The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2021; 28: 1266-1274. http://doi.org/10.5551/jat.58719

Association of the Estimated Coronary Artery Incidence Risk According to the Japan Atherosclerosis Society Guidelines 2017 with Cardio-Ankle Vascular Index

Mizuki Sata, Tomonori Okamura, Sei Harada, Daisuke Sugiyama, Kazuyo Kuwabara, Aya Hirata, Ayano Takeuchi, Miho Iida, Suzuka Kato, Minako Matsumoto, Ayako Kurihara and Toru Takebayashi

Department of Preventive Medicine and Public Health, Keio University School of Medicine, Tokyo, Japan

Aims: The categories in the comprehensive lipid and risk management guidelines were proposed by the Japan Atherosclerosis Society (JAS Guidelines 2017), which adopted the estimated 10 year absolute risk of coronary artery disease (CAD) incidence in the Suita score. We examined whether those categories were concordant with the degree of arterial stiffness.

Methods: In 2014, the cardio-ankle vascular index (CAVI), an arterial stiffness parameter, was measured in 1,972 Japanese participants aged 35–74 years in Tsuruoka City, Yamagata Prefecture, Japan. We examined the mean CAVI and the proportion and odds ratios (ORs) of CAVI ≥ 9.0 on the basis of the following three management classifications using the analysis of variance and logistic regression: "Category I (Low risk)," "Category II (Middle risk)," and "Category III (High risk)."

Results: The mean CAVI and proportion of CAVI ≥ 9.0 were 8.6 and 34.8% among males and 8.1 and 18.3% among females, respectively. The mean CAVI and proportion of CAVI ≥ 9.0 were associated with an estimated 10 year absolute risk for CAD among males and females, excluding High risk for females. These results were similar to the management classification by the guideline: the multivariable-adjusted ORs (95% confidence intervals) of CAVI ≥ 9.0 among Category II and Category III compared with those among Category I were 2.96 (1.61–5.43) and 7.33 (4.03–13.3) for males and 3.99 (2.55–6.24) and 3.34 (2.16–5.16) for females, respectively.

Conclusions: The risk stratification, which was proposed in the JAS Guidelines 2017, is concordant with the arterial stiffness parameter.

See editorial vol. 28: 1260-1262

Key words: Coronary artery disease, Absolute risk, Risk score, JAS Guidelines, Cardio-ankle vascular index

Introduction

Evaluation methods estimating the absolute risk of arteriosclerotic diseases have been developed and used in practice guidelines in several countries. The American College of Cardiology and the American Heart Association compiled guidelines for risk assessment of atherosclerotic cardiovascular disease events in 2013 [1]. The European Society of Cardiology and the European Atherosclerosis Society also summarized the guidelines for the management of dyslipidemias and the risk estimation chart of cardiovascular disease (CVD) in 2016 [2]. Furthermore, the Japan Atherosclerosis Society (JAS) proposed comprehensive lipid and risk management guidelines (JAS Guidelines 2017)[3] using the Suita score to estimate the 10 year absolute risk of coronary artery disease (CAD) and stratified individuals into three categories for the primary prevention of CAD. The Suita score was developed based on the Suita study, a community-based cohort study, to predict the future risk of CAD in the general population[4]. However, risk estimation based on a cohort study may include discrepancy with recent CAD incidence or mortality[5]

Address for correspondence: Mizuki Sata, Department of Preventive Medicine and Public Health, Keio University School of Medicine. 35 Shinanomachi, Shinjuku, Tokyo 160-8582, Japan. E-mail: msata@keio.jp

Received: June 24, 2020 Accepted for publication: January 6, 2021

because the baseline survey was usually performed several years prior. Actually, the baseline survey of the Suita study was performed from 1989 to 1994. Thus, there is a need to clarify the degree of subclinical atherosclerosis based on the guideline categories involving a current-day population.

Furthermore, the JAS Guidelines 2017 automatically classify individuals with diabetes mellitus (DM), chronic kidney disease (CKD), non-cardiogenic cerebral infarction, and peripheral artery disease (PAD) into Category III (High risk). Therefore, the appropriateness of including DM, CKD, non-cardiogenic cerebral infarction, and PAD in Category III for Japanese individuals should also be elucidated.

The cardio-vascular index (CAVI) is a noninvasive measure of arterial stiffness that is not influenced by blood pressure at the time of examination[6, 7]. Several studies have revealed a significant relationship between CAVI and the presence and severity of patients with CAD[8], hemodialysis[9, 10], and CKD[11]. Furthermore, CAVI is considered to be an independent long-term predictor for major adverse cardiovascular events after acute coronary syndrome[12].

Aim

We investigated whether the categories in the JAS Guidelines 2017, which estimate the 10 year absolute risk of CAD, was concordant with the degree of arterial stiffness assessed by CAVI[13, 14] in the general population.

Methods

Study Participants

This study included participants who enrolled in the Tsuruoka Metabolomics Cohort Study (TMCS), a population-based observational study that started in Tsuruoka City, Yamagata Prefecture, Japan. The baseline survey of this cohort study, which enrolled 11,002 participants aged 35–74 years, was conducted between April 2012 and March 2015. The details of TMCS have been described elsewhere[15-19]. The present cross-sectional study was based on data involving 2,033 participants who underwent CAVI from a baseline survey from April 2014 to March 2015. After excluding 38 persons who reported a history of CAD, 1 person whose data of total cholesterol (TC) was missing, and 24 persons whose triglyceride (TG) concentrations were ≥ 400 mg/dL because of the non-appropriate condition of use for the Friedwald's formula[20], a total of 1,972 individuals (909 males and 1,063 females) participated in the analyses. The Medical Ethics Committee of the School of Medicine, Keio University, Tokyo, Japan, approved this study (approval no. 20110264), and all participants provided written informed consent.

Study Examination and Measurement of CAVI

All data and samples were obtained in TMCS, including anthropometrics and clinical biochemistry. Information on lifestyle-related factors, such as the use of medications and smoking habits was collected through a standardized self-administered questionnaire and checked via face-to-face interview by trained interviewers. Data on physical measurements during the medical check-up were collected. The body mass index (BMI) was calculated as their weight (kg) divided by the square of their height (m^2). The blood pressure was measured twice on one occasion in the sitting position using an automated sphygmomanometer (Omron HBP-T105S-N) in each participant, and the mean value for each participant was used for analysis. Urinary protein was measured using a biuret method. Blood samples were collected from all participants after a 10 h fast. Serum levels of TC, TG, fasting plasma glucose, and creatinine were analyzed using enzymatic methods, and high-density lipoprotein cholesterol (HDL-C) levels were measured by a direct method. Glycated hemoglobin (HbA1c) was determined by a high-performance liquid chromatographic (HPLC) method. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using Friedwald's formula when plasma TG concentrations were <400 mg/dL[20]. The estimated glomerular filtration rate (eGFR) was calculated using the following formula: eGFR (mL/min per 1.73 m^2) $= 194 \times (\text{serum creatinine})^{-1.094} \times (\text{age})^{-0.287} \times$ (0.739 for females)[21].

Using a VaSera (VS-1500AN) CAVI instrument (Fukuda Denshi Co. Ltd., Tokyo, Japan), the CAVI was measured in the supine position. The VaSera is equipped with both measurement and calculation systems, which allowed for automatic calculation of the CAVI[6]. At the same time, the ankle-brachial index (ABI) was estimated by measuring the blood pressure of the brachial and tibial arteries.

Categorization of the Participants and Estimation of the 10 Year Absolute Risk of CAD

We classified the participants into the three categories proposed by the JAS Guidelines 2017. Because the calculation of the medication of hypertension and dyslipidemias were not included in the guidelines, we followed this in the present study. Individuals with either DM, CKD, non-cardiogenic

cerebral infarction, or PAD were considered to be at high risk *per se* for CAD incidence and were classified into "Category III (High risk)" without further assessment on the 10 year absolute risk of CAD. In the present study, DM was defined as fasting glucose ≥ 126 mg/dL, HbA1c ≥ 6.5%, or being under medication for diabetes. CKD was defined as positive for proteinuria or an eGFR of <60 mL/min per 1.73 m^2. PAD was defined as an ABI of <0.9 on either side. Although 30 persons reported a history of stroke, we did not collect information concerning the types of stroke. Therefore, non-cardiogenic cerebral infarction was beyond recognition. For the remaining individuals, we estimated the 10 year absolute risk of CAD based on the total score of each risk factor according to the Suita score[4]. For the calculation of this score, glucose intolerance was defined as a fasting glucose between 110 and 126 mg/dL or HbA1c between 6.0% and 6.5%. The score of family history of premature CAD was calculated as zero because accurate information was not collected for all participants. Based on the calculation, participants were classified into three categories: "Low risk (an estimated absolute risk of <2%)," "Middle risk (2%–9%)," and "High risk (≥ 9%)." Furthermore, these groups were added together with the initially defined "Category III (High risk)" individuals and divided into the following three management classifications from the JAS Guidelines 2017: "Category I (Low risk)," "Category II (Middle risk)," and "Category III (High risk)."

Statistical Analysis

We presented the characteristics of the study participants according to the risk assessment based on the Suita score as sex-specific means (standard deviation, SD) or proportions of traditional atherosclerotic risk factors. A CAVI of ≥ 9.0 leads to the diagnosis of suspected atherosclerosis[22]. Accordingly, first, we assessed the mean CAVI, as well as the proportion and odds ratios (ORs) of CAVI ≥ 9.0 according to the risk assessment based on the Suita score: "Low risk (an estimated absolute risk of <2%)," "Middle risk (2%–9%)," and "High risk (≥ 9%)." Second, we further stratified the participants in "Category III (High risk)" according to the presence or absence of DM, CKD, and PAD to compare the mean CAVI, and the proportion and ORs of CAVI ≥ 9.0 between these groups.

Differences in mean values or proportions according to the estimated absolute risk and management classification were tested via analysis of variance. We also used logistic regression models to calculate sex-specific ORs and 95% confidence intervals (CIs) for CAVI ≥ 9.0 according to the risk assessment. These models were adjusted for BMI (continuous) and drinking habit (current drinker or not). Furthermore, we also performed the stratification analysis according to the age group (< 65, ≥ 65 years old).

We performed all statistical analyses with SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA). All probability values for statistical tests were two-tailed, and *P*-values <0.05 were regarded as statistically significant.

Results

The mean CAVI and proportion of CAVI ≥ 9.0 were 8.6 and 34.8% among males and 8.1 and 18.3% among females, respectively.

Table 1 shows the characteristics of the study participants according to the categories based on the estimated 10 year absolute risk of CAD according to the Suita score and management classification by JAS Guidelines 2017. The mean age of the participants was higher among both males and females with a higher 10 year absolute risk. Systolic blood pressure, diastolic blood pressure, TC, LDL-C, and HbA1c were higher among participants of both sexes with a higher 10 year absolute risk. Meanwhile, the proportion of medication for hypertension and current smoking among males and the mean BMI and TG among females were higher with a higher 10 year absolute risk. Conversely, HDL-C and eGFR were lower.

Table 2 shows the association of the estimated 10 year absolute risk of CAD incidence with CAVI. The mean CAVI was associated with an increase in estimated 10 year absolute risk among both males and females. The proportion of CAVI ≥ 9.0 also increased among males and females, although there were none among the seven females with High risk. The multivariable-adjusted ORs (95% CI) of CAVI ≥ 9.0 among Middle risk and High risk compared with Low risk were 2.96 (1.61–5.43) and 10.1 (4.77–21.3) for males, respectively. The respective ORs among Middle risk was 4.19 (2.67–6.60) for females.

Table 3 shows the association of the categories described in the JAS Guidelines 2017 with CAVI. As shown in **Table 3 (A)**, there were positive associations of the mean CAVI, proportion of CAVI ≥ 9.0, and ORs of CAVI ≥ 9.0 with management classification among males and females. We further stratified the participants in Category III according to the presence or absence of DM, CKD, or PAD **(Table 3 (B))**. There were no differences between their presence and absence among both males and females. When

Table 1. Characteristics of study participants according to the estimated 10-year absolute risk for CAD incidence and the category for LDL-C management proposed by JAS Guidelines 2017

	Males					Females				
	Total	Estimated 10-year absolute risk for CAD incidence			Management classification	Total	Estimated 10-year absolute risk for CAD incidence			Management classification
		Low risk	Middle risk	High risk	Category III		Low risk	Middle risk	High risk	Category III
		< 2%	2 ≤ risk < 9%	9% ≤	DM, CKD, or PAD		< 2%	2 ≤ risk < 9%	9% ≤	DM, CKD, or PAD
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Number of participants, *n*	909	117	360	68	364	1,063	392	290	7	374
Age, y	64.6 ± 7.1	55.7 ± 8.8	64.9 ± 6.0	68.9 ± 4.1	66.3 ± 5.6	64.8 ± 6.7	61.4 ± 7.5	67.5 ± 4.4	69.3 ± 2.6	66.2 ± 5.8
Body mass index, kg/m^2	23.9 ± 3.0	23.4 ± 3.0	23.4 ± 2.6	23.9 ± 2.6	24.5 ± 3.3	23.1 ± 3.5	22.4 ± 3.3	23.4 ± 3.5	25.5 ± 4.6	23.6 ± 3.6
Systolic blood pressure, mmHg	132 ± 16	120 ± 12	131 ± 14	147 ± 19	135 ± 16	127 ± 18	118 ± 13	137 ± 15	160 ± 12	129 ± 19
Diastolic blood pressure, mmHg	80 ± 10	75 ± 8	81 ± 10	86 ± 10	80 ± 9	74 ± 10	70 ± 9	77 ± 9	86 ± 3	75 ± 10
Medication for hypertension, %	41.1	17.9	36.4	44.1	52.7	33.7	19.4	40.0	14.3	44.1
Total cholesterol, mg/dL	194 ± 30	191 ± 29	196 ± 27	210 ± 29	190 ± 31	208 ± 30	201 ± 29	215 ± 29	234 ± 26	209 ± 30
HDL-cholesterol, mg/dL	63 ± 17	67 ± 19	66 ± 17	61 ± 15	60 ± 16	73 ± 17	75 ± 16	72 ± 16	62 ± 20	71 ± 17
Triglycerides, mg/dL	117 ± 63	110 ± 64	111 ± 60	110 ± 51	126 ± 68	93 ± 43	84 ± 39	96 ± 44	114 ± 47	100 ± 43
LDL-cholesterol, mg/dL	107 ± 28	101 ± 27	109 ± 26	127 ± 25	104 ± 29	117 ± 28	109 ± 26	124 ± 28	149 ± 23	118 ± 28
Medication for dyslipidaemias, %	18.5	12.0	12.2	11.8	28.0	29.6	20.9	29.3	0	39.6
HbA1c (NGSP), %	5.8 ± 0.7	5.5 ± 0.2	5.6 ± 0.3	5.7 ± 0.3	6.2 ± 0.9	5.7 ± 0.4	5.6 ± 0.3	5.7 ± 0.3	6.0 ± 0.2	5.9 ± 0.6
Medication for diabetes mellitus, %	13.9	-	-	-	-	4.3	-	-	-	-
Creatinine, mg/dL	0.9 ± 0.2	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	1.0 ± 0.2	0.7 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.0	0.8 ± 0.1
eGFR, mL/min/1.73 m^2	69 ± 12	76 ± 11	73 ± 10	71 ± 8	62 ± 13	67 ± 12	73 ± 10	71 ± 10	71 ± 6	57 ± 10
Current smoker, %	18.0	16.2	18.3	22.1	17.6	1.8	2.8	2.4	0	0.3
Current drinker, %	74.3	76.1	76.7	69.1	72.3	23.2	29.1	22.4	42.9	17.4

Table 2. CAVI value according to the estimated absolute 10-year risk for CAD incidence

	Estimated 10-year absolute risk for CAD incidence			*p* for trend
	Low risk	Middle risk	High risk	
	< 2%	2 ≤ risk < 9%	9% ≤	
Males				
Number of participants, *n*	117	360	68	
Mean CAVI value (± SD)	7.7 ± 1.0	8.5 ± 1.1	9.1 ± 0.9	< 0.001
CAVI ≥ 9.0, %	12.0	28.3	55.9	< 0.001
Crude OR (95% CI)	1.0	2.91 (1.59 - 5.32)	9.32 (4.47 - 19.4)	
Multivariable OR (95% CI)[§]	1.0	2.96 (1.61 - 5.43)	10.1 (4.77 - 21.3)	
Females				
Number of participants, *n*	392	290	7	
Mean CAVI value (± SD)	7.7 ± 0.9	8.4 ± 0.9	8.4 ± 0.4	< 0.001
CAVI ≥ 9.0, %	8.4	25.9	0	< 0.001
Crude OR (95% CI)	1.0	3.80 (2.44 - 5.91)	-	
Multivariable OR (95% CI)[§]	1.0	4.19 (2.67 - 6.60)	-	

[§]Adjusted for body mass index (continuous) and drinking habit (current or not).

analyzing with respect to each disease, the mean CAVI and proportion of CAVI ≥ 9.0 in males with DM, CKD, or PAD were similar to those of Category III excluding DM, CKD, and PAD **(Table 3 (C, D, and E))**. Conversely, among females, mean CAVI and proportion of CAVI ≥ 9.0 in Category III excluding DM were lower than DM (8.2 versus 8.4, $P=0.090$ and 20.5% versus 30.4%, $P=0.040$), and those excluding PAD were higher than PAD (8.3 versus 7.2, $P=0.019$ and 22.8% versus 0%, $P=0.23$) **(Table 3 (C and E))**.

As shown in **Table 4**, among participants at ages of <65 years, the association between CAVI and the management classification did not change. Conversely, among those at ages of 65 and older, that association became weakened.

When we excluded 30 persons who reported a history of stroke, the results did not change (not shown in tables).

Discussion

We found that the risk stratification of the lipid management guidelines proposed by the JAS Guidelines 2017, which estimated the 10 year absolute risk of CAD incidence using the Suita score, was concordant with the mean CAVI and proportion of CAVI ≥ 9.0.

A previous systematic review, which included prospective studies of high-risk atherosclerosis patients, has reported that there was a modest association between CAVI and incident CVD risk. The pooled adjusted hazard ratio for CVD per one standard deviation increment of CAVI was 1.20 (95% CI: 1.05–1.36)[22]. In the previous study of 109 participants who underwent coronary angiography in Japan, the CAVI was significantly higher in the one-vessel disease (1VD) group than in the 0VD (no lesion) group ($P<0.05$) and was significantly higher in the two-vessel disease (2VD) and three-vessel disease (3VD) groups than in the 1VD group; the mean ± SD of CAVI was 8.6 ± 0.81 for 0VD, 9.29 ± 1.32 for 1VD, 10.34 ± 1.80 for 2VD, and 10.65 ± 1.41 for 3VD[23]. The cross-sectional study, which enrolled 95 participants who underwent cardiac computed tomography angiography in the United States, reported that correlation analysis showed a statistically significant relationship between CAVI and the segment involvement score (SIS) or a segment stenosis score (SSS) ($r^2=0.4$, $P<0.001$ for SIS; $r^2=0.36$, $P<0.001$ for SSS)[24]. Therefore, the results of the present study showing that the estimated absolute risk of CAD was concordant with the CAVI are acceptable.

DM[25, 26], CKD[27], and PAD[28] are essential high-risk statuses for CAD incidence; thus, individuals with either of these high-risk statuses were automatically classified into Category III (High risk) in the JAS Guidelines 2017. In the present study, we confirmed that the mean CAVI and proportion of CAVI in the participants with DM, CKD, or PAD were as severe as that observed in the participants in Category III excluding these risk factors among males, which supports the classification of the guidelines. Conversely, among females, the results of the present study showed a difference in the mean CAVI and proportion of CAVI in the participants with calculated ones compared with those in DM, PAD, or CKD. The CAVI of the participants with DM was higher than those in Category III excluding DM, which means that those with DM, especially for females, were at higher risk of atherosclerosis similar to a previous cohort study[29]. By contrast, the CAVI of those with PAD was lower than that of those in Category III excluding PAD. The definition of PAD may have affected this because an ABI of <0.9 is a cut-off point for the screening of PAD, and true severe PAD may not be included in our study population, which comprised community residents who participated in the baseline survey by themselves.

Similar to several Japanese cohort studies, once after adjustment of hypertension, diabetes, and hypercholesterolemia, BMI or waist circumference was not statistically significantly associated with CVD incidence in the Suita study[30]. Accordingly, the Suita score does not include BMI or waist circumference in the equation. However, we thought of BMI as a more principal component of atherosclerosis and added a covariate. In an additional analysis after exclusion for BMI, we observed similar findings in our multivariable analysis (data not shown).

To our best knowledge, this is the first study to report CAVI according to the absolute risk of CAD in the general population. Generally, the baseline hazard ratio of CAD incidence or mortality among a current-day population may differ substantially from those among the people of the past. Actually, from 1980 to 2012, age-adjusted CAD mortality rates in Japan fell by 61%, resulting in 75,700 fewer coronary heart disease (CHD) deaths in 2012 than if the age- and sex-specific mortality rates had remained unchanged[5]. Thus, it is needed to verify whether the degree of subclinical atherosclerosis based on the guideline categories is concordant with a current-day population. However, few studies were observed to examine the above-mentioned concordance. As for JAS Guidelines 2012, Kadota et al. reported that the intima-media thickness and plaque number were

Table 3. CAVI value according to the category for LDL-C management proposed by JAS Guidelines 2017

	Males					Females				
	Total	Management classification				Total	Management classification			
		Category I	Category II	Category III	*p* for trend		Category I	Category II	Category III	*p* for trend
(A)										
Number of participants, *n*	909	117	360	432		1,063	392	290	381	
Mean CAVI value (±SD)	8.6±1.1	7.7±1.0	8.5±1.1	8.9±1.1	<0.001	8.1±1.0	7.7±0.9	8.4±0.9	8.3±1.0	<0.001
CAVI ≥ 9.0, %	34.8	12.0	28.3	46.3	<0.001	18.3	8.4	25.9	22.6	<0.001
Crude OR (95% CI)		1.0	2.91 (1.59 - 5.31)	6.34 (3.52 - 11.4)			1.0	3.79 (2.44 - 5.91)	3.17 (2.06 - 4.87)	
Multivariable OR (95% CI)[§]		1.0	2.96 (1.61 - 5.43)	7.33 (4.03 - 13.3)			1.0	3.99 (2.55 - 6.24)	3.34 (2.16 - 5.16)	
				III (excluding DM, CKD, or PAD)	*p* for difference				III (excluding DM, CKD, or PAD)	*p* for difference
(B)										
Number of participants, *n*				68	364				7	374
Mean CAVI value (±SD)				9.1±0.9	8.8±1.1	0.11			8.4±0.4	8.3±1.0	0.74
CAVI ≥ 9.0, %				55.9	44.5	0.062			0	23.0	0.11
Crude OR (95% CI)		1.0	2.91 (1.59 - 5.31)	9.31 (4.46 - 19.4)	5.90 (3.25 - 10.7)		1.0	3.80 (2.44 - 5.91)	-	3.25 (2.11 - 5.00)	
Multivariable OR (95% CI)[§]		1.0	2.96 (1.61 - 5.43)	10.3 (4.88 - 21.6)	6.85 (3.74 - 12.6)		1.0	3.99 (2.55 - 6.24)	-	3.41 (2.20 - 5.27)	
				III (excluding DM)	DM	*p* for difference			III (excluding DM)	DM	*p* for difference
(C)										
Number of participants, *n*				253	179				302	79	
Mean CAVI value (±SD)				8.8±1.0	8.9±1.1	0.40			8.2±1.0	8.4±1.0	0.090
CAVI ≥ 9.0, %				44.7	48.6	0.38			20.5	30.4	0.040
Crude OR (95% CI)		1.0	2.91 (1.59 - 5.31)	5.93 (3.22 - 10.9)	6.95 (3.70 - 13.1)		1.0	3.79 (2.44 - 5.91)	2.81 (1.79 - 4.42)	4.75 (2.61 - 8.63)	
Multivariable OR (95% CI)[§]		1.0	2.96 (1.62 - 5.44)	6.54 (3.53 - 12.1)	8.83 (4.62 - 16.9)		1.0	4.03 (2.57 - 6.30)	2.92 (1.85 - 4.61)	5.56 (3.00 - 10.3)	
				III (excluding CKD)	CKD	*p* for difference			III (excluding CKD)	CKD	*p* for difference
(D)										
Number of participants, *n*				198	234				66	315	
Mean CAVI value (±SD)				8.9±1.1	8.9±1.1	0.77			8.2±0.9	8.3±1.0	0.75
CAVI ≥ 9.0, %				47.5	45.3	0.63			18.2	23.5	0.30
Crude OR (95% CI)		1.0	2.91 (1.59 - 5.31)	6.65 (3.56 - 12.4)	6.09 (3.29 - 11.3)		1.0	3.79 (2.44 - 5.91)	2.42 (1.18 - 5.00)	3.34 (2.15 - 5.19)	
Multivariable OR (95% CI)[§]		1.0	2.96 (1.61 - 5.43)	7.81 (4.14 - 14.7)	6.96 (3.73 - 13.0)		1.0	3.98 (2.55 - 6.23)	2.77 (1.33 - 5.76)	3.45 (2.20 - 5.39)	
				III (excluding PAD)	PAD	*p* for difference			III (excluding PAD)	PAD	*p* for difference
(E)										
Number of participants, *n*				424	8				377	4	
Mean CAVI value (±SD)				8.9±1.1	8.2±0.9	0.089			8.3±1.0	7.2±1.3	0.019
CAVI ≥ 9.0, %				46.5	37.5	0.59			22.8	0	0.23
Crude OR (95% CI)		1.0	2.91 (1.59 - 5.31)	6.38 (3.54 - 11.5)	4.41 (0.95 - 20.5)		1.0	3.80 (2.44 - 5.91)	3.22 (2.09 - 4.94)	-	
Multivariable OR (95% CI)[§]		1.0	2.96 (1.61 - 5.43)	7.43 (4.08 - 13.5)	4.05 (0.86 - 19.2)		1.0	3.99 (2.55 - 6.25)	3.38 (2.19 - 5.23)	-	

[§]Adjusted for body mass index (continuous) and drinking habit (current or not).

Table 4. Age stratified CAVI value according to the category for LDL-C management proposed by JAS Guidelines 2017

	Males				Females			
	Management classification			*p* for trend	Management classification			*p* for trend
	Category I	Category II	Category III		Category I	Category II	Category III	
Age < 65 years old								
Number of participants, *n*	99	149	123		258	60	125	
Mean CAVI value (± SD)	7.5 ± 0.8	8.0 ± 0.9	8.3 ± 1.0	< 0.001	7.5 ± 0.7	8.2 ± 0.7	7.7 ± 1.0	< 0.001
CAVI ≥ 9.0, %	7.1	15.4	20.3	0.021	2.7	11.7	8.8	0.0049
Crude OR (95% CI)	1.0	2.40 (0.99 - 5.83)	3.35 (1.38 - 8.12)		1.0	4.74 (1.59 - 14.1)	3.46 (1.31 - 9.16)	
Multivariable OR (95% CI)[§]	1.0	2.63 (1.07 - 6.48)	4.71 (1.86 - 11.9)		1.0	4.54 (1.52 - 13.6)	3.47 (1.30 - 9.29)	
Age ≥ 65 years old								
Number of participants, *n*	18	211	309		134	230	256	
Mean CAVI value (± SD)	8.7 ± 1.0	8.8 ± 1.1	9.1 ± 1.0	0.0012	8.2 ± 0.9	8.5 ± 0.9	8.6 ± 0.9	< 0.001
CAVI ≥ 9.0, %	38.9	37.4	56.6	< 0.001	19.4	29.6	29.3	0.070
Crude OR (95% CI)	1.0	0.940 (0.350 - 2.53)	2.05 (0.775 - 5.44)		1.0	1.74 (1.04 - 2.91)	1.72 (1.04 - 2.85)	
Multivariable OR (95% CI)[§]	1.0	0.968 (0.359 - 2.61)	2.24 (0.840 - 6.00)		1.0	1.91 (1.14 - 3.22)	1.93 (1.15 - 3.23)	

[§]Adjusted for body mass index (continuous) and drinking habit (current or not).

concordant with the 10 year absolute risk of CAD and the categories[31]. In the present study, we indicated that the categories in the JAS Guidelines 2017, which estimate the 10 year absolute risk of CAD, were concordant with the degree of arterial stiffness assessed by CAVI. The agreement between the CAD risk classification of the Suita score and the CAVI value is significant in that the CAD prediction score created for the Japanese in the 1990s is still useful for the Japanese in the 2010s, approximately 20 years after the date of the study. In the United States, a previous study reported that the proportion of participants with 0, 1, 2, 3, or 4 high test values (cardiovascular magnetic resonance, thoracic aortic calcification, coronary artery calcification, and carotid intima-media thickness) differed significantly across the Framingham 10 year CHD risk score strata (0%–9%, 10%–19%, or ≥ 20%) (Kruskal–Wallis test, $P<0.0001$) in men and women[32].

However, some limitations of the present study warrant discussion. First, non-cardiogenic cerebral infarction and family history were not considered during risk classification in this study. Second, although the JAS Guideline 2017 does not specify the definition for DM, CKD, or PAD in the risk classification flow chart, we only defined PAD by its screening criterion. That's why the magnitude of CAVI is smaller than that of Category III excluding PAD. Furthermore, clinical conditions of DM and CKD are very heterogeneous because of their severity and complicating diseases such as microvascular damage. Accordingly, the current JAS Guideline that assumes CAD risk of DM (or CKD) equivalent to that of Category III assessed by the Suita score should be revised in the future. Third, the number of females with "High risk," which was excluded individuals with either DM, CKD, or PAD, was small; thus, there is a possibility that we were not able to accurately evaluate the association between the CAVI and the estimated 10 year absolute risk of CAD incidence using Suita score among females. Finally, the JAS Guideline itself is designed to define the classification of lipid management goals. However, not only in the Suita score but also in the new pooled equation in the United States[1] has failed to include lipid-lowering therapy for their statistical risk assessment model. The risk assessment under lipid-lowering therapy such as statins is very difficult because of selection bias[33]. The present study included 483 patients on lipid treatment; thus, we excluded the participants on lipid treatment. Consequently, we observed almost similar results in **Table 3 (A)** (data not shown).

In conclusion, the risk stratification described in the comprehensive lipid and risk management guidelines proposed by the JAS Guidelines 2017 are concordant with the mean CAVI and proportion of CAVI ≥ 9.0 as an arterial stiffness parameter. Individuals classified to a higher category should

control their risk factors, such as lipid levels and other traditional risk factors of atherosclerosis, through lifestyle modification and medications.

Acknowledgement

We sincerely appreciate the staff of Tsuruoka City and Tsuruoka Kyoritsu Hospital in Yamagata Prefecture for their important contributions. We are also grateful to the members of the Tsuruoka Metabolomic Cohort Study team for their commitment to the project. This study was supported by research funds from the Yamagata Prefectural Government and the city of Tsuruoka, Grants-in-Aid for Scientific Research (B) (grant numbers JP24390168, JP15H04778), Grant-in-Aid for Challenging Exploratory Research (grant number 25670303) from the Japan Society for the Promotion of Science, and Grant-in-Aid for Comprehensive Research on Cardiovascular Disease and Life–Related Disease (grant number 20FA1002) from the Ministry of Health, Labor and Welfare, Health and Labor Sciences research grants, Japan. We would like to thank Editage (www.editage.com) for English language editing.

Conflict of Interest

None.

References

1) Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PWF: 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol, 2014; 63: 2935-2959
2) Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Ž, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WM, Vlachopoulos C, Wood DA, Zamorano JL: 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Developed with the special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR). Atherosclerosis, 2016; 253: 281-344
3) Kinoshita M, Yokote K, Arai H, Iida M, Ishigaki Y, Ishibashi S, Umemoto S, Egusa G, Ohmura H, Okamura T, Kihara S, Koba S, Saito I, Shoji T, Daida H, Tsukamoto K, Deguchi J, Dohi S, Dobashi K, Hamaguchi H, Hara M, Hiro T, Biro S, Fujioka Y, Maruyama C, Miyamoto Y, Murakami Y, Yokode M, Yoshida H, Rakugi H, Wakatsuki A, Yamashita S; Committee for Epidemiology and Clinical Management of Atherosclerosis: Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017. J Atheroscler Thromb, 2018; 25: 846-984
4) Nishimura K, Okamura T, Watanabe M, Nakai M, Takegami M, Higashiyama A, Kokubo Y, Okayama A, Miyamoto Y: Predicting coronary heart disease using risk factor categories for a Japanese urban population, and comparison with the framingham risk score: the suita study. J Atheroscler Thromb, 2014; 21: 784-798
5) Ogata S, Nishimura K, Guzman-Castillo M, Sumita Y, Nakai M, Nakao YM, Nishi N, Noguchi T, Sekikawa A, Saito Y, Watanabe T, Kobayashi Y, Okamura T, Ogawa H, Yasuda S, Miyamoto Y, Capewell S, O'Flaherty M: Explaining the decline in coronary heart disease mortality rates in Japan: Contributions of changes in risk factors and evidence-based treatments between 1980 and 2012. Int J Cardiol, 2019; 291: 183-188
6) 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
7) Shirai K, Suzuki K, Tsuda S, Shimizu K, Takata M, Yamamoto T, Maruyama M, Takahashi K: Comparison of Cardio-Ankle Vascular Index (CAVI) and CAVI0 in Large Healthy and Hypertensive Populations. J Atheroscler Thromb, 2019; 26: 603-615
8) 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; 72: 598-604
9) Ueyama K, Miyata M, Kubozono T, Nagaki A, Hamasaki S, Ueyama S, Tei C: Noninvasive indices of arterial stiffness in hemodialysis patients. Hypertens Res, 2009; 32: 716-720
10) Takenaka T, Hoshi H, Kato N, Kobayashi K, Takane H, Shoda J, Suzuki H: Cardio-ankle vascular index to screen cardiovascular diseases in patients with end-stage renal diseases. J Atheroscler Thromb, 2008; 15: 339-344
11) Kubozono T, Miyata M, Ueyama K, Nagaki A, Hamasaki S, Kusano K, Kubozono O, Tei C: Association between arterial stiffness and estimated glomerular filtration rate in the Japanese general population. J Atheroscler Thromb, 2009; 16: 840-845
12) Kirigaya J, Iwahashi N, Tahakashi H, Minamimoto Y, Gohbara M, Abe T, Akiyama E, Okada K, Matsuzawa Y, Maejima N, Hibi K, Kosuge M, Ebina T, Tamura K, Kimura K: Impact of Cardio-Ankle Vascular Index on Long-Term Outcome in Patients with Acute Coronary Syndrome. J Atheroscler Thromb, 2020; 27: 657-668
13) Kadota K, Takamura N, Aoyagi K, Yamasaki H, Usa T, Nakazato M, Maeda T, Wada M, Nakashima K, Abe K, Takeshima F, Ozono Y: Availability of cardio-ankle vascular index (CAVI) as a screening tool for atherosclerosis. Circ J, 2008; 72: 304-308
14) 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
15) Harada S, Takebayashi T, Kurihara A, Akiyama M, Suzuki A, Hatakeyama Y, Sugiyama D, Kuwabara K, Takeuchi A, Okamura T, Nishiwaki Y, Tanaka T, Hirayama A, Sugimoto M, Soga T, Tomita M: Metabolomic profiling reveals novel biomarkers of alcohol intake and alcohol-induced liver injury in community-dwelling men. Environ Health Prev Med, 2016; 21: 18-26
16) Iida M, Harada S, Kurihara A, Fukai K, Kuwabara K, Sugiyama D, Takeuchi A, Okamura T, Akiyama M, Nishiwaki Y, Suzuki A, Hirayama A, Sugimoto M, Soga T, Tomita M, Banno K, Aoki D, Takebayashi T: Profiling of plasma metabolites in postmenopausal women with metabolic syndrome. Menopause, 2016; 23: 749-758
17) Fukai K, Harada S, Iida M, Kurihara A, Takeuchi A, Kuwabara K, Sugiyama D, Okamura T, Akiyama M, Nishiwaki Y, Oguma Y, Suzuki A, Suzuki C, Hirayama A, Sugimoto M, Soga T, Tomita M, Takebayashi T: Metabolic Profiling of Total Physical Activity and Sedentary Behavior in Community-Dwelling Men. PLoS One, 2016; 11: e0164877
18) Sasaki M, Harada S, Kawasaki Y, Watanabe M, Ito H, Tanaka H, Takeuchi A, Tsubota K, Takebayashi T, Nishiwaki Y, Kawasaki R: Gender-specific association of early age-related macular degeneration with systemic and genetic factors in a Japanese population. Sci Rep, 2018; 8: 785
19) Fukushima K, Harada S, Takeuchi A, Kurihara A, Iida M, Fukai K, Kuwabara K, Kato S, Matsumoto M, Hirata A, Akiyama M, Tomita M, Hirayama A, Sato A, Suzuki C, Sugimoto M, Soga T, Sugiyama D, Okamura T, Takebayashi T: Association between dyslipidemia and plasma levels of branched-chain amino acids in the Japanese population without diabetes mellitus. J Clin Lipidol, 2019; 13: 932-939
20) Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem, 1972; 18: 499-502
21) Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A; Collaborators developing the Japanese equation for estimated GFR: Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis, 2009; 53: 982-992
22) Matsushita K, Ding N, Kim ED, Budoff M, Chirinos JA, Fernhall B, Hamburg NM, Kario K, Miyoshi T, Tanaka H, Townsend R: Cardio-ankle vascular index and cardiovascular disease: Systematic review and meta-analysis of prospective and cross-sectional studies. J Clin Hypertens (Greenwich), 2019; 21: 16-24
23) 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; 72: 598-604
24) Matsumoto S, Nakanishi R, Luo Y, Kim M, Alani A, Nezarat N, Dailing C, Budoff MJ: The relationship between cardio-ankle vascular index and subclinical atherosclerosis evaluated by cardiac computed tomographic angiography. Clin Cardiol, 2017; 40: 549-553
25) Saito I, Kokubo Y, Yamagishi K, Iso H, Inoue M, Tsugane S: Diabetes and the risk of coronary heart disease in the general Japanese population: the Japan Public Health Center-based prospective (JPHC) study. Atherosclerosis, 2011; 216: 187-191
26) Hayama-Terada M, Muraki I, Imano H, Kiyama M, Okada T, Yamagishi K, Cui R, Ohira T, Umesawa M, Sankai T, Sato S, Kitamura A, Iso H; CIRCS Investigators: Diabetes Trend and Impact on Risk of Cardiovascular Disease in Middle-Aged Japanese People- The CIRCS Study. Circ J, 2016; 80: 2343-2348
27) Ninomiya T, Kiyohara Y, Tokuda Y, Doi Y, Arima H, Harada A, Ohashi Y, Ueshima H; Japan Arteriosclerosis Longitudinal Study Group: Impact of kidney disease and blood pressure on the development of cardiovascular disease: an overview from the Japan Arteriosclerosis Longitudinal Study. Circulation, 2008; 118: 2694-2701
28) Cui R, Yamagishi K, Imano H, Ohira T, Tanigawa T, Hitsumoto S, Kiyama M, Okada T, Kitamura A, Iso H; CIRCS investigators: Relationship between the ankle-brachial index and the risk of coronary heart disease and stroke: the circulatory risk in communities study. J Atheroscler Thromb, 2014; 21: 1283-1289
29) Lee WL, Cheung AM, Cape D, Zinman B: Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. Diabetes Care, 2000; 23: 962-968
30) Furukawa Y, Kokubo Y, Okamura T, Watanabe M, Higashiyama A, Ono Y, Kawanishi K, Okayama A, Date C: The relationship between waist circumference and the risk of stroke and myocardial infarction in a Japanese urban cohort: the Suita study. Stroke, 2010; 41: 550-553
31) Kadota A, Miura K, Okamura T, Fujiyoshi A, Ohkubo T, Kadowaki T, Takashima N, Hisamatsu T, Nakamura Y, Kasagi F, Maegawa H, Kashiwagi A, Ueshima H; SESSA Research Group; NIPPON DATA80/90 Research Group: Carotid intima-media thickness and plaque in apparently healthy Japanese individuals with an estimated 10-year absolute risk of CAD death according to the Japan Atherosclerosis Society (JAS) guidelines 2012: the Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA). J Atheroscler Thromb, 2013; 20: 755-766
32) Kathiresan S, Larson MG, Keyes MJ, Polak JF, Wolf PA, D'Agostino RB, Jaffer FA, Clouse ME, Levy D, Manning WJ, O'Donnell CJ: Assessment by cardiovascular magnetic resonance, electron beam computed tomography, and carotid ultrasonography of the distribution of subclinical atherosclerosis across Framingham risk strata. Am J Cardiol, 2007; 99: 310-314
33) Daimon M, Oizumi T, Kameda W, Matsui J, Murakami H, Ueno Y, Kubota I, Yamashita H, Kayama T, Kato T: Association of Treatment for Hyperlipidemia with Decreased Total Mortality in Japanese Individuals: the Yamagata (Takahata) Study. J Atheroscler Thromb, 2015; 22: 1030-1039