

## Original Article

# Association between Pulse Wave Velocity and Coronary Artery Calcification in Japanese men

## the Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA)

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**Aim:** Pulse wave velocity (PWV) is a simple and valid clinical method for assessing arterial stiffness. Coronary artery calcification (CAC) is an intermediate stage in the process leading to overt cardiovascular disease (CVD) and an established determinant of coronary artery disease. This study aimed to examine the association between PWV and CAC in a population-based sample of Japanese men.

**Methods:** This is a cross-sectional study of 986 randomly selected men aged 40-79 years from Shiga, Japan. CVD-free participants were examined from 2006 to 2008. Brachial-ankle PWV (baPWV) was measured using an automatic waveform analyzer. CAC was assessed using computed tomography. Agatston scores  $\geq 10$  were defined as the presence of CAC.

**Results:** Prevalence of CAC progressively increased with rising levels of baPWV: 20.6%, 41.7%, 56.3%, and 66.7% across baPWV quartiles  $< 1378$ , 1378-1563, 1564-1849, and  $> 1849$  cm/s ( $P < 0.001$  for trend). Associations remained significant after adjusting for age and other factors, including body mass index, systolic blood pressure, pulse rate, total and high-density lipoprotein cholesterol, hemoglobin A1c, drinking, smoking and exercise status, and the use of medication to treat hypertension, dyslipidemia and diabetes ( $P = 0.042$  for trend). The optimal cutoff level of baPWV to detect CAC was 1612 cm/s using receiver operating characteristic curve analysis.

**Conclusions:** Arterial stiffness as defined by an elevated baPWV is associated with an increased prevalence of CAC in a general population-based setting among Japanese men.

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**Key words:** Arterial stiffness, Pulse wave velocity (PWV), Coronary artery calcification (CAC), Coronary artery diseases (CAD), Cardiovascular diseases (CVD)

### Introduction

Cardiovascular disease (CVD) is one of the leading causes of premature death in Japan and other countries<sup>1-3</sup>. The prevalence and incidence of CVD is expected to increase because of rapidly aging populations<sup>1,3,4</sup>. While current attention is largely based on

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the prevention of CVD, more effective strategies could include an increased focus on the preclinical phases of CVD prior to the onset of an overt CVD event.

Coronary artery calcification (CAC), measured by computed tomography (CT), is a reliable marker of subclinical coronary atherosclerosis, which can provide morphological evidence of subclinical atherosclerotic lesions<sup>5</sup>. Furthermore, CAC has been shown to be a strong independent predictor of future coronary events, including acute myocardial infarction, acute coronary syndrome, and other manifestations of CVD such as stroke<sup>6-8</sup>.

Pulse wave velocity (PWV) has been shown to be a reliable measure of arterial stiffness. While carotid-femoral PWV (cfPWV) is a measure of central arterial stiffness, brachial-ankle PWV (baPWV) appears to be a combined measure of central and peripheral arterial stiffness<sup>9-11</sup>. Because baPWV is non-invasive, convenient to measure, and requires little technical expertise, it is widely available. Both cfPWV and baPWV have been shown to be strong predictors of clinically evident CVD events<sup>12-17</sup>. However, few population-based observational studies have documented a link between either measurement and subclinical atherosclerosis, including CAC<sup>18, 19</sup>. Current evidence is largely based on studies in Western countries where the risk of coronary artery disease (CAD) is high. It is unclear if findings persist in low risk populations such as Japan. Whether more subtle relationships in low risk samples exist or can be identified is unknown.

## Aim

The objective of the present study is to examine the association between baPWV and CAC in a population-based sample of Japanese men enrolled in the Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA).

## Methods

### Study Design and Participants

SESSA is an epidemiological study of randomly selected men from the general population of Japan. Details of the study are described elsewhere<sup>8, 20, 21</sup>. In brief, 1094 community-dwelling men aged 40-79 years underwent comprehensive physical examinations following a rigid study protocol from May, 2006 to March, 2008. After excluding participants with prior CVD ( $n=99$ ) and those with missing information on baPWV ( $n=7$ ), a history of stroke ( $n=1$ ), or alcohol intake ( $n=1$ ), a total of 986 men were included in the present cross-sectional assessment of the relationship

between baPWV and subclinical atherosclerosis. This study was approved by the Institutional Review Board of Shiga University of Medical Science (No. 17-19, 17-83), and written informed consent was obtained from all participants.

### Risk Factor Measurement

Body weight and height were measured while the participants were wearing light clothing without shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Blood pressure and pulse rate were based on the average of two consecutive measurements in the right arm after participants emptied their bladders for urinalysis and sat quietly for at least five min using an automated sphygmomanometer (BP-8800; Omron Health Care Co. Ltd, Kyoto, Japan) with an appropriately-sized cuff. Information on medical history, medication use, the current use of cigarettes and alcohol, and exercise habits were obtained using a self-administered questionnaire followed by a review by trained research technicians. Participants were categorized as either currently or not currently drinking alcohol or smoking cigarettes. Exercise was categorized as current ( $\geq 1$  hour/week) and not current. Estimated 10-year absolute risk of CAD was calculated using the NIPPON DATA80 Risk Chart<sup>22</sup>.

### Blood Test

Venipuncture was performed early in the clinic visit following measurement of blood pressure after at least a 12-hour fast. Serum was separated by centrifugation (3000 revolutions per min, for 15 min) at 4°C within 90 min of drawing blood. Samples were sent for routine laboratory tests including the assessment of lipid profiles and glucose. Plasma glucose level was measured from NaF-treated plasma using a hexokinase glucose-6-phosphate-dehydrogenase enzymatic assay, and hemoglobin A1c (HbA1c) was measured by latex agglutination immunoassay (Kyowa Medix, Tokyo, Japan). Units of HbA1c were converted from HbA1c (JDS) to HbA1c (NGSP) using the following formula: NGSP (%) =  $1.02 \times \text{JDS} (\%) + 0.25\%$ <sup>23</sup>. Serum total cholesterol was measured using enzymatic assays, and high-density lipoprotein (HDL) cholesterol was measured using direct methods (Kyowa Medix, Tokyo, Japan). Serum lipids were measured at a single laboratory (Shiga Laboratory, Shiga, Japan) that has been certified for standardized lipid measurements according to the protocol of the Centers for Disease Control and Prevention/the Cholesterol Reference Method Laboratory Network (CDC/CRMLN)<sup>24</sup>.

### Pulse Wave Velocity

baPWV was measured while the participant was in a supine position after 5 min of rest using an automatic waveform analyzer (Form I PWV/ABI; Omron Health Care Co. Ltd, Kyoto, Japan)<sup>16, 25</sup>. Pressure waveforms of the brachial and tibial arteries were recorded by an oscillometric method using occlusion and sensing cuffs adapted to both arms and ankles without clothes. The average value of left and right baPWV was used in the present analysis. Electrocardiogram was monitored with electrodes placed on both wrists. Heart sounds S1 and S2 were detected by a microphone set on the left edge of the sternum at the fourth intercostal space. The automatic device calculated the path length for baPWV by using a height-based formula, and PWV was calculated as the distance between the two arterial sites divided by the time difference between waveforms conducted from the region of origin of aorta to arms and ankles.

### Coronary Artery Calcification (CAC)

CAC was measured by either electron-beam computed tomography (EBCT) in 691 sample members (70.1%) using a C-150 scanner (Imatron, South San Francisco, CA, USA) or by 16-channel multidetector row computed tomography (MDCT) in 295 sample members using an Aquilion scanner (Toshiba, Tokyo, Japan). Images were obtained from the level of the root of the aorta through the heart at a slice thickness of 3 mm with a scan time of 100 ms (EBCT) or 320 ms (MDCT). We acquired images at 70% of the cardiac cycle using electrocardiogram triggering during a single breath-hold. In this study, the amount of X-ray exposure because of CT imaging was approximately 4.7 mGy, which was almost half of that in clinical settings. Quantification of CAC was performed using a DICOM workstation and AccuImage software (AccuImage Diagnostics, South San Francisco, CA, USA). The presence of CAC was defined as a minimum of three contiguous pixels (area = 1 mm<sup>2</sup>) with density  $\geq$  130 Hounsfield units (HU). We placed a region of interest around each high-density lesion in the epicardial coronary arteries. Peak density (HU) and area (mm<sup>2</sup>) of the individual coronary calcifications were measured. A CAC score was calculated based on the methods of Agatston<sup>26</sup>. An Agatston score  $\geq$  10 is defined as definite CAC<sup>27</sup>. All CT images were read by a trained physician who was blinded from clinical information from the participants. The protocol described was adopted from a previous study<sup>8</sup>) in which the reproducibility of the scans showed an intraclass correlation of 0.98<sup>27</sup>. Since results of the current report are similar to the results of

a stratified analysis by CT-type, the definition of CAC by EBCT and MDCT are considered equivalent. Others have also reported comparable findings from CAC assessment by EBCT and MDCT<sup>28</sup>.

### Statistical Analysis

For the purpose of showing how study characteristics and levels of CAC vary with baPWV, data are presented by baPWV quartiles. Within quartiles, continuous study characteristics are presented as mean  $\pm$  standard deviation (SD). Dichotomous variables and the prevalence of CAC are presented as percentages. While data are presented within quartiles, tests for trend are based on modeling baPWV as an independent variable in its original continuous format. Study characteristics were modeled as dependent variables. For characteristics that are continuous, general linear regression was used. For dichotomous characteristics, including CAC prevalence, logistic regression was used. For CAC prevalence, models were adjusted for age alone and for age, BMI, systolic blood pressure, pulse rate, total and HDL cholesterol, HbA1c, current alcohol drinking (yes versus no), current smoking (yes versus no), currently exercising (yes versus no), the use of medication for the treatment of hypertension, dyslipidemia, and diabetes (yes versus no), and types of CT scanning (EBCT versus MDCT) using the forced entry method. Analyses were repeated separately for subgroups defined by age (aged 40-64 years vs 65-79 years) and use of medications for hypertension. While tests for trend were based on modeling baPWV as a continuous variable, odds ratios (OR) were also derived by comparing the odds of CAC in the top 3 quartiles of baPWV to the odds of CAC in the bottom quartile. A sensitivity analysis was also conducted after exclusion of participants with atrial fibrillation. To investigate cutoff level of baPWV to detect CAC, receiver operating characteristics (ROC) curve for the model was plotted, and the area under the ROC curve was obtained. The cutoff value of baPWV that optimizes the discriminating ability for the risk of prevalent CAC was determined as the point closest to (0, 1) on the ROC curve, which was calculated as “(1 - sensitivity)<sup>2</sup> + (1 - specificity)<sup>2</sup>,” or the point maximizing Youden index calculated as “sensitivity + specificity - 1.”<sup>29</sup>) OR per 1 SD increase in 10-year absolute risk of CAD based on the NIPPON DATA80 Risk Chart for CAC was also calculated in order to compare the strength of the association with that of baPWV. All reported *P*-values are based on two-sided levels of significance. Statistical analyses were performed with SPSS Statistics 22.0 for Windows (IBM, Chicago, IL, USA).

**Table 1.** Averages and percentages of the study characteristics of the participants according to the quartiles of baPWV: Japanese men aged 40-79, SESSA, 2006-2008

	Quartile of baPWV (cm/s)				P value
	< 1378	1378-1563	1564-1849	> 1849	
Sample size	246	247	247	246	
Age (years)	55.5 ± 9.7	61.9 ± 9.1	66.1 ± 7.9	70.3 ± 6.3	< 0.001
BMI (kg/m <sup>2</sup> )	23.4 ± 3.0	23.9 ± 3.2	23.5 ± 2.9	23.3 ± 2.9	0.095
Systolic blood pressure (mmHg)	120.8 ± 12.6	132.3 ± 14.3	139.8 ± 16.1	152.6 ± 17.4	< 0.001
Diastolic blood pressure (mmHg)	73.8 ± 9.1	79.9 ± 10.1	81.2 ± 9.5	84.7 ± 12.0	< 0.001
Pulse rate (bpm)	62.5 ± 8.3	62.8 ± 8.9	65.7 ± 9.7	67.8 ± 12.1	< 0.001
Total cholesterol (mg/dl)	209.0 ± 33.0	211.0 ± 33.0	210.0 ± 33.0	208.0 ± 36.0	0.792
HDL cholesterol (mg/dl)	60.7 ± 16.7	57.6 ± 16.3	59.6 ± 17.3	57.7 ± 17.3	0.112
Fasting glucose (mg/dl)	98.4 ± 17.1	99.1 ± 19.0	104.2 ± 21.6	108.3 ± 24.9	< 0.001
HbA1c (NGSP) (%)	5.78 ± 0.59	5.91 ± 0.66	6.05 ± 0.75	6.25 ± 1.03	< 0.001
Current drinkers (%)	76.8% (189)	78.5% (194)	80.6% (199)	73.2% (180)	0.150
Current smokers (%)	38.2% (94)	34.8% (86)	32.8% (81)	26.0% (64)	0.020
Currently exercising (%)	35.0% (86)	42.1% (104)	48.2% (119)	44.3% (109)	0.025
Medication for hypertension (%)	8.9% (22)	25.1% (62)	34.4% (85)	42.7% (105)	< 0.001
Medication for dyslipidemia (%)	5.3% (13)	10.5% (26)	14.2% (35)	17.9% (44)	< 0.001
Medication for diabetes (%)	2.0% (5)	6.9% (17)	10.1% (25)	17.9% (44)	< 0.001
Estimated 10-year absolute risk of CAD (%)*	0.16 ± 0.01	0.31 ± 0.02	0.52 ± 0.03	0.79 ± 0.04	< 0.001

Values are expressed as means ± standard deviations for continuous variables and as percentages (numbers with the characteristic) for categorical variables.

Abbreviations: baPWV, brachial-ankle pulse wave velocity; CAC, coronary artery calcification; BMI, body mass index; HDL, high-density lipoprotein; HbA1c, Hemoglobin A1c; SESSA, Shiga Epidemiological Study of Subclinical Atherosclerosis.

\*Estimated using the NIPPON DATA80 Risk Chart.

## Results

**Table 1** shows averages and percentages of the study characteristics of the participants according to quartiles of baPWV. Participants with higher baPWV levels were older and had higher systolic blood pressure, pulse rate, fasting glucose, HbA1c, and estimated 10-year absolute risk of CAD based on the NIPPON DATA80 Risk Chart. In contrast, baPWV was inversely related to cigarette smoking and positively related to current exercising. Use of medications for the treatment of hypertension, dyslipidemia, and diabetes increased with increasing levels of baPWV. Associations with the other factors were less apparent.

The prevalence of CAC across the baPWV quartiles is given in **Table 2**. Prevalence of CAC increased consistently with increasing levels of baPWV ( $p < 0.001$ ). Prevalence was increased more than 3-fold for men in the highest baPWV quartile versus men in the lowest quartile (66.7 versus 20.7%,  $p < 0.001$ ). Even in the adjacent 2<sup>nd</sup> quartile, CAC prevalence was double the prevalence in the lowest quartile (41.3 versus 20.7,  $p < 0.001$ ). The association remained significant after adjustment for age and the other confounding

factors. Relative to the lowest baPWV quartile, the age-adjusted odds of CAC increased from 1.98 (95% confidence interval: 1.30-3.00) in the 2<sup>nd</sup> quartile to 3.61 (95% confidence interval: 2.29-5.71) in the top quartile. Further adjustment for the other study features weakened the association, although CAC prevalence continued to be elevated in the top two quartiles versus the bottom quartile. In both instances, the odds of CAC was increased by at least 2-fold. In the 3<sup>rd</sup> quartile, the OR was 1.95 (95% confidence interval: 1.20-3.18). In the top quartile, it was 2.20 (95% confidence interval: 1.22-3.96). Similar results were obtained even after exclusion of participants with atrial fibrillation: multivariable ORs were 1.48, 2.01, and 2.22 in the 2<sup>nd</sup>, 3<sup>rd</sup>, and top quartiles compared with the lowest quartile ( $P$  for trend=0.031). Comparable results were also obtained after inclusion of pulse pressure as a covariate instead of systolic blood pressure into the multivariable-adjusted model: multivariable ORs were 1.53, 1.99, and 2.24 in the 2<sup>nd</sup>, 3<sup>rd</sup>, and top quartiles compared with the lowest quartile ( $P$  for trend=0.021). **Table 3** shows the association between baPWV and CAC among middle-aged and elderly men. Multivariable-adjusted ORs of CAC

**Table 2.** Prevalence and adjusted ORs of CAC according to quartiles of baPWV: Japanese men aged 40-79, SESSA, 2006-2008

	Quartile of baPWV (cm/s)				<i>P</i> for trend
	< 1378	1378-1563	1564-1849	> 1849	
No. of CAC/participants (CAC prevalence, %)	51/246 (20.7)	102/247 (41.3)	138/247 (55.9)	164/246 (66.7)	< 0.001
Age-adjusted OR (95% CI)	1.00	1.98 (1.30-3.00)	2.89 (1.88-4.42)	3.61 (2.29-5.71)	< 0.001
Multivariable-adjusted OR (95% CI)*	1.00	1.47 (0.94-2.30)	1.95 (1.20-3.18)	2.20 (1.22-3.96)	0.042

Abbreviations: baPWV, brachial-ankle pulse wave velocity; CAC, coronary artery calcification; CI, confidence interval; OR, odds ratio.

\*Adjusted for age, BMI, systolic blood pressure, pulse rate, total cholesterol, HDL cholesterol, HbA1c, drinking, smoking, and exercise status, the use of medication to treat hypertension, dyslipidemia, or diabetes, and types of CT scanning.

**Table 3.** Prevalence and adjusted ORs of CAC according to quartiles of baPWV for middle-aged and elderly men: Japanese men aged 40-79, SESSA, 2006-2008

	Quartiles of baPWV (cm/s)**				<i>P</i> for trend
	< 1378	1378-1563	1564-1849	> 1849	
Middle-age (aged 40-64 years)					
No. of CAC/participants (CAC prevalence, %)	39/207 (18.8)	50/150 (33.3)	60/118 (50.8)	26/49 (53.1)	< 0.001
Multivariable-adjusted OR (95% CI)*	1.00	1.45 (0.83-2.53)	2.41 (1.27-4.54)	2.24 (0.88-5.72)	0.035
Elderly (aged 65-79 years)					
No. of CAC/participants (CAC prevalence, %)	12/39 (30.8)	52/97 (53.6)	78/129 (60.5)	138/197 (70.1)	< 0.001
Multivariable-adjusted OR (95% CI)*	1.00	1.99 (0.87-4.56)	2.56 (1.11-5.88)	3.52 (1.46-8.52)	0.032

Abbreviations: baPWV, brachial-ankle pulse wave velocity; CAC, coronary artery calcification; CI, confidence interval; OR, odds ratio.

\*Adjusted for BMI, systolic blood pressure, pulse rate, total cholesterol, HDL cholesterol, HbA1c, drinking, smoking, and exercise status, the use of medication to treat hypertension, dyslipidemia, or diabetes, and types of CT scanning.

\*\**P* values for tests of heterogeneity of the effect of baPWV on CAC between age groups were 0.670 without adjustment and 0.527 with adjustment for the other characteristics.

**Table 4.** Prevalence and adjusted ORs of CAC according to quartiles of baPWV among participants with and without medications to treat HT: Japanese men aged 40-79, SESSA, 2006-2008

	Quartiles of baPWV (cm/s)**				<i>P</i> for trend
	< 1378	1378-1563	1564-1849	> 1849	
Participants without medications for HT					
No. of CAC/participants (CAC prevalence, %)	39/224 (17.4)	73/185 (39.5)	82/162 (50.6)	92/141 (65.2)	< 0.001
Multivariable-adjusted OR (95% CI)*	1.00	2.16 (1.30-3.58)	2.74 (1.54-4.86)	4.01 (1.96-8.23)	0.001
Participants on medications for HT					
No. of CAC/participants (CAC prevalence, %)	12/22 (54.5)	29/62 (46.8)	56/85 (65.9)	72/105 (68.6)	0.029
Multivariable-adjusted OR (95% CI)*	1.00	0.27 (0.08-0.90)	0.46 (0.14-1.49)	0.32 (0.08-1.22)	0.155

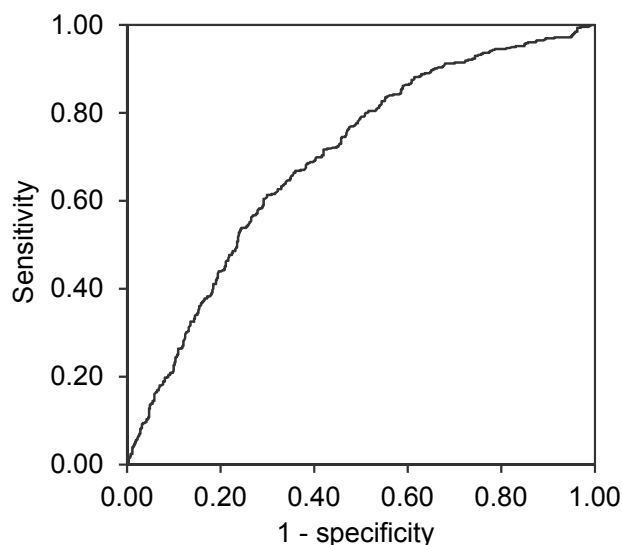
Abbreviations: baPWV, brachial-ankle pulse wave velocity; CAC, coronary artery calcification; HT, hypertension; CI, confidence interval; OR, odds ratio.

\*Adjusted for age, BMI, systolic blood pressure, pulse rate, total cholesterol, HDL cholesterol, HbA1c, drinking, smoking, and exercise status, the use of medication to treat dyslipidemia or diabetes and types of CT scanning.

\*\**P* values for tests of heterogeneity of the effect of baPWV on CAC between age groups were 0.024 without adjustment and 0.031 with adjustment for the other characteristics.

presence increased from 1.45 (95% confidence interval: 0.83-2.53) in the 2<sup>nd</sup> quartile to 2.41 (95% confidence interval: 1.27-4.54), while slight non-significant reduction was observed in the top quartile: 2.24 (95% confidence interval: 1.27-4.54). In elderly men, linear association was observed between baPWV and CAC.

Tests for heterogeneity between the age strata with and without adjustment for the study characteristics were not significant ( $P=0.670$  without adjustment and  $P=0.527$  with adjustment). **Table 4** shows the association between baPWV and CAC among participants with and without medications to treat hyperten-



**Fig. 1.** Receiver operating characteristics (ROC) curve for brachial-ankle pulse wave velocity (baPWV) to detect coronary artery calcification (CAC)

sion. The association between baPWV and CAC was strong and continuous among participants without medications to treat hypertension while there was no clear relationship among treated hypertensives ( $P$  for heterogeneity=0.024 without adjustment and 0.031 with adjustment). **Fig. 1** shows the ROC curve to investigate the cutoff level of baPWV to detect CAC. The area under the ROC curve was 0.696 (95% confidence interval: 0.664-0.729). The optimal cutoff value of baPWV was 1612cm/s with sensitivity of 0.61 and specificity of 0.70 based both on the analysis of the distance to (0, 1) on the ROC curve (0.489) and that of the Youden index (0.314).

Crude OR for prevalent CAC per 1 SD increase in estimated 10-year absolute risk of CAD based on the NIPPON DATA80 Risk Chart was 2.28 (95% confidence interval: 1.89-2.74), while crude OR per 1 SD increase in baPWV was 2.14 (95% confidence interval: 1.95-2.65).

## Discussion

This study demonstrates that baPWV is significantly associated with CAC in a general population-based setting of Japanese men. The association remains significant after adjustment for age and several risk factors commonly associated with a high risk of morbidity and mortality from CVD. To the best of our knowledge, this is the largest study to have demonstrated a link between baPWV and CAC in a general population-based sample in Japan. The present

study also confirms that associations exist in a group of individuals known to have a low risk of CAD, possibly suggesting that relationships are relevant for a broad group of individuals. To the best of our knowledge, the present analysis was also the first to conduct ROC analysis between baPWV and CAC. The optimal cutoff point of baPWV to detect CAC was approximately 1600 cm/s, which is lower than the threshold level of 1800 cm/s for prediction of future clinical CVD events in a Japanese population<sup>30</sup>.

In addition to Western populations<sup>31, 32</sup>, a number of hospital-based studies in Asia report a link between measures of arterial stiffness and CAC<sup>33-37</sup>. Limited evidence has been available from population-based studies. The Rotterdam study showed a close relationship between cfPWV and CAC among 1757 elderly individuals (with an average age of 71 years)<sup>18</sup>. Compared with participants in the lowest quartile of cfPWV, those in the highest quartile had 2.12-fold greater risk of advanced CAC before and after adjustment for confounding factors. Similarly, the Framingham Heart Study described a close link between cfPWV and calcification of the aorta and coronary artery among offspring of the original Framingham cohort and in third generation members<sup>19</sup>. In addition, cfPWV was found to be one of the strongest correlates of arterial calcification in a multivariable-adjusted model. A 1SD rise in cfPWV was associated with a 2.69-fold increase in the odds of thoracic calcification and a separate 1.47-fold increase in the odds of abdominal aortic calcification and CAC (all with  $P < 0.001$ ). The Korean Longitudinal Study on Health and Aging also investigated the correlation between cfPWV and CAC among 1,000 elderly Korean participants (aged 65 years and older) based on age- and sex-stratified random sample<sup>38</sup>. The correlation coefficient between cfPWV and CAC scores was 0.196 ( $P < 0.01$ ). While these are studies based largely on cfPWV, they are consistent with a general association between arterial stiffness and subclinical atherosclerosis in different regions of the world where the risk of CVD can vary markedly. In a cross-sectional study of 6,009 middle-aged Korean participants of a health examination at a hospital, those in the highest quartile of baPWV had 1.63-fold greater risk of CAC after adjustment for confounding factors<sup>39</sup>. ERA JUMP study also showed significant associations between baPWV and CAC prevalence among 1,131 participants from Japan, South Korea, and the United States (multivariable adjusted OR 1.36 per 1 SD rise in baPWV), but did not show separately significant associations for 235 Japanese Americans or 292 Japanese in Japan<sup>40</sup>. The present analysis from SESA con-

firmed the hypothesis generated from previous observational studies and demonstrated clear associations between baPWV and CAC in a general population of Japanese men.

Unfortunately, while most studies are related to cfPWV<sup>12-14, 41, 42</sup>, cfPWV measurement requires technical expertise. In contrast, measurement of baPWV is relatively simple. In Asia, it is widely available in clinical practice. Unlike cfPWV, baPWV is a less specific measure of the combination of central and peripheral arterial stiffness. In comparison, cfPWV is a measure of central arterial stiffness alone. In spite of this difference, studies have shown a close correlation between baPWV and cfPWV<sup>9-11</sup>. Other than subclinical disease, recent longitudinal studies have also reported that baPWV is associated with overt CVD events<sup>15-17, 30, 43-45</sup>. The present results merely extend this association to disease processes that can predate the appearance of overt CVD.

In the subgroup analyses of this study, there was no clear difference in the association of baPWV with CAC between middle-aged and elderly men (aged 40-64 years and 65-79 years). In contrast, there was significant heterogeneity in the association of baPWV with CAC according to the use of medications to treat hypertension: the association between baPWV and CAC was strong and continuous among participants without treatment while there was no clear relationship among treated hypertensives. No clear link between baPWV and CAC in treated hypertensives may be attributable to the fact that severe hypertensive subjects, who are at high-risk of CAC, are more likely to receive blood pressure lowering treatment, which may also lower baPWV levels.

While the association between baPWV and subclinical atherosclerosis is consistent with findings of associations between other measures of arterial stiffness and clinical and subclinical CVD, the current report has several limitations and raises some important questions. First, the study is cross-sectional. Because of this, it cannot be determined if high levels of baPWV predate or are the consequence of subclinical atherosclerosis. It may be that baPWV simply tracks or coincides with the development of subclinical atherosclerosis. Whether baPWV and CAC have different relationships with different forms of clinical CVD is still to be elucidated. This is relevant in Asian regions, such as Japan, where the risk of stroke is significantly greater than for CAD. Different relationships may be observed in the West where CAD is dominant. Second, the study included only men. Whether findings can be extended to Japanese women is especially interesting since the risk of CAD is

exceedingly low relative to other regions of the world. The importance of baPWV could also change as populations' age increases and as the prevalence of obesity and diabetes increases. Third, while the prognostic implication of advanced CAC is established among Caucasians in the United States, it is yet to be determined among Japanese men, as only 1 patient-based prospective study has found a predictive property for CAC among Japanese men, to our knowledge<sup>7</sup>. In addition, assessment of CAC using MDCT requires X-ray exposure. Therefore, it might be difficult to assess CAC as a marker of subclinical coronary atherosclerosis in daily clinical practice.

Some of the cited limitations can also lead to study strengths. While only Japanese men were enrolled, heterogeneity is less than in samples composed of a variety of ethnicities and cultural preferences. The sample size is reasonably large, allowing for the assessment of associations in middle-aged and elderly men. Cases of overt CVD are excluded, which further reduces the diversity of adverse correlates that act as confounding factors in groups that are at low and high risk of morbidity and mortality from CVD. Measurement of CAC also adhered to rigid standards according to procedures in Cardiovascular Institute at University of Pittsburgh.

## Conclusion

Arterial stiffness defined by high baPWV value is closely associated with CAC in a general population-based sample of Japanese men. Results suggest that baPWV can identify individuals with subclinical atherosclerosis who are also at an elevated risk of clinical vascular events and death. While measurement of baPWV is a simple, non-invasive, and low-cost method of measuring arterial stiffness, its use as an adjunct in defining CVD risk profiles warrants investigation.

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### COI

We do not have conflicts of interest to disclose.

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