardio-ankle Vascular Index in Hypertensive Middle-aged and Elderly Japanese Men. J Atheroscler Thromb, 2015; 22: 379-389
27) Shirai K, Hiruta N, Song M, Kurosu T, Suzuki J, Tomaru T, Miyashita Y, Saiki A, Takahashi M, Suzuki K, Takata M: Cardio-ankle vascular index (CAVI) as a novel indicator of arterial stiffness: theory, evidence and perspectives. J Atherosclero Thromb, 2011; 18: 924-938
28) Nagayama D, Endo K, Ohira M, Yamaguchi T, Ban N, Kawana H, Nagumo A, Saiki A, Oyama T, Miyashita Y, Shirai K: Effects of body weight reduction on cardio-ankle vascular index (CAVI). ORCP, 2013; 7: 139-145
29) Ohira M, Endo K, Oyama T, Yamaguchi T, Ban N, Kawana H, Nagayama D, Nagumo A, Saiki A, Murano T, Watanabe H, Miyashita Y, Shirai K: Improvement of postprandial hyperglycemia and arterial stiffness upon switching from premixed human insulin 30/70 to biphasic insulin aspart 30/70. Metabolism, 2011; 60: 878-885
30) Miyashita Y, Saiki A, Endo K, Ban N, Yamaguchi T, Kawana H, Nagayama D, Ohira M, Oyama T, Shirai K: Effects of olmesartan, an angiotensin II receptor blocker, and amlodipine, a calcium channel blocker, on Cardio-Ankle Vascular Index (CAVI) in type 2 diabetic subjects with hypertension. J Atheroscler Thromb, 2009; 16: 621-626
31) Miyashita Y, Endo K, Saiki A, Ban N, Yamaguchi T, Kawana H, Nagayama D, Ohira M, Oyama T, Shirai K: Effects of pitavastatin, a 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitor, on cardio-ankle vascular index in type 2 diabetic subjects. J Atheroscler Thromb, 2009; 16: 539-545
32) Miyashita Y, Endo K, Saiki A, Ban N, Nagumo A, Yamaguchi T, Kawana H, Nagayama D, Ohira M, Oyama T, Shirai K: Effect of ezetimibe monotherapy on lipid metabolism and arterial stiffness assessed by cardio-ankle vascular index in type 2 diabetic subjects. J Atheroscler Thromb, 2010; 17: 1070-1076
33) Nagayama D, Ohira M, Saiki A, Shirai K, Tatsuno I: Sarpogrelate hydrochloride decreases cardio-ankle vascular index accompanied by increased serum lipoprotein lipase mass in type 2 diabetic subjects. Int Heart J, 2014; 55: 337-341
34) Kim HJ, Nam JS, Park JS, Cho M, Kim CS, Ahn CW, Kwon HM, Hong BK, Yoon YW, Cha BS, Kim KR, Lee HC: Usefulness of brachial-ankle pulse wave velocity as a predictive marker of multiple coronary artery occlusive disease in Korean type 2 diabetes patients. Diabetes Res Clin Pract, 2009; 85: 30-34
35) Sugawara J, Hayashi K, Yokoi T, Cortez-Cooper MY, DeVan AE, Anton MA, Tanaka H: Brachial-ankle pulse wave velocity: an index of central arterial stiffness? J. Hum. Hypertens, 2005; 19: 401-406
36) Wen W, Luo R, Tang X, Tang L, Huang HX, Wen X, Hu S, Peng B: Age related progression of arterial stiffness and its elevated positive association with blood pressure in healthy people. Atherosclerosis, 2015; 238: 147-152
37) Izuhara M, Shioji K, Kadota S, Baba O, Takeuchi Y, Uegaito T, Mutsuo S, Matsuda M: Relationship of cardio-ankle vascular index (CAVI) to carotid and coronary arteriosclerosis. Circ J, 2008; 72: 1762-1767
38) O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson Jr SK: Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med, 1999; 340: 14-22
39) Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE: Common carotid intima-media thickness and risk of stroke and myocardial infarction: The Rotterdam Study. Circulation, 1997; 96: 1432-1437
40) Miyoshi T, Doi M, Hirohata S, Sakane K, Kamikawa S, Kitawaki T, Kaji Y, Kusano KF, Ninomiya Y, Kusachi S: Cardio-ankle vascular index is independently associated with the severity of coronary atherosclerosis and left ventricular function in patients with ischemic heart disease. J Atheroscler Thromb, 2010; 17: 249-258
41) Nagayama D, Yamaguchi T, Saiki A, Imamura H, Sato Y, Ban N, Kawana H, Nagumo A, Shirai K, Tatsuno I: High serum uric acid is associated with increased cardio-ankle vascular index (CAVI) in healthy Japanese subjects: A cross-sectional study. Atherosclerosis, 2015; 239: 163-168