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ORIGINAL ARTICLE

The relationship of brachial-ankle pulse wave velocity to future cardiovascular disease events in the general Japanese population: the Takashima Study

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Brachial-ankle pulse wave velocity (baPWV) is a non-invasive measure of arterial stiffness obtained using an automated system. Although baPWVs have been widely used as a non-invasive marker for evaluation of arterial stiffness, evidence for the prognostic value of baPWV in the general population is scarce. In this study, we assessed the association between baPWV and future cardiovascular disease (CVD) incidence in a Japanese population. From 2002 to 2009, baPWV was measured in a total of 4164 men and women without a history of CVD, and they were followed up until the end of 2009 with a median follow-up period of 6.5 years. Hazard ratios (HRs) for CVD incidence according to baPWV levels were calculated using a Cox proportional hazards model adjusted for potential confounding factors, including seated or supine blood pressure (BP). During the follow-up period, we observed 40 incident cases of CVD. In multivariable-adjusted model, baPWV as a continuous variable was not significantly associated with future CVD risk after adjustment for supine BP. However, compared with lower baPWV category ($<18\,m\,s^{-1}$), higher baPWV ($\geqslant 18.0\,m\,s^{-1}$) was significantly associated with an increased CVD risk (HR: 2.70, 95% confidence interval: 1.18–6.19). Higher baPWV ($\geqslant 18.0\,m\,s^{-1}$) would be an independent predictor of future CVD event in the general Japanese population.

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INTRODUCTION

Cardiovascular diseases (CVD) still remain the major cause of death in developed countries. Arterial stiffness is recognized as a major factor in the pathogenesis of CVD and pulse wave velocity (PWV) has been widely used as a non-invasive marker in the evaluation of arterial stiffness. Several methods are used to measure PWV: most frequently used are carotid-femoral PWV (cfPWV) and brachial-ankle PWV (baPWV). cfPWV has been reported to predict future mortality[1] and morbidity[2–4] from CVD.

baPWV is a relatively new non-invasive marker of arterial stiffness and has been widely used in Japan and other East Asian countries. The reproducibility of baPWV[5] and high correlation between baPWV and cfPWV[5–6] have been reported, and several longitudinal studies report an association between baPWV and CVD mortality in an elderly population (aged 65 years and more)[7,8] or total mortality in the general population.[9] The association of baPWV with CVD incident[10,11] was also reported in patient cohort studies. A recent meta-analysis of baPWV and CVD risk only includes patients and older populations.[12] There have thus been very few studies that report the association of baPWV with future CVD events in general populations.

In the present study, we assessed the association between baPWV and future first-ever CVD or stroke incident in the Takashima Study, a cohort study of the general Japanese population.

MATERIALS AND METHODS

Participants and follow-up

The Takashima Study comprises a population-based cohort study of the risk factors for CVD. The participants in this cohort study are residents aged 20 years or more, who underwent the annual health check-up for residents and gave written informed consent to participate in the study.[9] A total of 4637 residents agreed to participate in the baseline survey (a response rate of ~70%) during 2002–2009. Follow-up was censored at the time of moving outside of the city. We excluded 473 men and women in whom baPWV was not measured ($n=135$), who had a history of CVD ($n=137$), where information was missing at baseline survey ($n=199$) or in whom the ankle-brachial index was low (ankle-brachial index <0.9; $n=2$). Thus, 4164 participants (1548 men and 2616 women) were included in this analysis.

In the present study, the follow-up ascertainment ended on 31 December 2009. Vital status of the participants was determined from the basic resident register of the local government. First-ever CVD events were identified using the Takashima Cardio-cerebrovascular Disease Registry System. This system registers all patients who were residents in Takashima city (Takashima County). Details of case finding, the registration process and diagnostic criteria are described elsewhere.[13,14] In brief, we used multiple case-finding sources for case ascertainment that included hospital records and emergency ambulance service records. The acute myocardial infarction (AMI) and stroke diagnostic criteria used in the registry are those established for the Monitoring System for Cardiovascular Disease commissioned by the Ministry of Health and Welfare, Japan; these

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criteria are in accord with the World Health Organization's Monitoring of Trends and Determinants in Cardiovascular Disease project.[13,14] Validation of registered AMI events was based on information on medical history, clinical symptoms, electrocardiograph, as well as cardiac enzyme findings. For cases of out of hospital cardiac death, electrocardiograph findings and cardiac enzyme levels were often not available. In such cases, we had to base register the patients' location and symptoms at onset, and their history of coronary heart disease. Stroke was defined as sudden onset of neurological symptoms, which continued for a minimum of 24 h or resulted in death. The case definitions of stroke correspond to ICD10 I60.0–61.9 and I63.0–63.9, and the case definition of AMI correspond to ICD10 I21.0–21.9. CVD events were defined as the combination of stroke and AMI events. The Institutional Review Board of Shiga University of Medical Science approved the study protocol.

Biochemical and physical examinations

Baseline blood pressure (BP) was measured twice by trained observers using a standard electrical sphygmomanometer BP103iII (Omron Health Care Co. Ltd, Kyoto, Japan) applied to the right arm of seated participants after at least 5 min of rest. baPWV, supine BP and heart rate were measured in the supine position using a vascular profile device (BP-203RPE II Form I PWV/ABI; Omron Health Care Co. Ltd). Body mass index was calculated as weight divided by height squared ($kg\,m^{-2}$). We used a self-administered questionnaire that included lifestyle, clinical history, family history, smoking and alcohol drinking habit. The questionnaire was checked and collected by trained observers.

Non-fasting blood samples were obtained at the baseline survey. Serum was separated and centrifuged soon after blood coagulation. Blood samples were shipped to one laboratory (Kinkiyoken, Otsu, Japan) for blood measurements. Hemoglobin A1c was measured by latex agglutination immunoassay. Serum triglycerides, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol were also measured enzymatically.

Previous studies showed the risk stratification point about baPWV.[10,15] In this study, we categorized the participants into three groups according to their baPWV levels: low ($<14\,m\,s^{-1}$),[15] intermediate (14–17.9 $m\,s^{-1}$)[10] and high ($\geqslant 18\,m\,s^{-1}$).

Statistical analysis

Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs; and 95% confidence interval (CI)) of CVD incidence according to the three baPWV groups, with the low baPWV group as the reference. Multivariable-adjusted HRs for total and subtypes of CVD events were estimated using models adjusted for age, sex, smoking habits (non-smoker, past smoker and current smoker), alcohol drinking habits (non-drinker, past drinker and current drinker), body mass index, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, log-transferred triglyceride, hemoglobin A1c, heart rate and use of diabetic medication (model 2). We also added anti-hypertensive medication and seated or supine mean arterial BP (MBP) as covariates in an additional model (model 3 and model 4). baPWV was also analyzed as a continuous variable in multivariable-adjusted models to calculate the HR for a $2\,m\,s^{-1}$ increase in baPWV. All tests were two-tailed and a P-value <0.05 was considered statistically significant. All the analyses were performed by SPSS 18.0 (IBM, Armonk, NY, USA).

RESULTS

Baseline characteristics of study participants are shown in Table 1. Mean age was 58.9 ± 13.0 years and mean baPWV level was $15.48 \pm 3.74\,m\,s^{-1}$. Age, body mass index, systolic BP and diastolic BP increased as the baPWV categories increased ($P<0.001$). The proportions of men, treatment for diabetic and anti-hypertensive treatment were higher in higher baPWV categories ($P<0.001$). During the follow-up period (median = 6.5 years), 40 incident cases of CVD were observed; 29 events were stroke and 11 were AMI.

Table 2 shows adjusted HRs (95% CI) for a $2\,m\,s^{-1}$ increase in baPWV. A significant, positive association was observed between baPWV and total CVD events. The adjusted HR for total CVD events with a 2-$m\,s^{-1}$ increase in baPWV was 1.21 (95% CI: 1.05–1.40; model 2). A significant association remained after adjustment for treatment of hypertension and seated MBP (model 3). Similar results were observed after adjustment for treatment of hypertension and systolic BP. However, the association was attenuated and became non-significant after adjustment for supine MBP instead of seated MBP (model 4). The adjusted HR for total stroke events was similar to that for CVD events. A similar, but non-significant association was observed for AMI events (models 2, 3 and 4).

Table 1. Baseline characteristics of the study participants according to baPWV categories: the Takashima Study, Japan, 2002–2009

	<14 m s⁻¹	*14–17.9 m s⁻¹*	*⩾18 m s⁻¹*	P-*value*
Total number	1745	1542	877	
Age (years)	49.59 ± 12.14	63.48 ± 8.47	69.34 ± 7.90	<0.001
Male (%)	28.0%	41.3%	48.2%	<0.001
Body mass index ($kg\,m^{-2}$)	22.53 ± 3.09	23.25 ± 3.07	23.33 ± 2.89	<0.001
Seated systolic BP (mm Hg)	115.06 ± 14.23	132.06 ± 17.13	146.12 ± 19.90	<0.001
Seated diastolic BP (mm Hg)	69.68 ± 9.66	78.51 ± 10.81	83.08 ± 11.59	<0.001
Seated MBP (mm Hg)	84.80 ± 10.66	96.36 ± 12.19	104.09 ± 13.53	<0.001
Supine MBP (mm Hg)	89.08 ± 10.94	105.49 ± 12.19	116.45 ± 13.49	<0.001
Heart rate (beat per min)	63.81 ± 9.11	65.44 ± 10.37	69.22 ± 11.89	<0.001
HbA1c (%)	4.91 ± 0.49	5.14 ± 0.63	5.32 ± 0.89	<0.001
HDL cholesterol ($mg\,dl^{-1}$)	64.01 ± 15.81	60.92 ± 15.72	58.91 ± 15.32	<0.001
LDL cholesterol ($mg\,dl^{-1}$)	122.39 ± 31.78	128.28 ± 32.21	124.25 ± 32.48	<0.001
Triglyceride ($mg\,dl^{-1}$)	90.75 ± 57.47	109.77 ± 66.51	114.54 ± 66.93	<0.001
Smoking				<0.001
Non-smoker (%)	72.4	70.2	65.0	
Past smoker (%)	10.7	13.5	17.4	
Current smoker (%)	16.8	16.3	17.6	
Drinking				0.61
Non-drinker (%)	53.2	52.5	52.7	
Past drinker (%)	1.3	1.4	2.1	
Current drinker (%)	45.6	46.0	45.3	
Treatment of diabetes (%)	0.7	4.5	6.6	<0.001
Treatment of hypertension (%)	4.6	22.4	37.5	<0.001

Abbreviations: baPWV, brachial-ankle pulse wave velocity; BP, blood pressure; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MBP, mean arterial blood pressure. Values are number, rate (%) or mean ± s.d.

Table 2. HRs for CVD, stroke and AMI incidents for each 2 m s^{-1} increase in baPWV level: the Takashima Study, Japan, 2002–2009

	Model 1	*Model 2*	*Model 3*	*Model 4*
Total CVD incidence				
HR (95% CI)	1.25 (1.11–1.42)	1.21 (1.05–1.40)	1.20 (1.03–1.41)	1.15 (0.95–1.37)
Stroke incidence				
HR (95% CI)	1.24 (1.07–1.43)	1.19 (1.02–1.40)	1.19 (1.01–1.41)	1.15 (0.95–1.39)
AMI incidence				
HR (95% CI)	1.29 (1.00–1.66)	1.28 (0.93–1.76)	1.24 (0.86–1.80)	1.11 (0.74–1.67)

Abbreviations: 95% CI, 95% confidence interval; AMI, acute myocardial infarction; baPWV, brachial-ankle pulse wave velocity; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HR, hazard ratio; MBP, mean arterial blood pressure. Model 1 was adjusted for age and sex. Model 2 was adjusted for variables in Model 1, plus smoking habit, drinking habits, body mass index, HDL cholesterol, LDL cholesterol, log-transferred triglyceride, hemoglobin A1c, heart rate and diabetic medication. Model 3 was adjusted for variables in Model 2, plus anti-hypertensive medication and seated MBP. Model 4 was adjusted for variables in Model 2, plus anti-hypertensive medication and supine MBP.

Table 3. HRs for incidence of CVDs and stroke according to baPWV categories: the Takashima Study, Japan, 2002–2009

	< 14 m s^{-1}	*14–17.9 m s^{-1}*	*⩾ 18 m s^{-1}*
Number of participants	1745	1542	877
Total CVD incidents			
Number of incidents	3	13	24
Crude incidence rate[a]	36.2	182.6	632.1
HR (95% CI; model 1)	1 (Reference)	3.87 (1.01–14.81)	12.15 (3.00–49.22)
HR (95% CI)(model 2)	1 (Reference)	3.11 (0.80–12.04)	8.71 (2.08–36.54)
HR (95% CI; model 3)	1 (Reference)	3.26 (0.81–13.12)	9.48 (2.06–43.61)
HR (95% CI; model 4)	1 (Reference)	2.72 (0.67–11.06)	6.94 (1.43–33.73)
Total stroke incidents			
Number of incidents	3	8	18
Crude incidence rate[a]	36.2	112.3	472.1
HR (95% CI; model 1)	1 (Reference)	2.01 (0.48–8.39)	7.16 (1.66–30.95)
HR (95% CI; model 2)	1 (Reference)	1.69 (0.40–7.16)	5.45 (1.21–24.64)
HR (95% CI; model 3)	1 (Reference)	1.72 (0.39–7.55)	5.77 (1.16–28.80)
HR (95% CI; model 4)	1 (Reference)	1.48 (0.33–6.64)	4.46 (0.83–24.07)
		< 18 m s^{-1}	*⩾ 18 m s^{-1}*
Total CVD incidents			
Number of incidents		16	24
Crude incidence rate[a]		103.9	632.1
HR (95% CI; model 1)		1 (Reference)	3.99 (1.91–1.33)
HR (95% CI; model 2)		1 (Reference)	3.31 (1.55–7.06)
HR (95% CI; model 3)		1 (Reference)	3.26 (1.47–7.25)
HR (95% CI; model 4)		1 (Reference)	2.70 (1.18–6.19)
Total stroke incidents			
Number of incidents		11	18
Crude incidence rate[a]		71.4	472.1
HR (95% CI; model 1)		1 (Reference)	4.13 (1.73–9.85)
HR (95% CI; model 2)		1 (Reference)	3.54 (1.45–8.67)
HR (95% CI; model 3)		1 (Reference)	3.62 (1.42–9.23)
HR (95% CI; model 4)		1 (Reference)	3.12 (1.18–8.26)

Abbreviations: 95% CI, 95% confidence interval; baPWV, brachial-ankle pulse wave velocity; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HR, hazard ratio; MBP, mean arterial blood pressure. Model 1 was adjusted for age and sex. Model 2 was adjusted for variables in Model 1, plus smoking habit, drinking habits, body mass index, HDL cholesterol, LDL cholesterol, log-transferred triglyceride, hemoglobin A1c, heart rate and diabetic medication. Model 3 was adjusted for variables in Model 2, plus anti-hypertensive medication and seated MBP. Model 4 was adjusted for variables in Model 2, plus anti-hypertensive medication and supine MBP. [a]Crude incidence rates per 100 000 person-years for each incidents stratified by baPWV categories.

Table 3 shows adjusted HRs (95% CI) according to baPWV categories. HRs of total CVD and stroke events progressively increased as baPWV category rose (P for trend = 0.003 for CVD events and 0.016 for stroke events (model 2)). Compared with the low baPWV category, adjusted HRs for total CVD and stroke events in the high-baPWV category (⩾18 m s^{-1}) were significantly greater (HR 8.7 for total CVD and HR 5.5 for stroke). Significant associations of baPWV with CVD and stroke events remained after adjustment for treatment of hypertension and seated MBP (model 3). Significant associations of baPWV with CVD events remained after adjustment for supine MBP instead of seated MBP (model 4). Moreover, compared with the combined low and intermediate

level baPWV groups, the adjusted HRs for CVD and stroke incidence were significantly higher in the high-baPWV group in all models.

DISCUSSION

On the basis of these observations in a general Japanese population, increased baPWV was a predictor of future CVD and stroke events. The adjusted HR for total CVD events for a 2-m s^{-1} increase in baPWV was attenuated and non-significant to 1.15 (95% CI: 0.95–1.37). Compared with the low baPWV category (<18.0 m s^{-1}), the adjusted HR for total CVD events in the high-baPWV ($\geqslant 18$ m s^{-1}) category was ~ 3.

The European Society of Hypertension and the European Society of Cardiology 2007 Guidelines for the Management of Arterial Hypertension recommend measurement of PWV to evaluate subclinical organ damage.[16] In western populations, several studies of cfPWV assess the prognostic value of PWV in both the general population[3] and the patients.[2] Although baPWV was reported to be highly correlated with cfPWV,[5,6] there have been few reports to provide a direct relationship between baPWV and CVD events in a large general population.

It has been reported that baPWV predicts future CVD incidents in patients on hemodialysis[17] and in patients with essential hypertension;[11] it also predicts future CVD death in patients with acute coronary syndrome[10] and in general population of elderly subjects.[7,8] However, several studies reported no significant association between baPWV and CVD risk in patients with past history of CVD,[18] hemodialysis[19] or diabetes.[20] Our previous report showed that baPWV predicts future all-cause mortality in this population.[9] In addition, other cross-sectional studies from Japan and East Asian countries reported the association of baPWV with CVD risk factors and markers.[5,21–24] A recent meta-analysis reported a significant association between baPWV and CVD events;[12] however, this meta-analysis was based on 4769 patients and 775 elderly participants (aged 65 years and more). Thus, there have been few studies that report the association of baPWV with CVD events in general adult populations.

These previous studies have examined the associations between baPWV and future risk with adjustment for seated BP,[7,9] with adjustment for supine BP[11] and without any adjustment for BP.[8,10,19] However, the associations might be necessarily adjusted for supine BP as supine BP was measured concurrently with baPWV in the same position. In our study, after adjustment for supine MBP, the association of baPWV as a continuous variable with CVD risk became non-significant. However, higher CVD risk with baPWV $\geqslant 18.0$ m s^{-1} remained statistically significant.

Although baPWV is a reproducible, non-invasive and simple method to evaluate arterial stiffness, there has been much debate about whether baPWV reflects aortic arterial stiffness. Several reports demonstrated that baPWV reflects aortic arterial stiffness,[5,6,25,26] but some components of baPWV might be determined by peripheral arterial stiffness.[6] A cross-sectional study demonstrated that cfPWV was associated with the volume of white matter lesion but not with lacunar infarcts and micro-bleeds.[27] Conversely, association of baPWV with white matter hyperintensities,[28] higher numbers of lacunar infarcts[29] and cerebral micro-bleeds[30] were reported in several cross-sectional studies. In Japan, lacunar stroke consists of a major part of ischemic stroke, whereas in western countries, large thromboembolic stroke is dominant.[31] Therefore, baPWV, as a tool for evaluating both central and peripheral arteries, would be preferable for assessing subclinical organ damage in Asian populations. Further longitudinal studies are needed to examine the association of baPWV and cfPWV with lacunar stroke.

Two prior cohort studies reported that adjusted HRs of higher baPWV for total CVD events were 2.97 in patients with essential hypertension[11] and 9.22 in patients with acute coronary syndrome,[10] compared with those with a lower baPWV (the cut-off values were 17.5 and 18.0 m s^{-1}, respectively). In the present study, the adjusted HR for CVD incidence in the high-baPWV group was ~ 3 (with a cut-off value of 18.0 m s^{-1}), which was similar to the former finding in people with essential hypertension.

The present study has several limitations. First, because of lack of aortic and peripheral PWV measurement, we could not evaluate the different prognostic value of baPWV, aortic and peripheral PWV. Although several reports demonstrated that baPWV reflects aortic arterial stiffness, there has been much debate about whether baPWV reflects aortic arterial stiffness. Second, because of smaller number of AMI events, the study was underpowered to evaluate any association with AMI. Third, because of the low number of stroke events, we could not examine the association of baPWV with subtype of stroke events. Fourth, because of the smaller number of CVD events, we could not examine the association between baPWV and CVD events stratified by sex.

In conclusion, the present study demonstrated that higher baPWV (18 m s^{-1} and above) was an independent predictor of CVD events in a general Japanese population. baPWV measurement might be a useful and feasible method for CVD risk stratification in the general population.

What is known about topic:

- Brachial-ankle pulse wave velocity (baPWV) is a non-invasive measure of arterial stiffness and has been widely used in Japan and other East Asian countries. baPWV was reported to predict future CVD incidents in high-risk people.

What this study adds:

- In a general population, higher baPWV $\geqslant 18.0$ m s^{-1} was an independent predictor of future cardiovascular disease (CVD) event. baPWV measurement might be a useful CVD risk stratification tool in a general population.

CONFLICT OF INTEREST

The Takashima Study is partially supported by Omron Health Care Co. Ltd, but all authors have full access to all the data and take responsibility for their integrity and the accuracy of the analysis. The sponsor of the study had no role in the study design, conduct of the study, data collection, data interpretation or preparation of the report.

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Author contributions: All authors contributed to the study concept, design, analysis, interpretation of data and preparation of the manuscript.

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