Brachial-Ankle Pulse Wave Velocity and the Risk Prediction of Cardiovascular Disease

An Individual Participant Data Meta-Analysis

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Abstract—An individual participant data meta-analysis was conducted in the data of 14 673 Japanese participants without a history of cardiovascular disease (CVD) to examine the association of the brachial-ankle pulse wave velocity (baPWV) with the risk of development of CVD. During the average 6.4-year follow-up period, 687 participants died and 735 developed cardiovascular events. A higher baPWV was significantly associated with a higher risk of CVD, even after adjustments for conventional risk factors (P for trend <0.001). When the baPWV values were classified into quintiles, the multivariable-adjusted hazard ratio for CVD increased significantly as the baPWV quintile increased. The hazard ratio in the subjects with baPWV values in quintile 5 versus that in those with the values in quintile 1 was 3.50 (2.14–5.74; P<0.001). Every 1 SD increase of the baPWV was associated with a 1.19-fold (1.10–1.29; P<0.001) increase in the risk of CVD. Moreover, addition of baPWV to a model incorporating the Framingham risk score significantly increased the C statistics from 0.8026 to 0.8131 (P<0.001) and also improved the category-free net reclassification (0.247; P<0.001). The present meta-analysis clearly established baPWV as an independent predictor of the risk of development of CVD in Japanese subjects without preexisting CVD. Thus, measurement of the baPWV could enhance the efficacy of prediction of the risk of development of CVD over that of the Framingham risk score, which is based on the traditional cardiovascular risk factors. **(*Hypertension*. 2017;69:1045-1052. DOI: 10.1161/HYPERTENSIONAHA.117.09097.)** ● **Online Data Supplement**

Key Words: arterial stiffness ■ brachial-ankle pulse wave velocity ■ cardiovascular disease ■ individual participant data meta-analysis ■ risk factors

Arterial stiffness is well-recognized as an important predictor of development of cardiovascular disease (CVD),[1,2] and meta-analyses of prospective cohort studies have revealed that increase in the carotid-femoral pulse wave velocity (cfPWV) is associated with an increase in the risk of development of CVD.[3,4] However, the cfPWV is measured by tonometry or Doppler, which requires specialized training and exposure of the inguinal region.[5,6]

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In the early 2000s, a simple device for measurement of the brachial-ankle pulse wave velocity (baPWV) was launched for clinical use.[7] baPWV is automatically measured using a separate cuff for each of the 4 limbs by an oscillometric method. baPWV may be more easily applied in clinical practice than the cfPWV because of the simplicity and ease of its measurement.[7,8] baPWV has been reported to be closely correlated with the directly measured aortic PWV and cfPWV.[9] A recent meta-analysis using summary data from the literature has demonstrated that higher levels of baPWV were associated with an increased risk of development of CVD.[10] However, most of the studies included in the meta-analyses were conducted in patients with a high CVD risk (patients with CVD or end-stage renal disease), and thus, the usefulness of baPWV to assess the risk of development of CVD in subjects with a low to intermediate CVD risk as assessed using the Framingham risk score (FRS) had not been clearly elucidated. Furthermore, these studies did not determine the predictive ability for CVD over that of the traditional risk factors. Therefore, we conducted a meta-analysis using individual participant data (IPD) from prospective cohort studies to clarify whether baPWV could be used as an independent marker to predict the risk of development of CVD in subjects without preexisting CVD.

Methods

Study Population

J-BAVEL (Japan Brachial-Ankle Pulse Wave Velocity Individual Participant Data Meta-Analysis of Prospective Studies) is an IPD meta-analysis of cohort studies that investigated the association between the baPWV and all-cause mortality and CVD risk, conducted by the baPWV IPD meta-analysis study group. This collaborative study included the data from 14 cohort studies conducted in Japan (9 published and 5 unpublished studies).[11–24] The study was conducted with the approval of the Ethical Guidelines Committee of Tokyo Medical University (No 2655 2014).

Figure 1 depicts the process used to select the study population. We excluded 5506 subjects from the analyses (the details of the exclusions and inaccurate baPWV measurement[25] are described in Appendix S1 in the online-only Data Supplement). A final total of 13 381 subjects from 7 cohorts were included in the analysis for all-cause mortality (5 published studies[12,13,15,17,18] and 2 unpublished studies[14,16]), and 14 673 participants from 8 studies (5 published studies[12,13,15,17,18] and 3 unpublished studies[11,14,16]) were included in the analysis for CVD risk.

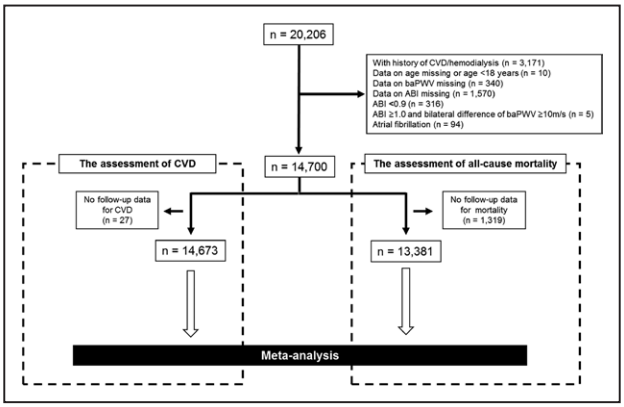

Figure 1. Flow chart of the participant selection procedure. ABI indicates ankle brachial pressure index; baPWV, brachial-ankle pulse wave velocity; and CVD, cardiovascular disease.

Measurement of baPWV and Ankle Brachial Pressure Index, Risk Factors, End Points, and Statistical Analysis

Detailed information on the measurement of the baPWV and ankle brachial pressure index, risk factors, end points, and statistical analysis are provided in Appendix S1. To estimate the CVD risk of individual participants, the FRS[26] was calculated, and the study subjects were categorized into low (10 year risk, <10%), intermediate (10 year risk, 10% to 20%), and high risk (10 year risk, ≥20%) groups.[26,27]

Summary of Statistical Analysis

The meta-analysis was conducted according to the Meta-Analysis of Observational Studies in Epidemiology guidelines (Appendix S1).[28] The consistency in the area under the receiver operating characteristic curves (ie, C statistics) among models was estimated using DeLong's method.[29] Discriminatory ability was evaluated by calculating the category-free net reclassification improvement and integrated discrimination improvement.[30,31] A 2-sided P value of <0.05 was considered to indicate statistical significance in all the analyses. The analyses were performed using the SAS software package, version 9.3 (SAS Institute Inc, Cary, NC), and the Stata software (release 13; StataCorp, College Station, TX).

Results

Characteristics of the Included Studies

The clinical characteristics of the 8 studies included in the analysis are listed in Table 1. During the follow-up period, a total of 687 participants died, and a total of 735 participants developed CVD. The numbers of CVD events in each cohort are shown in Table S1.

Association of baPWV With the All-Cause Mortality

Information on the baPWV and all-cause mortality was available in 7 studies. Table 2 shows the pooled estimate of the adjusted hazard ratio (HR) for all-cause mortality according to the baPWV values. The age- and sex-adjusted HR increased linearly with increase of the baPWV (P for trend =0.006). The HR for all-cause mortality in participants with baPWV levels in quintile 5 was 1.32 (95% confidence interval [CI], 0.94–1.87) in comparison with that in those with the values in quintile 1. The age- and sex-adjusted risk of all-cause mortality increased by 17% (95% CI, 9%–26%) per every 1 SD increase of the baPWV. There was no evidence of heterogeneity in the effects across studies (P for heterogeneity =0.92; I^2=0.0%; Figure S1A). However, this linear association was weakened after adjustments for potential confounding factors (P for trend =0.23), although the association was significant in the analysis conducted using baPWV as a continuous variable.

Association of baPWV With the Risk of CVD

The association between baPWV and the risk of CVD was examined in 8 studies. The age- and sex-adjusted pooled HR for the development of CVD increased linearly with increase of the baPWV quintile (Table 2; P for trend <0.001). Every 1 SD increase of the baPWV was associated with a 1.21-fold (95% CI, 1.13–1.30) increase in the risk of CVD. These associations remained substantially unchanged even after adjustments for potential confounding factors. There was evidence of marginally significant heterogeneity in the effects of the associations across studies (I^2=49.1%; P for heterogeneity

Table 1. Baseline Characteristics of the Included Cohorts

Cohort	Population	No of Subjects	Age, y	Men, %	Follow-Up Periods,* y	Mean baPWV, m/s	Mean Brachial SBP, mm Hg	Mean Brachial DBP, mm Hg	Use of Antihypertensive Agents, %	Mean HbA_{1c}, %	Mean BMI, kg/m^2	Mean TCHOL, mmol/L	Mean HDLC, mmol/L	Current Smoking Habits, %
Ehime Study[11]	Community	1315	65 (9)	39	4.3	15.80 (3.23)	126 (30)	73 (10)	29	5.9 (0.6)	23.2 (3.1)	5.66 (0.95)	1.75 (0.47)	6
Hisayama Study[12]	Community	2884	60 (12)	43	7.0	16.61 (4.45)	134 (20)	78 (11)	21	5.4 (0.8)	23.2 (3.3)	5.29 (0.90)	1.63 (0.42)	23
Iwate Study[13]	Community	955	59 (11)	47	7.9	14.77 (2.88)	128 (17)	77 (11)	25	5.5 (0.8)	24.1 (3.2)	5.01 (0.87)	1.42 (0.38)	23
Ohasama Study[14]	Community	783	66 (7)	32	5.5	16.73 (3.70)	140 (18)	82 (10)	38	5.7 (0.7)	23.9 (3.1)	5.42 (0.87)	1.54 (0.38)	11
Takashima Study[15]	Community	4575	59 (13)	37	8.8	15.21 (3.56)	134 (20)	79 (12)	18	5.4 (0.7)	23.0 (3.1)	5.37 (0.92)	1.60 (0.41)	16
J-HOP Study[16]	Patients with CVD risk†	852	61 (11)	47	5.8	16.00 (2.95)	135 (16)	80 (11)	76	5.9 (0.9)	24.6 (3.4)	5.20 (0.83)	1.46 (0.37)	12
NOAH Study[17]	HT patients‡	446	59 (12)	56	5.5	16.58 (3.29)	136 (19)	82 (12)	37	5.9 (1.2)	24.3 (3.4)	5.49 (0.96)	1.48 (0.44)	24
Kyushu Prevention Study of Atherosclerosis[18]	DM patients§	2890	59 (12)	60	3.1	17.09 (4.14)	135 (20)	81 (11)	32	8.2 (2.2)	24.7 (4.1)	5.30 (1.04)	1.36 (0.44)	26
Total		14700	60 (12)	44	6.4	16.05 (3.86)	134 (21)	79 (11)	28	6.0 (1.6)	24.7 (4.1)	5.34 (0.94)	1.55 (0.43)	19

Numbers in parentheses represent the standard deviations. baPWV indicates brachial-ankle pulse wave velocity; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HbA_{1c}, hemoglobin A_{1c}; HDLC, serum high-density lipoprotein cholesterol; HT, hypertension; J-HOP, Japan Morning Surge Home Blood Pressure; N, number; NOAH, Noninvasive Atherosclerotic Evaluation of Hypertension; SBP, systolic blood pressure; and TCHOL, serum total cholesterol.

*The mean follow-up period was derived from the analysis for cardiovascular disease.

†The J-HOP study included patients with any of the following cardiovascular risk factors: hypertension, impaired glucose tolerance or diabetes mellitus, dyslipidemia, smoking habit, chronic renal disease, atrial fibrillation, metabolic syndrome, and sleep apnea syndrome.

‡The NOAH study included outpatients diagnosed as having essential hypertension.

§The Kyushu Prevention Study of Atherosclerosis included outpatients diagnosed as having diabetes mellitus.

=0.056; Figure S1B). The source of this heterogeneity was considered to be the cohort of diabetic patients because the significant heterogeneity disappeared after exclusion of the Kyushu Prevention Study of Atherosclerosis cohort (I^2=0.0%; *P* for heterogeneity =0.97). With regard to the subtypes of CVD, similar associations were observed for ischemic heart disease and stroke (Table S2).

Estimation of the Risk Assessment Ability for CVD

To assess the effect of baPWV on the accuracy of the risk assessment for CVD, we compared the area under the receiver operating characteristic curves among the FRS, baPWV, and FRS+baPWV (Figure S2). In all the study participants, the addition of baPWV to a model incorporating the FRS significantly increased the C statistics from 0.8026 to 0.8131 (*P*<0.001). As shown in Table 3, in all the study participants, addition of baPWV to the model incorporating FRS significantly improved the accuracy of the risk assessment for CVD. The category-free net reclassification improvement and integrated discrimination improvement improved significantly to 0.247 (*P*<0.001) and 0.0068 (*P*<0.001), respectively, with addition of the baPWV to the model incorporating the FRS (Table 3).

The cutoff value of the baPWV for predicting the future risk of CVD occurrence was also examined. The point on the receiver operating characteristic curve that was closest to yielding the ideal of 100% sensitivity and 100% specificity was 15.91 m/s (Figure S3A), and the value that minimized the Youden Index was 15.43 m/s (Figure S3B).

Subgroup Analysis

As shown in Figure 2, every 1 SD increase of the baPWV was associated with a 1.39-fold (95% CI, 1.16–1.67) increase in the risk of CVD in the subgroup without hypertension, whereas the association was weaker in the subgroup with hypertension (HR, 1.17; 95% CI, 1.07–1.28; *P* for interaction =0.04). Similarly, there was a significant interaction between the baPWV and diabetes mellitus; the magnitude of the association between the baPWV and the incidence of CVD tended to be greater in the subgroup without diabetes mellitus (HR, 1.25; 95% CI, 1.11–1.42) as compared with that in the subgroup with diabetes mellitus (HR, 1.10; 95% CI, 0.97–1.24; *P* for interaction <0.001). With regard to the CVD risk status defined by the FRS, the association was stronger in the subjects classified as being at low risk as compared with that in the subjects classified as being at intermediate-high risk (*P* for interaction <0.001), although the HR for CVD increased significantly with increase of the baPWV in both subgroups. Similar results were obtained when the subjects were categorized into 3 rather than 2 risk groups (low, intermediate, and high risk). In addition, we evaluated the mutual interaction between the baPWV and traditional risk factors (hypertension and diabetes mellitus) in the development of CVD (Figure 3). The risk of CVD increased linearly with increase of the baPWV, irrespective of the presence or absence of hypertension (Figure 3A). With regard to diabetes mellitus, the HR for CVD increased steeply with increasing baPWV levels in

Table 2. Association of the baPWV With the Risk of All-Cause Mortality and the Development of Cardiovascular Disease

baPWV	No of Event/No of Subjects	Age- and Sex-Adjusted			Multivariate Adjusted*		
		HR (95% CI)	*P* Value	*P* for Trend	HR (95% CI)	*P* Value	*P* for Trend
All-cause mortality (n=13 381 death =687)†							
<12.87	47/2673	1.00 (reference)			1.00 (reference)		
12.88–14.51	75/2683	0.91 (0.63–1.31)	0.61		0.99 (0.66–1.50)	0.98	
14.52–16.25	123/2670	1.06 (0.75–1.50)	0.75	0.006	1.03 (0.69–1.54)	0.88	0.23
16.26–18.81	174/2679	1.21 (0.86–1.70)	0.27		1.19 (0.79–1.78)	0.41	
≥18.82	268/2676	1.32 (0.94–1.87)	0.11		1.18 (0.76–1.84)	0.46	
Every 1 SD (3.91 m/s) increment of baPWV	687/13 381	1.17 (1.09–1.26)	<0.001		1.13 (1.03–1.25)	0.01	
Cardiovascular disease (n=14 673, event=735)‡§							
<12.88	30/2930	1.00 (reference)			1.00 (reference)		
12.89–14.52	99/2940	2.08 (1.38–3.14)	<0.001		2.31 (1.40–3.80)	0.001	
14.53–16.23	137/2936	2.43 (1.62–3.64)	<0.001	<0.001	2.53 (1.55–4.14)	<0.001	<0.001
16.24–18.75	184/2933	2.72 (1.82–4.07)	<0.001		2.95 (1.82–4.81)	<0.001	
≥18.76	285/2934	3.40 (2.27–5.09)	<0.001		3.50 (2.14–5.74)	<0.001	
Every 1 SD (3.85 m/s) increment of baPWV	735/14 673	1.21 (1.13–1.30)	<0.001		1.19 (1.10–1.29)	<0.001	

baPWV indicates brachial-ankle pulse wave velocity; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; J-HOP, Japan Morning Surge Home Blood Pressure; N, number; NOAH, Noninvasive Atherosclerotic Evaluation of Hypertension; and SD, standard deviation.

*Adjusted for age, sex, brachial systolic blood pressure, history of use of antihypertensive agents, hemoglobin A_{1c}, body mass index, serum total cholesterol, serum high-density lipoprotein cholesterol, and current smoking habit.

†The Hisayama, Iwate, Ohasama, Takashima, J-HOP, NOAH, and Kyushu Prevention Study of Atherosclerosis study cohorts were included in the analysis for mortality.

‡The Ehime, Hisayama, Iwate, Ohasama, Takashima, J-HOP, NOAH, and Kyushu Prevention Study of Atherosclerosis study cohorts were included in the analysis for the development of cardiovascular disease.

§Cardiovascular disease in the Ohasama study was defined as a composite of CVD death and stroke.

the subjects without diabetes mellitus (*P* for trend <0.001), whereas only a trend toward moderate increase was observed in those with diabetes mellitus (*P* for trend =0.02), indicating a significant interaction (Figure 3B; P for interaction =0.001). The HR for CVD of the fourth quintile range of baPWV in subjects without diabetes mellitus was higher than the HR of the lowest quintile range of baPWV in those with diabetes mellitus.

Next, we assessed whether the ability of baPWV to predict the risk of future CVD development differed by the CVD risk assessed based on the FRS (Table 3). In participants with a low FRS, the area under the receiver operating characteristic curve increased significantly with the addition of baPWV to the model incorporating the FRS. Inclusion of baPWV to the model incorporating the FRS significantly improved the category-free net reclassification improvement and integrated discrimination improvement in low and intermediate-high risk subgroups. The magnitude of the improvements in the metrics tended to be greater in the low-risk FRS group as compared with that in the subjects with intermediate-high risk FRS groups (Table 3). The overall tendencies were broadly similar when the intermediate-high risk FRS group was further divided into intermediate-risk FRS and high-risk FRS groups.

Discussion

This IPD meta-analysis of the data from prospective cohort studies showed that baPWV provided additional predictive information for CVD occurrence, over that obtained from the conventional CVD risk score (ie, the net reclassification improvement increased significantly after inclusion of baPWV to the model based on FRS).

A literature-based meta-analysis has shown that every 1 m/s increase of the baPWV was associated with a 12% increase in the risk of CVD occurrence, which corresponds to a 3.1-fold increase of the CVD risk per every 10 m/s increase of the baPWV.[10] However, more than half of the study participants in this literature-based meta-analysis were patients with CVD or end-stage kidney disease,[10] with a poor prognosis (ie, very high–risk subjects). The usefulness of baPWV for precise prediction of CVD development in the relatively low- to medium-risk population was yet to be elucidated. In the present study, the IPD meta-analysis revealed that elevated baPWV was associated with an elevated risk of occurrence of CVD, independent of the conventional cardiovascular risk factors, in a population with a relatively low to intermediate risk of development of CVD (general population and hypertensive/diabetic patients). Thus, the findings of our study suggest that measurement of the baPWV may be a tool for CVD

Table 3. Discrimination and Reclassification Statistics (95% CIs) for Cardiovascular Disease After Addition of baPWV to a Model Incorporating the Framingham Risk Score

Subjects	Model	C Statistic	Category-Free NRI	IDI
All participants	FRS	0.8026 (0.7844–0.8207)		
	FRS+baPWV	0.8131 (0.7958–0.8304)	0.247 (0.160–0.335)	0.0068 (0.0035–0.0100)
		P<0.001	*P*<0.001	*P*<0.001
FRS low (men ≤5, women ≤9)	FRS	0.7967 (0.7575–0.8359)		
	FRS+baPWV	0.8214 (0.7842–0.8585)	0.334 (0.162–0.506)	0.0096 (0.0038–0.0154)
		P=0.004	*P*<0.001	*P*=0.001
FRS intermediate-high (men ≥6, women ≥10)	FRS	0.7370 (0.7016–0.7724)		
	FRS+baPWV	0.7465 (0.7127–0.7803)	0.232 (0.129–0.334)	0.0059 (0.0027–0.0091)
		P=0.71	*P*<0.001	*P*<0.001
FRS low (men ≤5, women ≤9)	FRS	0.7967 (0.7575–0.8359)		
	FRS+baPWV	0.8214 (0.7842–0.8585)	0.334 (0.162–0.506)	0.0096 (0.0038–0.0154)
		P=0.004	*P*<0.001	*P*=0.001
FRS intermediate (men 6–8, women 10–14)	FRS	0.7421 (0.7206–0.7636)		
	FRS+baPWV	0.7510 (0.7182–0.7837)	0.194 (0.046–0.342)	0.0040 (0.0008—0.0071)
		P=0.66	*P*=0.01	*P*=0.01
FRS high (men ≥9, women ≥15)	FRS	0.7003 (0.6853–0.7154)		
	FRS+baPWV	0.7104 (0.6879–7329)	0.245 (0.101–0.388)	0.0065 (0.0015–0.0114)
		P=0.47	*P*<0.001	*P*=0.01

Model FRS included the Framingham risk score and type of cohort (Ehime, Hisayama, Iwate, Ohasama, Takashima, J-HOP, NOAH, and Kyushu Prevention Study of Atherosclerosis). baPWV indicates brachial-ankle pulse wave velocity; CI, confidence interval; FRS, Framingham risk score; IDI, integrated discrimination improvement; J-HOP, Japan Morning Surge Home Blood Pressure; NOAH, Noninvasive Atherosclerotic Evaluation of Hypertension; and NRI, net reclassification improvement.

risk prediction that can be applied more broadly in general clinical settings.

In this study, the magnitude of the effect of increase of the baPWV on the risk of development of CVD was greater in the participants without diabetes mellitus or hypertension than in those with either/both of these diseases. Furthermore, the predictive ability of baPWV for future development of CVD was better than that of FRS in the population with a low risk of development of CVD. While the ability of the baPWV to reclassify was small, these findings may propose the applicability of baPWV measurement for prediction of CVD development, especially in subjects with a low CVD risk. The baPWV measurement is simple because it just involves measurement of the blood pressure in all 4 extremities with an oscillometric cuff device.[7,8] Therefore, measurement of the baPWV may provide additional predictive information for future development of CVD in subjects with a low CVD risk registered in health screening programs for CVD.

The exact reason why the effect of the baPWV on the risk of CVD differed according to the FRS or the presence/ absence of hypertension or diabetes mellitus is unclear, but there are several plausible mechanisms: increased arterial stiffness attenuates the cushioning effect of the large arteries, leading to increased cardiac afterload, decreased coronary blood flow, increased transmission of pulsatile energy to the peripheral microcirculation, and microvascular damage, resulting in an increased risk of development of CVD.[32] However, subjects with hypertension or diabetes mellitus are also more likely to have endothelial dysfunction and vascular inflammation in addition to increased arterial stiffness, possibly leading to plaque formation and rupture and development of CVD.[33]

For the subjects with intermediate CVD risk, the strategy for cardiovascular risk stratification has not yet been fully established.[27] Because the number of subjects with intermediate CVD risk is large, a biomarker that is simple and easy to measure is needed.[27,34] It might be difficult to incorporate measurement of the cfPWV, a reference standard for PWV, in routine clinical settings[5,6,34] because of the technical difficulties involved in its measurement. On the other hand, several questions and concerns regarding measurement of baPWV have also been raised.[35] The present study clearly demonstrated the applicability of baPWV as a predictor of future cardiovascular events, even when the subjects included in the analysis were limited to those with intermediate CVD risk. Thus, we propose that baPWV is applicable for CVD risk assessment in routine clinical practice, even in subjects with intermediate CVD risk.

The strengths of the present study were the inclusion of a large number of participants, the use of IPD, which allowed for sufficient statistical power to detect differences, the adjustments for confounders, and the subgroup analyses. In addition, the present study also evaluated the enhanced predictive ability of baPWV over that of the conventional risk factors for predicting the future risk of development of CVD.

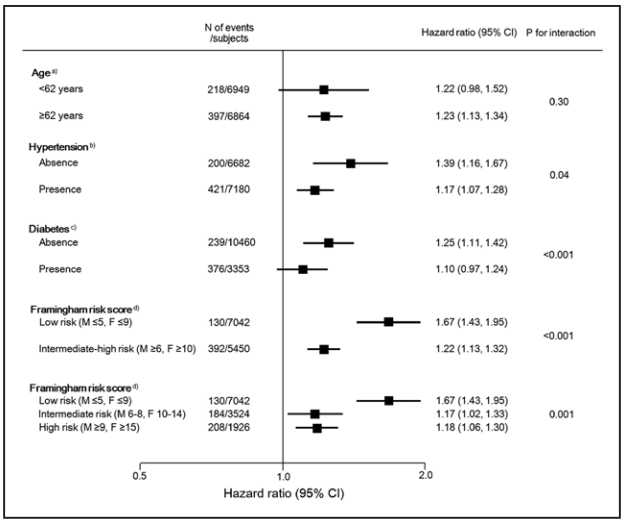

Figure 2. Comparisons of hazard ratios for the development of cardiovascular disease per every 1 SD increase of the baPWV levels in subgroups of age, hypertension, diabetes mellitus, and Framingham risk score. baPWV indicates brachial-ankle pulse wave velocity; BMI, body mass index; CI, confidence interval; M, men; SBP, systolic blood pressure; and W, women. [a]Multivariate adjustment was made for sex, brachial SBP, history of use of antihypertensive agents, diabetes mellitus, BMI, serum total cholesterol, serum high-density lipoprotein cholesterol, and current smoking habit. [b]Multivariate adjustment was made for age, sex, diabetes mellitus, BMI, serum total cholesterol, serum high-density lipoprotein cholesterol, and current smoking habit. [c]Multivariate adjustment was made for age, sex, brachial SBP, use of history of use of antihypertensive agents, BMI, serum total cholesterol, serum high-density lipoprotein cholesterol, and current smoking habit. [d]The risk estimates were made without adjustments.

Several limitations should also be noted. First, all the studies included in this meta-analysis were conducted in a Japanese population with low to intermediate CVD risk. Therefore, it would be difficult to generalize the current findings to other races/ethnicities or populations with a high CVD risk. Second, the definition of cardiovascular outcomes was not prespecified, which may be one of the sources of the heterogeneity in the findings across studies. However, there is no evidence of significant heterogeneity of the results among studies that used different definitions for CVD outcomes (eg, the Ohasama study and other studies), and also, our findings were not substantially altered by exclusion of the Ohasama study cohort from our analyses.[14] Third, differences in mean baPWV levels were observed even in the community-based cohorts. For example, the difference was 1.84 m/s between the Hisayama and Iwate study cohorts, despite the absence of any differences in the demographic characteristics between the 2 cohorts. However, the difference decreased to 1.15 m/s after adjustment for SBP, one of the determinants of the baPWV. Thus, the difference in SBP between the 2 cohorts (Hisayama =134 mm Hg versus Iwate =128 mm Hg) could possibly explain the difference in the baPWV. Fourth, the multivariable-adjusted analysis in the present study failed to reveal a significant association between the baPWV and the all-cause mortality. This was probably because of the effect of death from causes other than CVD, such as deaths because of cancer or infection, which are less likely to be associated with arterial stiffness. Fifth, the Takashima Study reported an unusually high rate of fatal events. Therefore, we conducted a sensitivity analysis to examine the predictive ability of the baPWV for future development of CVD in the subjects after excluding the Takashima study cohort, and the predictive ability remained unchanged (data not shown).

Perspectives

The findings of the present meta-analysis clearly showed that elevated values of the baPWV were associated with an elevated risk of CVD in Japanese subjects. The baPWV provided additional predictive information for future CVD over that obtained from the traditional risk factors in patients without preexisting CVD. These findings suggest that the baPWV could serve as a marker of the future risk of development of CVD in clinical practice, in both patients with low and intermediate-high CVD risk.

Appendix

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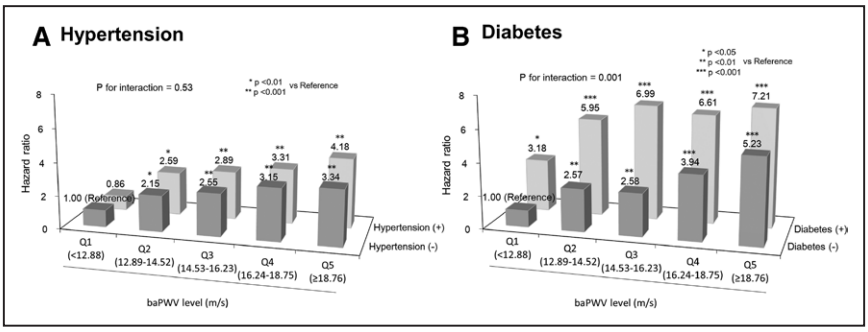

Figure 3. Multivariate-adjusted hazard ratios for the development of cardiovascular disease according to baPWV level by the presence or absence of hypertension or diabetes mellitus. **A**, Multivariate adjustment was made for age, sex, diabetes mellitus, body mass index, serum total cholesterol, serum high-density lipoprotein cholesterol, and current smoking habit. **B**, Multivariate adjustment was made for age, sex, brachial systolic blood pressure, history of use of antihypertensive agents, body mass index, serum total cholesterol, serum high-density lipoprotein cholesterol, and current smoking habit. baPWV indicates brachial-ankle pulse wave velocity; and Q, quintile range.

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Disclosures

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Novelty and Significance

What Is New?

- This individual participant data meta-analysis showed that inclusion of brachial-ankle pulse wave velocity (baPWV) in the risk assessment significantly improved the accuracy of prediction of the risk of cardiovascular disease (CVD) events over that assessed using the conventional CVD risk score (Framingham risk score) alone in subjects without preexisting CVD.

What Is Relevant?

- An elevated baPWV is well known to be associated with an elevated risk of development of CVD in the future. However, the usefulness of baPWV as a predictor of CVD risk had not been clarified in subjects with a low to intermediate CVD risk.

Summary

baPWV was identified as an independent predictor of future CVD events, independent of the traditional CVD risk factors, in a population with a relatively low to intermediate risk of CVD and provided additional predictive information for the development of CVD over that obtained from the traditional CVD risk factors. Measurement of the baPWV may be a tool for CVD risk prediction in general clinical practice in subjects with a low to intermediate CVD risk.