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\(^6\).
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 (\(r=0.93, p<0.0001\)). 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 Daichi 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-
which is sufficiently small for clinical usage and indicates that CAVI has good reproducibility\textsuperscript{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)\textsuperscript{19}).

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**Fig. 1.** Patients description.

1562 outpatients with metabolic disorders underwent CAVI measurement

- 482 subjects excluded
  - Patients already had cardiovascular events at baseline
  - Patients with low ABI or with atrial fibrillation

1080 subjects were screened

- 77 subjects were lost to follow-up
  - 46 died
  - 13 moved to another city
  - 18 were lost for unknown reasons

1003 subjects were followed-up prospectively and analyzed (follow-up duration 6.7 ± 1.6 years)
**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). 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/m²), 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.

**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/m², p=0.008 for trend) decreased as CAVI became higher. Smoking rate and prevalence of dyslipidemia did not differ between quartiles. Preva-

**Table 1. Characteristics of participants at baseline**

| Characteristic                  | 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/m²)                    | 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
- a-Gl (%)        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 car- dio-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; a-Gl, a-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/m² and over), smoking, diabetes mellitus, hypertension and dyslipidemia.
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/m²) 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%
CAVI Predicts Cardiovascular Events

(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. 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. 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. In addition, cardiorespiratory fitness was also reported to be associated with CAVI in hypertensive middle-aged and elderly Japanese men.

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. Using CAVI, clinicians can evaluate the severity of arteriosclerosis in

Fig. 2. Kaplan-Meier survival curves showing cardiovascular events according to quartiles of CAVI.
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. 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. Furthermore, baPWV was strongly correlated with aortic (carotid-femoral) PWV, an established index of central arterial stiffness. 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.

Furthermore, Izuhara et al. 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. Furthermore, strong correlation between CAVI and IMT were reported. However, CAVI probably reflects the effect of therapy on vascular function and is measured swiftly.

| Table 3. Characteristics of participants with and those without future cardiovascular events |
|--------------------------------------|------------------|------------------|------------------|
|                                      | Cardiovascular event | + (n=90)         | - (n=913)        | p value        |
|                                      |                   | 9.86±2.03        | 9.19±1.55        | <0.001 a       |
| CAVI                                 | Male ratio (%)    | 74.4             | 49.0             | <0.001 b       |
|                                      | Age (years)       | 65.7±9.1         | 62.2±11.3        | 0.001 a        |
|                                      | BMI (kg/m²)       | 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.
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

This work was supported by Japan Health Pro-

### 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.

### 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.
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