Aim: The arterial pressure–volume index (API) and arterial velocity–pulse index (AVI) are novel measurement indices of arterial stiffness. This study was performed to examine the screening validity of the API and AVI for preclinical atherosclerosis in Japanese community-dwelling adults.

Methods: We conducted a cross-sectional study of 2,809 participants aged ≥ 40 years who underwent Japanese national medical check-ups from 2014 to 2016. Preclinical atherosclerosis was defined as a mean carotid intima–media thickness (CIMT) of ≥ 1.0 mm. Multivariable linear regression analysis was performed to investigate the association of CIMT with API and AVI, adjusting for body mass index, sex, and the Framingham–D’Agostino score. We also examined receiver operating characteristic curves, sensitivity, and specificity to predict preclinical atherosclerosis defined by the CIMT. The cardio-ankle vascular index was also measured for comparison with the API and AVI.

Results: Of 2,809 participants, 68 (2.4%) had preclinical atherosclerosis. In the multivariable linear regression analysis, the API and AVI maintained a positive association with the mean CIMT (B = 2.6, P = 0.009 and B = 3.7, P = 0.001, respectively). The cut-offs of the API and AVI that demonstrated better sensitivity and specificity for detection of subclinical atherosclerosis were 31 [area under the curve (AUC), 0.64] and 29 (AUC, 0.60).

Conclusions: The API and AVI were positively associated with preclinical carotid atherosclerosis independent of the participants’ cardiovascular risk. The ability of these scores to predict carotid atherosclerosis could make them a useful screening tool for atherosclerosis.
measured by high-resolution B-mode ultrasound is a widely accepted method of assessing atherosclerosis. An increased CIMT is a potent predictor of future cardiovascular and cerebrovascular events. However, several methodological weaknesses must be considered when measuring the CIMT, such as the definition of carotid plaques, the choice of measurement sites, and assessment of the maximum or minimum CIMT.

The cardio-ankle vascular index (CAVI) and brachial-ankle pulse wave velocity are also measures of the overall arterial stiffness from the origin of the aorta to the ankle and can be used to estimate the risk of atherosclerosis. In a prospective cohort of Japanese outpatients with metabolic disorders, the CAVI was an independent predictor of future cardiovascular events. In a cross-sectional study of a Korean middle-aged population, arterial stiffness as measured by the brachial-ankle pulse wave velocity was associated with composite preclinical atherosclerosis.

Previous studies have revealed the clinical significance of these indices and the correlation of the API and AVI with the CIMT or CAVI in healthy Japanese adults. However, the screening validity of these indices for preclinical atherosclerosis has not been investigated.

**Aim**

The aim of this study was to evaluate the screening validity of the API and AVI for preclinical atherosclerosis in Japanese community-dwelling adults.

**Methods**

**Study Setting and Participants**

The Nagasaki Islands Study was a prospective cohort study performed in Goto city of the western islands of Japan. The participants were recruited upon medical check-ups, and members of the general population aged ≥40 years living in Goto city were targeted for enrollment. The recruitment process has been described elsewhere. We enrolled 3,517 participants (1,355 men and 2,162 women) from 2014 to 2016. Of the 3,517 participants, we excluded those with an apparent past or present history of stroke (n = 137) or ischemic heart disease (n = 221). We also excluded those with missing data regarding their medical history (n = 3), smoking status (n = 5), API and AVI (n = 146), CIMT (n = 6), and cholesterol profile (n = 200). In total, 2,809 participants with a mean age of 69.5 years (standard deviation, 9.6 years; range, 40–94 years) were evaluated.

The protocol for the Nagasaki Islands Study was approved by the Ethics Committee for the Use of Humans of Nagasaki University (project registration number: 14051404; Nagasaki, Japan). Written informed consent was obtained from all participants.

**Data Collection and Laboratory Measurements**

Body weight and height were measured with an automatic body composition analyzer (BF-220; Tanita, Tokyo, Japan) at the time of blood drawing, and the body mass index (BMI) was then calculated. Abdominal circumference was measured with an inelastic measuring tape placed over the skin at the level of the umbilical point. Trained medical technologists measured the API, AVI, systolic blood pressure, and diastolic blood pressure at rest using cuff oscillometry with a PASEA AVE-1500 (Shisei Datum, Tokyo, Japan). The cuff was wrapped around one side of the upper arm of seated participants. Blood samples were obtained. After coagulation, each blood sample was centrifuged and the serum separated. The serum levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, creatinine, and glycated hemoglobin were measured using standard laboratory procedures. Trained interviewers obtained information on the participants’ smoking status, alcohol intake, medical history, and use of antihypertensive agents, hypoglycemic agents, and lipid-lowering drugs. The smoking status and drinking status were categorized as “never,” “ex,” or “current.” The risk of atherosclerotic disease was estimated using the risk equation (D’Agostino scale) based on the Framingham study. The D’Agostino scale includes age, total cholesterol, high-density lipoprotein cholesterol, and systolic blood pressure as quantitative variables and sex, drug treatment for hypertension, smoking, and a history of diabetes mellitus as dichotomous variables.

**Measurements of CIMT and CAVI**

Research doctors or laboratory technicians measured the CIMT by ultrasonographic examination of the left and right carotid arteries using a LOGIQ Book XP with a 10-MHz transducer (GE Healthcare, Milwaukee, WI, USA) that was programmed with the CIMT measurement software Intimascope (Cross Media Ltd., Tokyo, Japan). The protocol used in this study has been described in detail elsewhere. The mean CIMT was calculated as the mean of the right and left CIMT measurements with carotid plaque excluded. Preclinical atherosclerosis was defined as a mean CIMT of ≥1.0 mm.
oscillometric method, and it is used as an accurate measure of vascular stiffness that does not depend on blood pressure at the time of measurement. The averages of the right and left CAVI were used for analysis. (The CAVI was only available in subsample of 1,753 participants because the measurement sites were restricted at the time of the medical check-ups.)

**Statistical Analyses**

We calculated correlation coefficients between the API or AVI and atherosclerosis risk factors as continuous variables. Simple and multivariable linear regression analysis was performed to investigate the association between the CIMT and API, AVI, or CAVI. The Framingham–D’Agostino score, sex, height, and BMI were included in the adjustment model. We examined receiver operating characteristic curves, sensitivity, and specificity to predict preclinical atherosclerosis.

**Table 1.** Characteristics of the study participants (n = 2,809)

| Characteristics                        | Total   |
|----------------------------------------|---------|
| Age (years)                            | 69.5 ± 9.6 |
| Women                                  | 1,733 (61.7) |
| Height (cm)                            | 155.5 ± 9.0 |
| Body mass index (kg/m²)                | 23.2 ± 3.4 |
| Abdominal circumference (cm)           | 84.1 ± 9.3 |
| Systolic blood pressure (mmHg)         | 136.9 ± 19.8 |
| Diastolic blood pressure (mmHg)        | 75.8 ± 11.5 |
| Pulse pressure (mmHg)                  | 61.2 ± 17.4 |
| Hemoglobin A1c (%)                     | 5.7 ± 0.6 |
| Total cholesterol (mg/dL)              | 201.4 ± 33.9 |
| LDL cholesterol (mg/dL)                | 120.1 ± 29.1 |
| HDL cholesterol (mg/dL)                | 59.9 ± 14.5 |
| Triglycerides (mg/dL)                  | 106.8 ± 66.2 |
| Mean CIMT (mm)                         | 0.70 ± 0.14 |
| Mean CIMT > 1.0 mm                     | 68 (2.4) |
| Maximum carotid intima-media thickness (mm) | 0.87 ± 0.18 |
| CAVI score §                          | 8.41 ± 1.19 |
| Hypertension                           | 1,775 (63.2) |
| Antihypertensive Drug Use              | 1,168 (41.6) |
| Diabetes mellitus                      | 284 (10.1) |
| Antidiabetic Drug Use                  | 184 (6.6) |
| Dyslipidemia                           | 1,435 (51.1) |
| Lipid Lowering Drug Use                | 527 (18.8) |
| Current Smoker                         | 268 (9.5) |
| Framingham–D’Agostino                 | 14.5 ± 4.5 |
| API                                    | 30.7 ± 8.1 |
| AVI                                    | 27.6 ± 8.8 |

Data are presented as mean ± standard deviation or n (%). API, arterial pressure–volume index; AVI, arterial velocity–pulse index; CIMT, carotid intima–media thickness; CAVI, cardio-ankle vascular index; LDL, low-density lipoprotein; HDL, high-density lipoprotein. § For data on CAVI: n = 1,753.

**Results**

Table 1 shows the characteristics of the study participants. The mean API, AVI, and CAVI were 30.7, 27.6, and 8.41, respectively. A total of 2.4% of the participants had a mean CIMT of ≥ 1.0 mm.

The API was positively correlated with age, male sex, BMI, abdominal circumference, systolic blood pressure, pulse pressure, glycated hemoglobin, mean CIMT, maximum CIMT, CAVI, and the Framingham–D’Agostino score and negatively correlated with height (Table 2). The AVI was positively correlated with age, male sex, systolic and diastolic blood pressure, pulse pressure, mean CIMT, maximum CIMT, CAVI, and the Framingham–D’Agostino score but negatively correlated with height, BMI, abdominal circumference, and triglycerides.

In the multivariable linear regression analysis, the vascular structure and function parameters (API, AVI, and CAVI) maintained a positive association with the mean CIMT (B = 2.4, P = 0.017; B = 3.2, P = 0.004; and B = 1.3, P < 0.001, respectively) after adjusting for BMI, sex, height, and the Framingham–D’Agostino score (Table 3).

Like the mean CIMT, these indices also maintained a positive association with the maximum CIMT (B = 1.6, P = 0.037; B = 2.4, P = 0.004; and B = 0.8, P < 0.001, respectively) even after adjustments.

The cut-offs of the API, AVI, and CAVI that demonstrated better sensitivity and specificity for detection of subclinical atherosclerosis as defined by a mean CIMT of ≥ 1.0 mm were 31 [sensitivity, 0.67; specificity, 0.54; area under the curve (AUC), 0.64], 29 (sensitivity, 0.67; specificity, 0.54; AUC, 0.60), and 8.9 (sensitivity, 0.72; specificity, 0.68; AUC, 0.71), respectively (Fig. 1).

**Discussion**

The present study is the first to evaluate the relationships of the API and AVI with preclinical atherosclerosis as defined by the CIMT in Japanese healthy adults. The API and AVI were positively associated with the mean CIMT, independent of the participants’ cardiovascular risk. The cut-offs of the API and AVI that were more sensitive and specific for predicting preclinical atherosclerosis with a mean CIMT of ≥ 1.0 mm were 31 and 29, respectively.
Although the API and AVI had a lower AUC, sensitivity, and specificity than the CAVI, evaluation is simple and convenient, can be performed in the sitting position, and takes less time. These merits made the API and AVI fit for use in screening preclinical atherosclerosis in broad clinical and public health settings.

### Association between API and CIMT

An observational study of consecutive Japanese patients who underwent coronary angiography showed...
Therefore, we speculated that the association between the AVI and CIMT may share a common background mechanism associated with the central blood pressure.

The Discrepancy in the Correlation of API or AVI with Other Parameters

The negative correlation of the AVI with the BMI, abdominal circumference, and triglycerides should be explained because these parameters are related to arterial stiffness or atherosclerosis. A discrepancy between the API and AVI in terms of their correlation with BMI, abdominal circumference, and triglycerides was seen in a large-scale cross-sectional study in Japan14, although the correlation coefficient between the AVI and triglycerides was not a negative value but instead was not statistically significant. This might indicate that this discrepancy is based on the theoretical char-

Association between AVI and CIMT

The AVI can reflect the central arterial stiffness10, and the AVI is significantly associated with the central blood pressure12,24,25. One study showed that increased augmentation of the central blood pressure was associated with the CIMT in patients with type 2 diabetes26. Therefore, we speculated that the association between the AVI and CIMT may share a common background mechanism associated with the central blood pressure.

Fig. 1. Receiver operating characteristic curve for predicting a mean CIMT of ≥1.0 mm using the API, AVI, and CAVI.

|          | Cut-off value | Sensitivity | Specificity | AUC (95% CI) |
|----------|---------------|-------------|-------------|--------------|
| CAVI     | 8.9           | 0.72        | 0.68        | 0.71 (0.63 - 0.79) |
| API      | 31            | 0.67        | 0.54        | 0.64 (0.56 - 0.72) |
| AVI      | 29            | 0.67        | 0.54        | 0.60 (0.51 - 0.69) |

API, arterial pressure–volume index; AVI, arterial velocity–pulse index; CIMT, carotid intima–media thickness; CAVI, cardio-ankle vascular index; AUC, area under the receiver operating characteristic curve; CI, confidence interval.

Presence of a mean CIMT of ≥1.0 mm
acteristic of AVI measurement\(^{20}\). The AVI is derived from the amplitude of oscillometric reflected waveforms. The value of these waveforms is influenced by age and peripheral arterial resistance\(^{20}\). Thus, the AVI is strongly correlated with age\(^{4}\). In the current study, the correlation coefficient between the AVI and age was larger than that between the API and age. We investigated the association between AVI and BMI in the linear regression analysis to determine the presence of a confounding effect by age. Attenuation of the beta coefficient after adjustment for age was found, suggesting the presence of partial confounding (B\(\approx\)\(-0.25\), P<0.001 to B\(\approx\)-0.22, P<0.001). However, this does not fully explain the discrepancy.

We observed that the AVI was positively correlated with diastolic blood pressure, while the API was not. A possible explanation is that the API is theoretically derived using the collapsing behavior of the artery\(^{27}\). To derive the API, the slopes of the pressure–volume curve are calculated from the occlusive cuff pressure for pulse pressure and the amplitude of cuff oscillations\(^{10}\). In the present study, the pulse pressure was strongly correlated with the API (correlation coefficient, 0.75; P<0.001) as well as with the systolic blood pressure (0.65, P<0.001). According to the Framingham Heart Study, the diastolic blood pressure generally starts to decline after the age of 50 to 60 years while the pulse pressure continues to steeply rise\(^{28}\). Most of our study participants comprised older people aged ≥60 years (86%). Consequently, age-related hemodynamic patterns may affect calculation of the API, but not the AVI.

Further investigation is needed to clarify these differences between the API and AVI.

Limitations

The main limitation of this study was its cross-sectional design, which prevented us from establishing cause–effect relationships.

Another weakness of this study is that only 2.4% of the participants had a mean CIMT of ≥1.0 mm. However, we treated the mean and maximum CIMT as a continuous variable in the linear regression analysis. We also analyzed the data using a mean CIMT of ≥0.9 mm as the definition of atherosclerosis. The number of cases thus increased to 225 (8.0%), and the AUCs for predicting a mean CIMT of ≥0.9 mm using the API and AVI were 0.63 (95% confidence interval, 0.58–0.67) and 0.64 (95% confidence interval, 0.59–0.69), respectively. Therefore, the lower reliability due to the small number of cases (mean CIMT of ≥1.0 mm) did not seem to bias the results.

Conclusion

The API and AVI showed a positive association with preclinical carotid atherosclerosis independent of the participants’ cardiovascular risk. The ability of these indices to predict carotid atherosclerosis is less sensitive than the CAVI in Japanese healthy adults. However, considering the several merits of evaluation using the API and AVI, these methods can be a useful tool to screen people for atherosclerosis.

Acknowledgments

The work was supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (25291107). The financial sponsor played no role in the design, execution, analysis and interpretation of data, or writing of the study.

The authors thank Angela Morben, DVM, ELS from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Disclosure Statement

The authors declare no conflict of interest.

References

1) Nezu T, Hosomi N, Aoki S, Matsumoto M: Carotid Intima-Media Thickness for Atherosclerosis. J Atheroscler Thromb 2016; 23: 18-31
2) Chambless LE, Heiss G, Folsom AR, Rosamond W, Szkoł M, Sharrett AR, Clegg LX: Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. Am J Epidemiol 1997; 146: 483-494
3) Chambless LE, Folsom AR, Clegg LX, Sharrett AR, Shahar E, Nieto FJ, Rosamond WD, Evans G: Carotid wall thickness is predictive of incident clinical stroke: the Atherosclerosis Risk in Communities (ARIC) study. Am J Epidemiol 2000; 151: 478-487
4) 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
5) O’Leary DH, Polak JE, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr: Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med 1999; 340: 14-22
6) Lorenz MW, Polak JF, Kavousi M, Mathiesen EB, Völzke H, Tuomainen TP, Sander D, Plichtar M, Catapano AL, Robertson CM, Kiechl S, Rundek T, Desvarieux M, Lind L, Schmid C, DasMahapatra P, Gao L, Ziegelbauer K, Bots ML, Thompson SG; PROG-IMT Study Group: Car-
17) Yanase T, Nasu S, Mukuta Y, Shimizu Y, Nishihara T, Wada M, Nakashima K, Abe Y, Kusano Y, Aoyagi K: Evaluation of clinical markers of atherosclerosis in young and elderly Japanese adults. Clin Chem Lab Med 2006; 44: 824-829

18) Hara T, Takeda N, Akashi S, Nakazato M, Maeda T, Yamada T, Takamura N, Akashi S, Nakazato M, Nakano Y, Wakasaka H, Furuta H, Nishi M, Nonj K: Cardio-ankle vascular index measures arterial wall stiffness independent of blood pressure. Diabetes Res Clin Pract 2008: 80: 265-270

19) Ibata J, Sasaki H, Kakimoto T, Matsuno S, Nakatani M, Kobayashi M, Tatsuki K, Nakanada Y, Wakasaka H, Furuta H, Nishi M, Nonj K: Cardio-ankle vascular index measures arterial wall stiffness independent of blood pressure. Diabetes Res Clin Pract 2008: 80: 265-270

20) Gomez-Sanchez L, Garcia-Ortiz L, Patino-Alonso MC, Recio-Rodriguez JL, Frontera G, Ramos R, Martí R, Agudo-Conde C, Rodriguez-Sanchez E, Maderuelo-Fernández JA, Gomez-Marcos MA; MARK Group: 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; 22: 901-911

21) Suzuki J, Kurosawa T, Kon T, Tomaru T: Impact of cardiovascular risk factors on progression of atherosclerosis in younger patients: evaluation by carotid duplex ultrasonography and cardio-ankle vascular index (CAVI). J Atheroscler Thromb 2014; 21: 554-562

22) Takagi A, Ogawa H, Wakeyama T, Iwami T, Kimura M, Hadano Y, Matsuda S, Miyazaki Y, Hiritatsu A, Matsu- zaki M: Cardio-ankle vascular index is superior to brachial-ankle pulse wave velocity as an index of arterial stiffness. Hypertens Res 2008; 31: 1347-1355

23) Hods HN, Mack WJ, LaBree L, Selzer RH, Liu CR, Liu CH, Azen SP: The role of carotid arterial intima-media thickness in predicting clinical coronary events. Ann Intern Med 1998; 128: 262-269

24) Sute D, Yamamoto E, Tanaka T, Hirata Y, Sakamoto K, Tsuchi K, Kojima S, Nishiyama K, Kaikita K, Hokimoto S, Jinnouchi H, Ogawa H: Association of estimated central blood pressure measured non-invasively with pulse wave velocity in patients with coronary artery disease. Int J Cardiol Heart Vasc 2015; 8: 52-54

25) Sute D, Yamamoto E, Tanaka T, Hirata Y, Sakamoto K, Tsuchi K, Kojima S, Nishiyama K, Kaikita K, Hokimoto S, Jinnouchi H, Ogawa H: The accuracy of central blood pressure waveform by novel mathematical transformation of non-invasive measurement. Int J Cardiol 2015; 189: 244-246

26) Westerbacka J, Leinonen E, Salonen JT, Salonen R, Huukka A, Yki-Järvinen H, Taskinen MR: Increased augmentation of central blood pressure is associated with increases in carotid intima-media thickness in type 2 diabetic patients. Diabetologia 2005; 48: 1654-1662

27) Forster FK, Turney D: Oscillometric determination of diastolic, mean and systolic blood pressure—a numerical model. J Biomech Eng 1986; 108: 359-364

28) Franklin SS, Gustin W 4th, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D: Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. Circulation 1997; 96: 308-315