

Cutoff Values of Brachial-Ankle Pulse Wave Velocity for Atherosclerotic Risks by Age and Sex in the Japanese General Population

Ryuko Mori^{1,2}, Masaaki Miyata², Takuro Kubozono³, Naoko Inadome², Shin Kawasoe³, Satoko Ojima³, Takeko Kawabata³, Anwar Ahmed Salim³, Hironori Miyahara⁴, Kouichi Tokushige⁵ and Mitsuru Ohishi³

¹ International Center for Island Studies, Kagoshima University, Kagoshima, Japan.

² School of Health Sciences, Faculty of Medicine, Kagoshima University, Kagoshima, Japan.

³ Department of Cardiovascular Medicine and Hypertension, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan.

⁴ Kagoshima Kouseiren Medical Health Care Center, Kagoshima, Japan.

⁵ Kagoshima Kouseiren Hospital, Kagoshima, Japan.

Aim: In this study, we aim to analyze the correlation between brachial-ankle pulse wave velocity (baPWV) and Suita score or Framingham risk score and obtain the cutoff value of baPWV by sex and age for cardiovascular risk, as assessed by these scores in the large Japanese annual health checkup data.

Methods: In total, 25,602 participants (14,539 men and 11,063 women), who had their annual health checkups, were included in this study. Cutoff values of baPWV for the moderate- and high-risk groups stratified by sex and age were obtained using a receiver operating characteristic (ROC) curve analysis.

Results: As per our findings, the Suita score demonstrated better correlations with baPWV than the Framingham risk score in both sexes (men, Suita score $R^2=0.41$ and Framingham risk score $R^2=0.37$; women, Suita score $R^2=0.54$ and Framingham risk score $R^2=0.33$). The ROC curve analysis demonstrated the cutoff values of baPWV for moderate- and high-risk groups estimated using the Suita score, and they are as follows: in men, the baPWV cutoff values were 1,350 cm/s in the 40s, 1,430 cm/s in the 50s, 1,520 cm/s in the 60s, and 1,880 cm/s in the 70s. In women, the baPWV cutoff values were 1,350 cm/s in the 40s, 1,430 cm/s in the 50s, 1,570 cm/s in the 60s, and 1,800 cm/s in the 70s.

Conclusions: We demonstrated that baPWV significantly correlated with the Suita score or Framingham risk score in both men and women, with the former presenting a stronger correlation than the latter. We propose the cutoff values of baPWV for moderate- and high-risk groups estimated using the Suita score.

Key words: Brachial-ankle pulse wave velocity, Suita score, Framingham risk score

Introduction

Coronary heart disease (CHD) has been identified as one of the major causes of death and disability worldwide, and its incidence has seen a steady increase in developed countries¹⁾. Risk factors for atherosclerosis include hypertension, dyslipidemia, diabetes mellitus (DM), chronic kidney disease (CKD), cigarette smoking, age, and male sex²⁻⁵⁾.

There are several exceptional models for cardiac risk prediction using atherosclerotic risk factors. In the USA, the Framingham risk score was developed to assess the relative importance of CHD risk factors and quantify the absolute level of CHD risk for individuals⁶⁾. This CHD score using age, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), blood pressure (BP), DM, and smoking is known to estimate the risk for

Address for correspondence: Takuro Kubozono, Department of Cardiovascular Medicine and Hypertension, Graduate School of Medical and Dental Sciences, Kagoshima University, 8-35-1 Sakuragaoka, Kagoshima City, Kagoshima 890-8520, Japan E-mail: kubozono@m.kufm.kagoshima-u.ac.jp

Received: March 2, 2022 Accepted for publication: June 13, 2022

Copyright©2022 Japan Atherosclerosis Society

This article is distributed under the terms of the latest version of CC BY-NC-SA defined by the Creative Commons Attribution License.

Advance Publication Journal of Atherosclerosis and Thrombosis

Accepted for publication: June 13, 2022 Published online: August 20, 2022

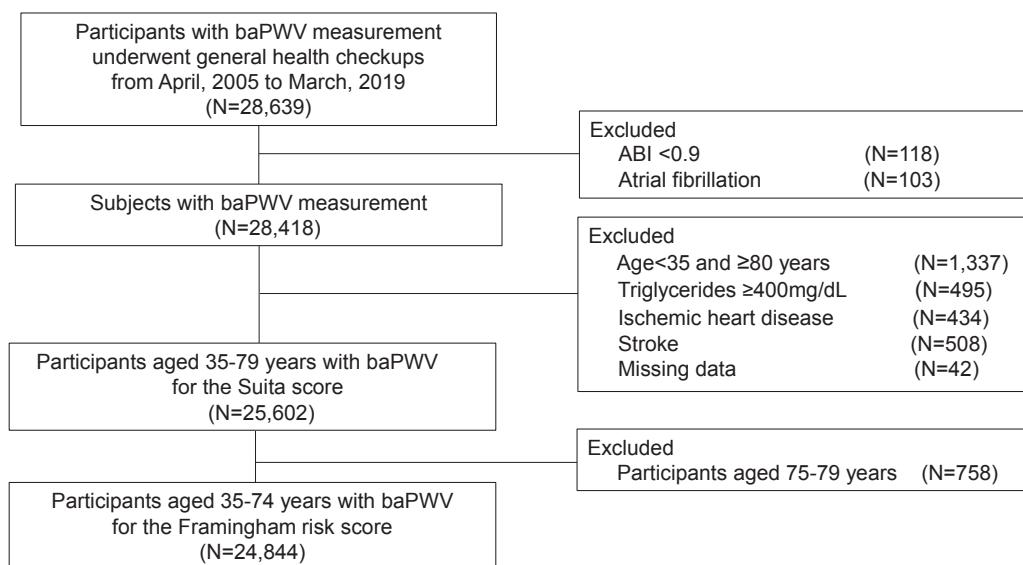


Fig. 1. Flow diagram for the selection of participants

baPWV, brachial-ankle pulse wave velocity; ABI, ankle brachial pressure index

CHD over a period of 10 years based on the Framingham experience in individuals aged 30–74 years⁷⁾. Meanwhile, in Japan, the Saita score is used to predict the 10-year risk for the development of CHD in Japanese participants aged 35–79 years, and it is calculated based on age, sex, LDL-C, HDL-C, DM, BP, smoking habits, and the estimated glomerular filtration rate (eGFR)⁵⁾. The Saita score, including CKD as a coronary risk factor, was found to be more accurate in terms of predicting CHD than the original Framingham risk scores in the Japanese population⁵⁾.

As an index of arterial stiffness, a simple, noninvasive, automatic method of measuring brachial-ankle pulse wave velocity (baPWV) has been developed and used in clinical practice and large cohort studies^{8–12)}. The baPWV showed prognostic predictability independent of conventional atherosclerotic risk factors, and a meta-analysis of baPWV using prospective cohort studies demonstrated that baPWV could be used as an independent marker to predict the risk of cardiovascular disease (CVD) in subjects who have no preexisting CVD¹¹⁾. Yamashina et al. have analyzed the baPWV and Framingham risk score in 10,828 subjects who had their annual health checkup examinations, and a baPWV >1,400 cm/s was found to be an independent variable for the risk stratification for high or moderate risk determined using the Framingham risk score⁸⁾. However, there is yet no study that has analyzed the association between baPWV and Saita score and compared the impact of baPWV between the Framingham risk score and Saita

score. Moreover, to extend the clinical usefulness of baPWV, we need to obtain an appropriate cutoff value of baPWV for CHD risk stratified by sex and age to manage the general population.

Aim

In this study, we aimed to analyze the correlation between baPWV and Saita score or Framingham risk score and obtain the cutoff value of baPWV stratified by sex and age as a marker of cardiovascular risk, which is estimated using the Saita score or Framingham risk score in the large Japanese annual health checkup data.

Methods

Study Population

This cross-sectional study has analyzed the data of participants who have undergone regular health checkups at the JA Kagoshima Kouseiren Medical Health Care Center between April 2005 and March 2019. **Fig. 1** shows a flowchart of the selection process for the survey participants. Only the results of the first visit were used to avoid double counting if the participants had undergone multiple examinations during the study period. The 28,639 individuals whose baPWV was measured were then recruited, and participants with an ankle brachial index (ABI) of < 0.9 ($n=118$) and atrial fibrillation ($n=103$) were excluded because baPWV cannot be accurately

measured in these participants. Moreover, participants aged <35 years and ≥ 80 years were excluded, as the Saita score could not be calculated in these participants. LDL-C cannot be calculated using the Friedewald equation in individuals with triglycerides (TG) ≥ 400 mg/dL; thus, these individuals were also excluded from the analysis. Moreover, individuals with ischemic heart disease ($n=434$) or stroke ($n=508$) were excluded. Finally, participants aged 35–79 years with baPWV measurement ($n=25,602$) were analyzed for the Saita score. Subsequently, for the Framingham risk score, participants aged 75–79 years were excluded, and those aged 35–74 years ($n=24,844$) were analyzed.

This present study conformed to the Declaration of Helsinki and was approved by the Institutional Ethics Committees of the Graduate School of Medical and Dental Sciences, Kagoshima University, and JA Kagoshima Kouseiren Hospital. We obtained informed consent for the use of their health checkup data via an opt-out option.

Data Collection

BP was measured using a mercury sphygmomanometer after the participant sat at rest for 5 min. Blood samples were collected following overnight fasting. Biochemical parameters, such as LDL-C, HDL-C, TG, and FBS, were measured using standard methods. The eGFR was determined according to the new Japanese coefficient for the modified isotope dilution mass spectrometry-traceable Modification of Diet in the Renal Disease study equation¹³⁾ as follows:

$$\text{men: eGFR} = 194 \times \text{SCr}^{-1.094} \times \text{age}^{-0.287}$$

$$\text{women: eGFR} = 194 \times \text{SCr}^{-1.094} \times \text{age}^{-0.287} \times 0.739$$

Data with regard to medical history of hypertension, DM, dyslipidemia, medication, cigarette smoking, and concomitant diseases were obtained using self-administered questionnaires. Body mass index (BMI) was calculated for each individual using body weight (kg) and height (m), and a BMI ≥ 25 kg/m² was considered to indicate obesity. Cardiovascular risk factors were defined as follows: hypertension, defined as a systolic BP (SBP) ≥ 140 mmHg and/or diastolic BP (DBP) ≥ 90 mmHg or current use of antihypertensive medications¹⁴⁾; dyslipidemia, defined as an LDL-C ≥ 140 mg/dL, HDL-C <40 mg/dL, TG ≥ 150 mg/dL, or use of lipid-lowering agents¹⁵⁾; and DM, defined as an FBS >126 mg/dL or treatment with oral hypoglycemic agents or insulin¹⁶⁾.

The baPWV was measured as previously reported^{8, 9)} and automatically calculated using a Colin waveform analyzer (Colin, Komaki, Japan) according

to the equation baPWV=(D1-D2)/T1, where D1 is the distance from the aortic root to the right ankle and D2 is the distance from the heart to the right upper arm. These distances were calculated automatically based on the individual's height. T1 refers to the time from the onset of the rise in the pulse volume record of the right upper arm to the onset of the rise in the pulse volume record of the right ankle. The BP of the extremity was measured automatically using the Colin waveform analyzer when baPWV was measured, and ABI was subsequently measured.

We used the Saita score in Japan and the Framingham risk score in the USA in this study. The Saita score is a risk score used to predict the 10-year risk for the development of CHD in Japanese participants aged 35–79 years, and it is calculated based on age, sex, LDL-C, HDL-C, DM, BP, smoking habits, and eGFR⁵⁾. Since a Saita score ≥ 41 was considered as a moderate-risk factor for CHD and a Saita score ≥ 56 was associated with a high-risk factor for CHD, we defined participants with a high or moderate risk for CHD as having a Saita score of ≥ 41. The Framingham risk score population study was developed to calculate a score predictive of the 10-year risk of CHD among Americans aged 30–74 years without CHD or stroke⁷⁾. The Framingham risk scores were calculated based on age, sex, LDL-C, HDL-C, BP, DM, and smoking status. To estimate the CHD risk of individuals, the Framingham risk score⁷⁾ was calculated, and the study participants were thereafter categorized into low- (10-year risk, <10%), intermediate- (10-year risk, 10%–20%), and high-risk (10-year risk, ≥ 20%) groups^{7, 17)}.

Statistical Analysis

Continuous variables are presented as the mean value ± standard deviation because the data were normally distributed. Categorical variables are expressed as the number of participants and percentages. We have analyzed men and women separately. Further, we analyzed the associations between baPWV and Saita score or Framingham risk score using nonlinear regression models implemented in the statistical program R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Australia). A receiver operating characteristic (ROC) curve analysis was performed to estimate the baPWV cutoff value for predicting the moderate and high risk of CHD. The value with the highest sum of sensitivity and specificity was identified as the cutoff value. Furthermore, we stratified the analyses by age group in both men and women. Statistical analysis except for nonlinear regression analysis was performed using

Table 1. Clinical characteristics of men and women

	Men n=14,539	Women n=11,063
Age (years)	54.2 ± 11.1	55.5 ± 10.8
BMI (kg/m ²)	23.8 ± 3.1	22.7 ± 3.5
LDL-C (mg/dL)	126.2 ± 31.3	132.1 ± 31.6
HDL-C (mg/dL)	56.6 ± 14.3	65.0 ± 14.6
TG (mg/dL)	124.6 ± 68.9	90.4 ± 48.2
FBS (mg/dL)	107.1 ± 22.3	100.1 ± 16.8
SBP (mmHg)	123.4 ± 16.9	117.9 ± 17.9
DBP (mmHg)	78.0 ± 11.2	72.7 ± 10.9
Hypertension, n (%)	4,931 (33.9)	2,754 (24.9)
Dyslipidemia, n (%)	7,774 (53.5)	5,376 (48.6)
Diabetes mellitus, n (%)	1,681 (11.6)	557 (5.0)
Obesity, n (%)	4,575 (31.5)	2,411 (21.8)
Current smoker, n (%)	4,951 (34.1)	529 (4.8)
eGFR (mL/min/1.73m ²)	78.2 ± 14.8	79.9 ± 15.0
baPWV (cm/s)	1,501.7 ± 306.9	1,434.0 ± 302.2

Values are presented as mean ± standard deviation or frequency (percentage).

BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; FBS, fasting blood sugar; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; and baPWV, brachial-ankle pulse wave velocity.

JMP Pro version 15 (SAS Institute Inc., Cary, NC, USA). A *p*-value <0.05 was considered to be statistically significant.

Results

Clinical Characteristics of Men and Women Participants

The clinical features of the participants according to sex are summarized in **Table 1**. In total, 25,602 individuals (14,539 men and 11,063 women) without atherosclerotic CVD were included in this analysis. The mean age was 54.2 ± 11.1 years for men and 55.5 ± 10.8 years for women, and the mean baPWV was 1,501.7 ± 306.9 cm/s for men and 1,434.0 ± 302.2 cm/s for women. As for the other clinical characteristics, data on BMI, LDL-C, TG, HDL-C, FBS, SBP, DBP, hypertension, dyslipidemia, obesity, smoking, and eGFR in men and women are summarized in **Table 1**.

Clinical Characteristics in Each Risk Category Estimated Using the Saita Score

Overall, the number of participants in the low-risk group based on the Saita score was 14,251; that in the moderate-risk group was 9,618; and that in the high-risk group was 1,733. The mean Saita score was 29.7 ± 7.8 in the low-risk group, 47.0 ± 4.1 in the moderate-risk group, and 59.5 ± 3.6 in the high-risk

group. The mean baPWV was 1,327.0 ± 195.8 in the low-risk group, 1,612.4 ± 296.2 in the moderate-risk group, and 1,892.2 ± 358.9 in the high-risk group.

We have subsequently examined the data by gender. **Table 2** shows the clinical background in each risk group estimated using the Saita score according to sex. For men, the Saita score was 32.3 ± 5.7 in the low-risk group (*n*=6,214), 47.5 ± 4.1 in the moderate-risk group (*n*=6,707), and 59.6 ± 3.6 in the high-risk group (*n*=1,618). The mean baPWV in men was 1,328.9 ± 170.5 cm/s in the low-risk group, 1,569.4 ± 279.4 cm/s in the moderate-risk group, and 1,884.8 ± 361.4 cm/s in the high-risk group. For women, the Saita score was 27.6 ± 8.6 in the low-risk group (*n*=8,037), 46.1 ± 3.8 in the moderate-risk group (*n*=2,911), and 57.9 ± 2.2 in the high-risk group (*n*=115). The mean baPWV in women was 1,325.5 ± 213.3 cm/s in the low-risk group, 1,711.3 ± 309.8 cm/s in the moderate-risk group, and 1,995.0 ± 304.5 cm/s in the high-risk group. Other clinical characteristics, such as LDL-C, TG, HDL-C, FBS, SBP, DBP, smoking, and eGFR stratified by sex, are presented in **Table 2**.

Relationship Between baPWV and Saita Score

As shown in **Fig. 2**, the correlation between baPWV and the Saita score (**Figs. 2A and B**) and the ROC curve between baPWV and the Saita score demonstrate a more-than-moderate risk stratification

Table 2. Clinical characteristics of the participants in each risk group as estimated using the Suita score

	Men (n=14,539)			Women (n=11,063)		
	Low risk n=6,214	Moderate risk n=6,707	High risk n=1,618	Low risk n=8,037	Moderate risk n=2,911	High risk n=115
Age (years)	46.0 ± 7.9	58.6 ± 8.4	68.0 ± 6.4	51.6 ± 9.4	65.7 ± 6.5	70.4 ± 5.1
LDL-C (mg/dL)	119.3 ± 29.9	129.8 ± 31.4	137.1 ± 30.7	126.1 ± 29.4	147.4 ± 31.4	164.0 ± 30.4
HDL-C (mg/dL)	57.6 ± 14.3	56.5 ± 14.2	53.1 ± 13.9	66.3 ± 14.6	61.9 ± 14.0	53.7 ± 13.4
TG (mg/dL)	123.8 ± 71.1	125.9 ± 68.4	122.6 ± 61.8	84.6 ± 45.4	104.9 ± 51.5	126.9 ± 58.7
FBS (mg/dL)	101.0 ± 13.9	109.8 ± 24.3	119.9 ± 30.6	97.7 ± 13.2	106.0 ± 22.0	123.7 ± 30.2
SBP (mmHg)	114.7 ± 12.6	127.4 ± 15.9	140.7 ± 15.6	112.2 ± 15.0	132.5 ± 15.5	149.6 ± 15.6
DBP (mmHg)	74.1 ± 9.8	80.7 ± 11.3	81.4 ± 11.0	70.7 ± 10.3	77.9 ± 10.7	80.9 ± 12.3
Current smoker, n (%)	2,282 (36.7)	2,204 (32.9)	465 (28.7)	421 (5.2)	104 (3.6)	4 (3.5)
eGFR (mL/min/1.73m ²)	82.5 ± 13.4	76.3 ± 14.3	69.3 ± 16.0	82.3 ± 14.4	73.9 ± 14.4	65.7 ± 19.0
baPWV (cm/s)	1,328.9 ± 170.5	1,569.4 ± 279.4	1,884.8 ± 361.4	1,325.5 ± 213.3	1,711.3 ± 309.8	1,995.0 ± 304.5
Suita score	32.3 ± 5.7	47.5 ± 4.1	59.6 ± 3.6	27.6 ± 8.6	46.1 ± 3.8	57.9 ± 2.2

Values are presented as mean ± standard deviation or frequency (percentage).

LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; FBS, fasting blood sugar; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; and baPWV, brachial-ankle pulse wave velocity.

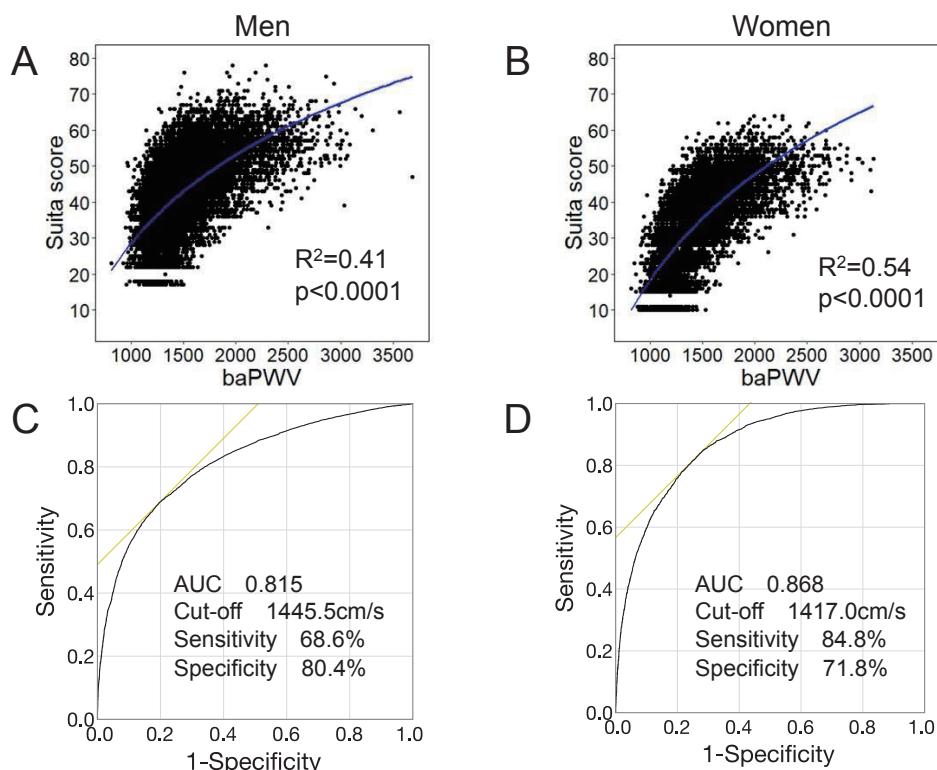


Fig. 2. Correlations of baPWV with the Suita score (A, B) and receiver operating characteristic curve between baPWV and a more-than-moderate risk stratification by the Suita score (C, D)

baPWV, brachial-ankle pulse wave velocity; AUC, area under the curve

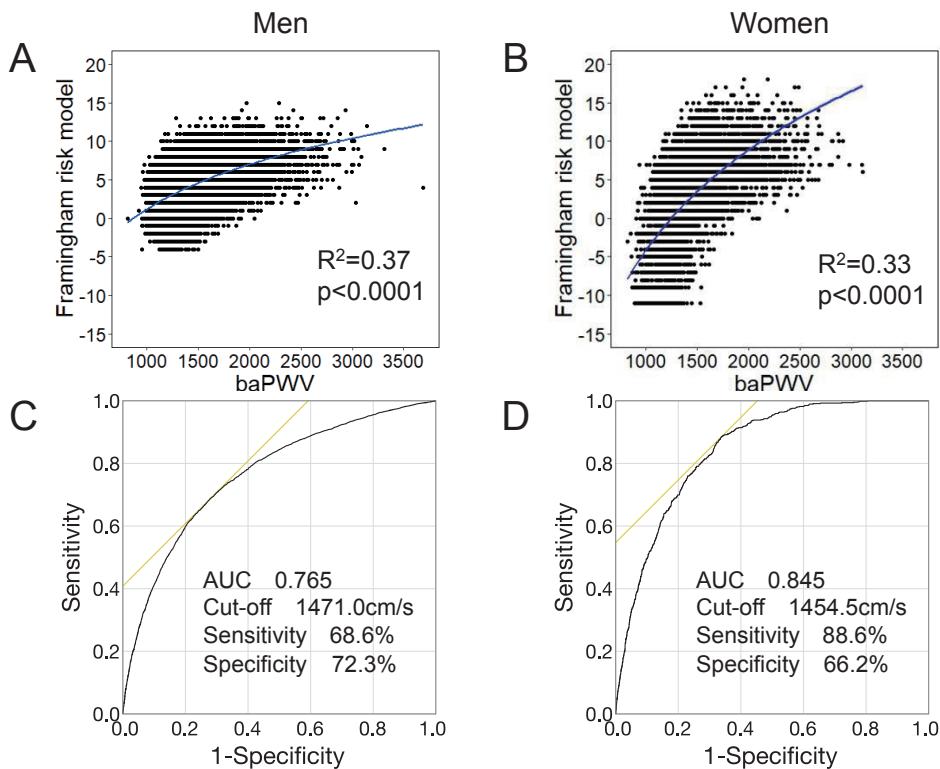


Fig. 3. Correlations of baPWV with the Framingham risk score (A, B) and receiver operating characteristic curve between baPWV and a more-than-moderate risk stratification by the Framingham risk score (C, D)

baPWV, brachial-ankle pulse wave velocity; AUC, area under the curve

(**Figs. 2C and D**). A significant correlation can be noted between baPWV and the Suita score in both men and women (**Figs. 2A and B**) (men, $R^2=0.41$ and $p<0.0001$; women, $R^2=0.54$ and $p<0.0001$). To explore an optimal baPWV cutoff point, we chose the point that represents the largest sum of sensitivity and specificity based on the ROC analysis. The area under the curve (AUC) in men was 0.815, and the sensitivity and specificity were 68.6% and 80.4%, respectively, with a baPWV of 1445.5 cm/s as the cutoff value (**Fig. 2C**). Meanwhile, the AUC in women was 0.868, and the sensitivity and specificity were 84.8% and 71.8%, respectively, with a baPWV of 1417.0 cm/s as the cutoff value (**Fig. 2D**).

Fig. 3 shows the correlations between baPWV and Framingham risk score (**Figs. 3A and B**) and the ROC curve between baPWV and the Framingham risk score showing a more-than-moderate stratification (**Figs. 3C and D**). A significant correlation was observed between the baPWV and Framingham risk score in both men and women (**Figs. 3A and B**) (men, $R^2=0.37$ and $p<0.0001$; women, $R^2=0.33$ and $p<0.0001$). The AUC in men was 0.765, and the sensitivity and specificity were 68.6% and 72.3%, respectively, with a baPWV of 1,471.0 cm/s as the

cutoff value (**Fig. 3C**). Meanwhile, the AUC in women was 0.845, and the sensitivity and specificity were 88.6% and 66.2%, respectively, with a baPWV of 1,454.5 cm/s as the cutoff value (**Fig. 3D**).

Both scores were compared among men and women. In the correlation between baPWV and both scores, the Suita score was found to demonstrate better correlations than the Framingham risk score in both sexes (men, Suita score $R^2=0.41$ and Framingham risk score $R^2=0.37$; women, Suita score $R^2=0.54$ and Framingham risk score $R^2=0.33$).

Furthermore, the Suita score was noted to have a better AUC than the Framingham risk score in both sexes (men, Suita score vs. Framingham risk score: 0.815 vs. 0.765; women, Suita score vs. Framingham risk score: 0.868 vs. 0.845).

Cutoff Values of baPWV for the Moderate- and High-Risk Groups as Estimated Using the Suita Score or Framingham Risk Score According to Age in Men and Women

We analyzed the association of baPWV cutoff values to moderate and high risk estimated using the Suita score or Framingham risk score according to age in men and women (**Table 3**). Participants were

Table 3. Association between baPWV and a more-than-moderate risk stratification estimated using the Suita score or Framingham risk score according to age

Suita score										
	Men					Women				
	n	AUC	baPWV value	Sensitivity	Specificity	n	AUC	baPWV value	Sensitivity	Specificity
40-49 years old	3,701	0.705	1,350.5	63.6	66.7	2,261	0.879	1,334.5	83.3	79.3
50-59 years old	4,331	0.706	1,427.5	61.3	69.5	3,588	0.778	1,433.0	70.3	71.1
60-69 years old	3,505	0.733	1,516.0	66.1	70.9	3,073	0.735	1,566.5	63.8	71.5
70-79 years old	1,442	0.631	1,874.5	45.8	78.6	1,146	0.688	1,796.5	54.1	73.4

Framingham risk score										
	Men					Women				
	n	AUC	baPWV value	Sensitivity	Specificity	n	AUC	baPWV value	Sensitivity	Specificity
40-49 years old	3,701	0.699	1,393.0	60.4	71.0	2,261	0.827	1,270.5	100.0	64.9
50-59 years old	4,331	0.618	1,528.5	44.9	73.7	3,588	0.806	1,456.0	78.4	70.1
60-69 years old	3,505	0.623	1,519.5	67.6	51.2	3,073	0.758	1,647.5	69.8	70.1
70-74 years old	1,024	0.577	1,954.5	35.1	81.4	806	0.672	1,925.0	53.0	73.2

baPWV, brachial-ankle pulse wave velocity; and AUC, area under the curve

divided into groups based on age: 35–39 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years for the Suita score, and 35–39 years, 40–49 years, 50–59 years, 60–69 years, 70–74 years for the Framingham risk score. The cutoff value was noted to increase with age for both scores, except for the Framingham risk score in men. Moreover, **Figs. 2 and 3** show that the Suita score is more suitable for the Japanese population. Therefore, we propose the cutoff values of baPWV for moderate- and high-risk groups estimated using the Suita score as follows: in men, the baPWV cutoff values were 1,350 cm/s in the 40s, 1,430 cm/s in the 50s, 1,520 cm/s in the 60s, and 1,880 cm/s in the 70s. In women, the baPWV cutoff values were 1,350 cm/s in their 40s, 1,430 cm/s in the 50s, 1,570 cm/s in the 60s, and 1,800 cm/s in the 70s. Unfortunately, we cannot propose the cutoff values of baPWV in the 30s because the number of participants in their 30s was too small for analysis.

Discussion

Among the 25,602 subjects who went to have their annual health checkups, we demonstrated that baPWV was significantly correlated with the Suita score or Framingham risk score in both sexes, but the Suita score was noted to exhibit better correlations than the Framingham risk score. As shown in the Results section, we thus propose the cutoff values of

baPWV for the moderate- and high-risk groups that were estimated using the Suita score in both sexes.

To the best of our knowledge, this present study is the first report to propose the cutoff values of baPWV stratified by sex and age for moderate- and high-risk groups of participants with CHD using the Suita score. Yamashina et al. reported a significant correlation between baPWV and the Framingham risk score in both sexes (men, $r=0.58$ and $p<0.01$; women, $r=0.64$ and $p<0.01$) in 10,828 subjects who had their annual health screening checkups (6,716 men and 4,112 women aged 30–74 years). Our study confirmed a similar correlation between baPWV and the Framingham risk score (men, $R^2=0.37$ and $p<0.0001$; women, $R^2=0.33$ and $p<0.0001$). Although Yamashina et al. proposed a cutoff value of 1,400 cm/s to differentiate between high- and severe-risk stratifications using the Framingham risk score for both sexes⁸, we demonstrated similar cutoff values of 1,471.0 cm/s and 1,454.5 cm/s for men and women, respectively.

Previous cohort studies have also reported the cutoff values of baPWV to predict future CHD events. Among the 4,164 individuals from the Japanese general population with a mean age of 58.9 ± 13.0 years who underwent a median follow-up period of 6.5 years, high baPWV ($\geq 1,800$ cm/s) was determined to be significantly associated with an increased CVD risk¹⁸. In Japanese participants with

hypertension, several cohort studies have proposed baPWV cutoff values ranging from 1,750 to 1,830 cm/s to predict future cardiovascular events¹⁹⁻²¹. Although these previous studies were able to propose the cutoff values of baPWV to predict future CHD, this present study suggests a cutoff value of baPWV for individuals with moderate- or high-CHD risk in the general population. We believe that our cutoff values will be useful in terms of identifying individuals at moderate or high risk of CHD during health checkups, thus allowing early intervention.

Age and sex have been identified to be important risk factors for atherosclerosis. Several previous studies have reported that baPWV increased with age and that there are differences in baPWV between men and women in the general population^{9, 22-24}. No study has reported the age- and sex-specific cutoff value of baPWV to predict cardiovascular prognosis. Thus, in this present study, the cutoff values of baPWV for moderate- and high-risk CHD were noted to increase with age, with the same values in the 40s and 50s in both sexes but different in the 60s and 70s.

The Framingham risk model has been identified as a popular risk prediction score for CHD⁷. However, it should be noted that the estimated incidence of CHD using the Framingham risk score prediction model often does not match with the actual incidence rate in some countries. Therefore, different prediction scores have been developed for several countries²⁵⁻²⁸. The Saita score was reported to be superior to the Framingham risk score in Japanese population; this finding is consistent with the results of this present study as the Saita score was determined to be better than the Framingham risk score as a feasible marker for predicting CHD in the Japanese general population. We speculate several reasons why baPWV had a stronger correlation with the Saita Score than with the Framingham risk score in the general Japanese population. First, the incidence of CHD is lower in Japan than in the USA. Second, the impact of race on the incidence of CHD varies between Japanese and Americans; therefore, the Saita score may be more suitable for the Japanese cohort. The third reason is the difference in terms of the score component. The two scores are different in that CKD is incorporated into the Saita score, which may be crucial in predicting CHD in the general Japanese population⁵. However, in women aged 50–69 years, the Framingham risk score was noted to be better in terms of predicting moderate and high risks of CHD based on baPWV than the Saita score. We speculate that this is probably because menopausal women are more susceptible to CHD than menstruating women; thus, the Framingham risk score may be more suitable

for menopausal women compared with the Saita score.

Limitations

This study has several limitations. First, individuals were limited to those who underwent annual health checkups at a single facility in Japan. Therefore, selection bias may be present, as the subjects in this study were noted to be health-conscious. Second, since this present study was cross-sectional, the cutoff values of baPWV would need to be confirmed in a large prospective study. Third, the study population was not strictly selected according to random sampling methods, but its large sample size ($n=25,602$) would compensate for this limitation.

Conclusions

Among the 25,602 subjects who had their annual health checkups, baPWV was determined to significantly correlate with the Saita score or Framingham risk score in both men and women. The Saita score demonstrated better correlations with baPWV than the Framingham risk score in men and women, as the former presented with a stronger correlation than the latter. We thus propose the cutoff values of baPWV for the moderate- and high-CHD risk groups that were estimated using the Saita score. However, further cross-sectional or longitudinal multicenter studies are needed to confirm our baPWV cutoff values for moderate- and high-CHD risk stratified by age and sex.

Conflict of Interest

The authors declare no conflicts of interest.

Acknowledgements

We thank the medical staff at the Kagoshima Kouseiren Medical Health Care Center for their support in the collection of the health checkup data.

Notice of Grant Support

This work was supported by JSPS KAKENHI Grant Number JP20K11072.

References

- McGovern PG, Pankow JS, Shahar E, Doliszny KM, Folsom AR, Blackburn H, and Luepker RV: Recent trends in acute coronary heart disease-mortality,

- morbidity, medical care, and risk factors. The Minnesota Heart Survey Investigators. *N Engl J Med*, 1996; 334: 884-890
- 2) Gordon T and Kannel WB: Multiple risk functions for predicting coronary heart disease: the concept, accuracy, and application. *Am Heart J*, 1982; 103: 1031-1039
 - 3) Kannel WB and McGee DL: Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. *Diabetes Care*, 1979; 2: 120-126
 - 4) Gordon T, Castelli WP, Hjortland MC, Kannel WB, and Dawber TR: Diabetes, blood lipids, and the role of obesity in coronary heart disease risk for women. The Framingham study. *Ann Intern Med*, 1977; 87: 393-397
 - 5) Nishimura K, Okamura T, Watanabe M, Nakai M, Takegami M, Higashiyama A, Kokubo Y, Okayama A, and Miyamoto Y: Predicting coronary heart disease using risk factor categories for a Japanese urban population, and comparison with the Framingham risk score: The Saito study. *J Atheroscler Thromb*, 2014; 21: 784-798
 - 6) D'Agostino RB Sr, Grundy S, Sullivan LM, and Wilson P: Validation of the Framingham coronary heart disease prediction scores: Results of a multiple ethnic groups investigation. *JAMA*, 2001; 286: 180-187
 - 7) Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, and Kannel WB: Prediction of coronary heart disease using risk factor categories. *Circulation*, 1998; 97: 1837-1847
 - 8) Yamashina A, Tomiyama H, Arai T, Hirose K, Koji Y, Hirayama Y, Yamamoto Y, and Hori S: Brachial-ankle pulse wave velocity as a marker of atherosclerotic vascular damage and cardiovascular risk. *Hypertens Res*, 2003; 26: 615-622
 - 9) Kubo T, Miyata M, Minagoe S, Setoyama S, Maruyama I, and Tei C: A simple oscillometric technique for determining new indices of arterial distensibility. *Hypertens Res*, 2002; 25: 351-358
 - 10) Aso K, Miyata M, Kubo T, Hashiguchi H, Fukudome M, Fukushima E, Koriyama N, Nakazaki M, Minagoe S, and Tei C: Brachial-ankle pulse wave velocity is useful for evaluation of complications in type 2 diabetic patients. *Hypertens Res*, 2003; 26: 807-813
 - 11) Ohkuma T, Ninomiya T, Tomiyama H, Kario K, Hoshide S, Kita Y, Inoguchi T, Maeda Y, Kohara K, Tabara Y, Nakamura M, Ohkubo T, Watada H, Munakata M, Ohishi M, Ito N, Nakamura M, Shoji T, Vlachopoulos C, and Yamashina A: Brachial-ankle pulse wave velocity and the risk prediction of cardiovascular disease: An individual participant data meta-analysis. *Hypertension*, 2017; 69: 1045-1052
 - 12) Kubozono T, Miyata M, Kawasoe S, Ojima S, Yoshifuku S, Miyahara H, Maenohara S, and Ohishi M: High pulse wave velocity has a strong impact on early carotid atherosclerosis in a Japanese general male population. *Circ J*, 2017; 81: 310-315
 - 13) Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, and Hishida A: Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*, 2009; 53: 982-992
 - 14) Umemura S, Arima H, Arima S, Asayama K, Dohi Y, Hirooka Y, Horio T, Hoshide S, Ikeda S, Ishimitsu T, Ito M, Ito S, Iwashima Y, Kai H, Kamide K, Kanno Y, Kashihara N, Kawano Y, Kikuchi T, Kitamura K, Kitazono T, Kohara K, Kudo M, Kumagai H, Matsumura K, Matsuura H, Miura K, Mukoyama M, Nakamura S, Ohkubo T, Ohya Y, Okura T, Rakugi H, Saitoh S, Shibata H, Shimosawa T, Suzuki H, Takahashi S, Tamura K, Tomiyama H, Tsuchihashi T, Ueda S, Uehara Y, Urata H, and Hirawa N: The Japanese society of hypertension guidelines for the management of hypertension (JSH 2019). *Hypertens Res*, 2019; 42: 1235-1481
 - 15) 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, and 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
 - 16) Araki E, Goto A, Kondo T, Noda M, Noto H, Origasa H, Osawa H, Taguchi A, Tanizawa Y, Tobe K, and Yoshioka N: Japanese clinical practice guideline for diabetes 2019. *J Diabetes Investig*, 2020; 11: 165-223
 - 17) Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JM, Kushner FG, Lauer MS, Shaw LJ, Smith SC Jr, Taylor AJ, Weintraub WS, Wenger NK, Jacobs AK, Smith SC Jr, Anderson JL, Albert N, Buller CE, Creager MA, Ettinger SM, Guyton RA, Halperin JL, Hochman JS, Kushner FG, Nishimura R, Ohman EM, Page RL, Stevenson WG, Tarkington LG, Yancy CW, and American College of Cardiology Foundation; American Heart Association: 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American college of cardiology foundation/American heart association task force on practice guidelines. *J Am Coll Cardiol*, 2010; 56: e50-e103
 - 18) Takashima N, Turin TC, Matsui K, Rumana N, Nakamura Y, Kadota A, Saito Y, Sugihara H, Morita Y, Ichikawa M, Hirose K, Kawakami K, Hamajima N, Miura K, Ueshima H, and Kita Y: The relationship of brachial-ankle pulse wave velocity to future cardiovascular disease events in the general Japanese population: The Takashima study. *J Hum Hypertens*, 2014; 28: 323-327
 - 19) Munakata M, Konno S, Miura Y, and Yoshinaga K; J-TOPP Study Group: Prognostic significance of the brachial-ankle pulse wave velocity in patients with essential hypertension: final results of the J-TOPP study. *Hypertens Res*, 2012; 35: 839-842
 - 20) Kawai T, Ohishi M, Onishi M, Ito N, Takeya Y, Maekawa Y, and Rakugi H: Cut-off value of brachial-ankle pulse wave velocity to predict cardiovascular disease in hypertensive patients: a cohort study. *J Atheroscler Thromb*, 2013; 20: 391-400
 - 21) Ohkuma T, Tomiyama H, Ninomiya T, Kario K, Hoshide S, Kita Y, Inoguchi T, Maeda Y, Kohara K, Tabara Y, Nakamura M, Ohkubo T, Watada H, Munakata M, Ohishi M, Ito N, Nakamura M, Shoji T, Vlachopoulos C, and Yamashina A: Proposed Cutoff Value of Brachial-Ankle Pulse Wave Velocity for the Management of

- Hypertension. Circ J, 2017; 81: 1540-1542
- 22) Tomiyama H, Yamashina A, Arai T, Hirose K, Koji Y, Chikamori T, Hori S, Yamamoto Y, Doba N, and Hinohara S: Influences of age and gender on results of noninvasive brachial-ankle pulse wave velocity measurement--a survey of 12517 subjects. Atherosclerosis, 2003; 166: 303-309
- 23) Kubozono T, Miyata M, Ueyama K, Nagaki A, Otsuji Y, Kusano K, Kubozono O, and Tei C: Clinical significance and reproducibility of new arterial distensibility index. Circ J, 2007; 71: 89-94
- 24) Jang SY, Ju EY, Huh EH, Kim JH, and Kim DK: Determinants of brachial-ankle pulse wave velocity and carotid-femoral pulse wave velocity in healthy Koreans. J Korean Med Sci, 2014; 29: 798-804
- 25) Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, and Wilson PWF: American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 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. Circulation, 2014; 129: 49-73
- 26) JBS3 Board: Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). Heart, 2014; 100(Suppl 2): ii1-ii67
- 27) Hippisley-Cox J, Coupland C, Robson J, and Brindle P: Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. BMJ, 2010; 341: c6624
- 28) Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetière P, Jousilahti P, Keil U, Njølstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, and Graham IM: Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J, 2003; 24: 987-1003